Conflict of Interest Declaration

“I have the following financial relationships with the manufacturers(s) of pertussis vaccines:”

Speaker in programs supported by: Sanofipasteur and GSK

Consultant for: Sanofipasteur and GSK

“My plan is to give what I hope is a balanced presentation using the best available evidence to support my conclusions and recommendations.

I do intend to discuss an unapproved use of commercial products in my presentation.”
PERTUSSIS EXPERTS EXAMINE
DIFFERENT PARTS OF THE ELEPHANT

MILLER

MANCLARK

SATO

MORTIMER

LAWYERS $$

OLIN

HINMAN
A Bit of History
History
(from Lapin 1943)

• In contrast to other severe epidemic infectious diseases (i.e., smallpox, polio, and measles), pertussis lacks an ancient history (Homes, 1940)
• 1414 illness began in France (Nils Rosen von Rosenstein, 1766)
• 1578: first epidemic (Ballonius)
• Well-recognized in Europe by the middle of the 18th century
**Bordetella**

- 1906: Bordet and Gengou isolate *B. pertussis*
- ~1910: Ferry, McGowan, and perhaps others isolated *B. bronchiseptica* from dogs with distemper
- 1930s: *B. parapertussis* isolated by Eldering and Kendrick and Bradford and Slavin
- 1995: *B. holmesii* isolated from patients in Massachusetts with pertussis-like illness

*From Mattoo and Cherry, Clin Micr Rev 2005;18:326-382*
**Description of Pertussis**

Guillamue de Baillou (Ballonius) 1578*

“Especially that common cough called Quinta or Quintana. The lung is so irritated that, in its attempt by every effort to cast forth the cause of the trouble, it can neither admit breath nor easily give it forth again. The sick person seems to swell up, and, as if about to strangle, holds his breath clinging in the midst of his jaws – for they are free from this annoyance of coughing sometimes for the space of four or five hours, then the paroxysm of coughing returns. Very frequently the belly happens to be upset.”

Whooping Cough: A Summary of its Peculiar Features-1940*

- Lacks an ancient history
- The cough in the spasmodic stage is distinctive though we don’t know why
- It kills more girl babies than boys
- There is no fever during the spasmodic stage, nor are there any physical findings

*from Bacillary and Rickettsial Infections, Acute and Chronic a Textbook (Black Death to White Plague) by William H. Holmes, Professor of Medicine, Northwestern University Medical School
Pertussis as described by L. Emmett Holt in 1902

- Clinical pertussis was remarkably similar to the illness seen today
- However, some findings were more pronounced, and complications were more frequent
- Hemorrhagic complications were much more common than today
- During the summer infants with pertussis nearly always had accompanying diarrhea
- Infants with severe posttussive vomiting and poor food intake often developed malnutrition
Pertussis Facts
2011

• DTaP vaccines are less reactogenic than DTP vaccines, however they are less efficacious
• Of all our routine vaccines (except influenza) pertussis vaccines are the least effective
• *B. pertussis* infections are common in all age groups and this is not new
• Most adolescent and adult cases are not diagnosed as pertussis
• Young infants get pertussis from adolescent and adult family members
• The potential severity of pertussis in young infants is often not recognized by health care providers
• The Dx of severe pertussis in young infants is often not made
Review

1) Clinical characteristics
2) Epidemiology
3) Dx and Rx
4) Prevention of pertussis by immunization
5) Why vaccines fail
Clinical
Major Manifestations of Typical Pertussis

Three-stage illness (catarrhal, paroxysmal and convalescent) that lasts 4-12 weeks

Specific manifestations

- paroxysmal cough
- lack of fever
- no systemic illness
- coryza; no pharyngitis
- posttussive vomiting
- posttussive whoop
- absolute lymphocytosis
Click here if video doesn’t start
Total Duration of Cough in 247 German Children with *B. pertussis* Infections

April 1991-February 1992

<table>
<thead>
<tr>
<th>Total Days of Cough</th>
<th>No.</th>
<th>%</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>11</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>8-14</td>
<td>28</td>
<td>11.3</td>
<td>15.8</td>
</tr>
<tr>
<td>15-21</td>
<td>24</td>
<td>9.7</td>
<td>25.5</td>
</tr>
<tr>
<td>22-28</td>
<td>54</td>
<td>21.9</td>
<td>47.4</td>
</tr>
<tr>
<td>&gt;28</td>
<td>130</td>
<td>52.6</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Young Infants
Click Here
Pertussis in Young Infants

• Initially infant looks deceptively well; coryza, sneezing, clearing throat, no fever, mild cough

• Paroxysmal stage: gagging, gasping, eye bulging, bradycardia, cyanosis, vomiting

• Leukocytosis with lymphocytosis

• Apneic episodes

• Seizures

• Respiratory distress

• Pneumonia

• Adenovirus or RSV coinfection can confuse picture
Pertussis Infant Deaths (38) in California 1998-2009*

- 97% less than 3 months of age
- 55% neonates
- 82% hispanic
- 91% had WBC counts greater than 35,000
- 92% had pneumonia
- 42% had pulmonary hypertension

*J.Chang CDPH and J.Cherry
Pathophysiology of fatal *Bordetella pertussis* infection in infants

Christopher D. Paddock, Claire Langston, Anthony A. Gal, Sherif R. Zaki, and James D. Cherry
Infection of tracheal epithelium with *Bordetella pertussis*

- Ciliostasis, epithelial damage, and compromised mucociliary clearance
- Pulmonary infection with *B. pertussis*
  - Apnea
  - Necrotizing bronchiolitis/pneumonia
  - Toxin-mediated leukocytosis

- Hypoxemia
- Acute respiratory distress syndrome
  - Pulmonary vasoconstriction
  - Increased whole blood mass
  - Increased vascular resistance

- Pulmonary hypertension
- Cardiac failure and shock

Mattel Children's Hospital at UCLA
Source of Pertussis in Infants
CDC Study – Infant Pertussis: Who Was the Source?

- 774 infant cases from 4 states
- 264 cases had source identified
- Sources:
  - Mother 32%
  - Sibling 20%
  - Father 15%
  - Grandparent 8%
  - Other 25%

Age of Pertussis Source* for Infants

*219 source-persons with known age

Transmission of Pertussis to Young Infants

Wendelboe et al. PIDJ 2007;26:293-299

91 ≤ 6 month olds cases; source identified in 44 (48%).

- mothers: 41%
- fathers: 20%
- siblings: 18%
- aunt/uncle: 11%
- friend/cousin: 11%
- grandparent: 7%
- part-time caretaker: 2%

* There were multiple source patients in some instances
Transmission of Pertussis to Young Infants

Wendelboe et al PIDJ 2007;26:293-299

Age of 49 source patients

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 13</td>
<td>14%</td>
</tr>
<tr>
<td>13-18</td>
<td>16%</td>
</tr>
<tr>
<td>19-39</td>
<td>61%</td>
</tr>
<tr>
<td>40-64</td>
<td>8%</td>
</tr>
</tbody>
</table>
Prospective Multinational Study of Pertussis Infection in Hospitalized Infants and Their Household Contacts

Kowalzik et al. *PIDJ* 2007;26:238-242

99 PICU Infants
30 household contacts identified

Mother 50%
Another adult 20%
Sibling 17%
Father 10%
Another child 3%
## Source of Infection in Young Children

Wendelboe et al PIDJ 2007;26:293-299

|                  | Renacoq* | Crowcroft et al† | Halperin et al|||
|------------------|----------|------------------|----------------|
| Source Patients  | 53       | 42               | 40             |
| Parent           | 56%      | 42%              | 20%            |
| Sibling          | 23%      | N/A              | 53%            |

* [http://www.invs.sante.fr/surveillance/coquelunche/donnees_96_04.pdf](http://www.invs.sante.fr/surveillance/coquelunche/donnees_96_04.pdf)
† Arch Dis Child 2003; 88: 802-806
|| CID 1999; 28: 1238-1243
Adolescents and Adults
Adult Pertussis: A Salesman’s Dream—and an Epidemiologist’s nightmare

Paul E. M. Fine
Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, U.K.
Pertussis Pete*

1. Peter G. boarded with his sister in Harlem.
2. Two nieces and one nephew contracted whooping cough. Peter began to cough a few weeks later.
3. Beginning of March Peter visited another sister in Brooklyn and 8 days later her children developed pertussis.
4. Peter went to live with brother; a week later the brother’s child developed pertussis.
5. Peter moved to cousin’s house and shortly thereafter neighbor’s child developed pertussis.
6. April 20th Peter sailed for Italy having enlisted in the army.

Pertussis in Adults

Conclusions

1. Adult pertussis occurs more frequently than generally assumed.

2. Second attacks are more frequent than commonly believed.

3. Illness starts with insidious cough 1-3 weeks after exposure, lasts 5-6 weeks or longer, worse at night, gagging and choking common, and thick, white, tenacious phlegm is raised.


Mannerstedt G, J. Pediatrics. 1934;5:596
Grandmothers Cough*
Faroe Islands 1914-15

• It is worthy of note that many of the substantiated cases of whooping cough were second attacks so called “grandmothers whooping cough”; however, these were always light and shorter in duration than the first attacks.

*Madsen T. Boston M&S J. 1925;192:50.
Adult Pertussis in Vaccine Efficacy Trials

Gothenburg – Seven adult primary cases
Stockholm I – Four of 59 primary cases were adults
II – Seven of 329 primary cases were adults
Mainz – 18 of 121 primary cases were adults
Erlangen – In 60 families an adult was the primary case in 29 (48%) instances.
B.A.L. is a 47 year-old M.D.

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/3/96</td>
<td>Mild URI with lacrimation</td>
</tr>
<tr>
<td>5/27/96</td>
<td>Onset cough</td>
</tr>
<tr>
<td>5/28-31/96</td>
<td>Airline trips – severe paroxysmal cough, worse at night and intercostal pain</td>
</tr>
<tr>
<td>6/1/96</td>
<td>Rx prednisone and antitussives</td>
</tr>
<tr>
<td>6/6/96</td>
<td>Rx Ofloxacin; culture for pertussis</td>
</tr>
<tr>
<td>6/11/96</td>
<td>Culture positive; Rx Azithromycin</td>
</tr>
</tbody>
</table>

Cough lasted three months, 47 people at hospital received antibiotic prophylaxis, source 13 year old daughter
Musher and Keitel, Hospital Practice. 1995;30:65

- A 49 year-old woman presented with severe paroxysmal coughing an disabling pleuritic pain of one week’s duration. PE revealed a haggard, afebrile woman who appeared to be exhausted. The exam interrupted by paroxysms followed by whoop. Chest x-ray revealed fractured left rib. Paroxysmal cough continued for 4 weeks and associated with another rib fracture. Illness lasted two months.
C.A. is a 43 year-old Pediatric Anesthesiologist

In 1994 developed a “cold with nasal congestion, sore throat, and myalgia.” Because worsening symptoms he took Theraflu, Nyquil, and Sudafed. One week later severe paroxysmal cough which was so bad that his children thought he was choking and slapped him on the back. Dx by PMD: asthma. Symptoms persisted. Rx erythromycin for “mycoplasma.” Dx eventually made by JDC following hallway consultation.
H.M.W. is a middle-aged Research Microbiologist

Developed a mild cough in August 1996. After two weeks a colleague suggested she see an M.D. because cough was annoying him. “This began the first of about half a dozen visits to Kaiser. Kaiser M.D.s thought it was nothing or asthma, and she was concerned about a tumor. Paroxysms so bad she slept sitting up and outside. She could not catch her breath and had urinary incontinence with paroxysms. Her chest hurt so bad that she suspected a broken rib. After six weeks her boss called me and the classic cough noted. Her illness lasted three months.
A 56 yr old UCLA professor became ill with an afebrile illness with severe paroxysmal cough in March 2002. He was seen by an ENT physician and then his internist at UCLA in April. Chest and sinus x-rays were normal. His “choking episodes” were severe. He was treated with steroids, an antihistamine, a tranquilizer, and subsequently amoxicillin. The patient was seen by 3 physicians and the diagnoses were “uniformly vague.”

The patient’s wife developed the same illness 2 weeks after it’s onset in the patient. Their 3 children remained well. At the time of a well child visit the UCLA pediatrician diagnosed pertussis in the professor and his wife and this diagnosis was confirmed by serology. The patient’s illness lasted 11 weeks.
PD Dr. Johannes Liese

Pertussisfall nach Nasopharyngealabstrich bei 30-jähriger Mutter und 6-monatigem Säugling
Seventyone Year Old Man (MD) with Pertussis

- Age 5 had pertussis; 20 yrs ago wife had pertussis
- 7/5/09 Exposed on airplane
- 7/15/09 Onset of cough illness
- 7/18/09 Sweating episode
- 7/29/09 First whoop; Rx azithromycin
- 8/3/09 Internist Dx “cough variant asthma”; decided to rule out insulinoma; Rx predisone
- 8/7/09 ENT Dx Wegener’s granulomatosis; CT head and neck
- 8/14/09 PCR positive
- Aug-Oct coughing continued without improvement
- Nov relapse of cough during a cold
Sweating Episodes

• "I noticed that I felt faint and was sweating profusely”
• “My wife noticed that I had become drenched with sweat and that I looked gray”
• “After about 20 minutes, the sensation of light-headedness and the diaphoresis abated”
• “My internist also decided to rule out insulinoma as a cause of the episodes of light-headedness and diaphoresis”
### SYMPTOMS OF PERTUSSIS IN ADOLESCENTS AND ADULTS*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysms</td>
<td>99</td>
</tr>
<tr>
<td>Posttussive apnea</td>
<td>87</td>
</tr>
<tr>
<td>Posttussive vomiting</td>
<td>65</td>
</tr>
<tr>
<td>Whoop</td>
<td>69</td>
</tr>
<tr>
<td>Sweating episode</td>
<td>32</td>
</tr>
</tbody>
</table>

* De Serres et al. JID 2000; 187: 174-9
## COMPLICATIONS OF PERTUSSIS IN 664 ADOLESCENTS AND ADULTS*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>13</td>
</tr>
<tr>
<td>Otitis media</td>
<td>4</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
</tr>
<tr>
<td>Rib Fracture</td>
<td>2</td>
</tr>
<tr>
<td>Fainting</td>
<td>2</td>
</tr>
</tbody>
</table>

*De Serres et al. JID 2000; 187: 174-9
An Epidemic of Pertussis Among Elderly People in a Religious Institution in the Netherlands


Residents and personnel 99
Attack rate 49%
Death rate in residents (intracranial bleeding) 5% (4/75)
## Clinical Diagnoses Assigned by the Primary Care Providers and Antibiotic Therapy in Students with Cough ≥ 6 Days (Mink et al. CID 1992; 14: 464-471)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Subjects with <em>B. pertussis</em> infection (n = 31)</th>
<th>Subjects without <em>B. pertussis</em> infection (n = 84)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>URI</td>
<td>39%</td>
<td>33%</td>
<td>0.68</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>48%</td>
<td>64%</td>
<td>0.14</td>
</tr>
<tr>
<td>Otitis/Sinusitis/Pharyngitis</td>
<td>0%</td>
<td>10%</td>
<td>0.11</td>
</tr>
<tr>
<td>Pertussis</td>
<td>0%</td>
<td>1%</td>
<td>0.99</td>
</tr>
<tr>
<td>Other</td>
<td>16%</td>
<td>8%</td>
<td>0.30</td>
</tr>
<tr>
<td>Antibiotics taken for illness prior to clinic visit</td>
<td>23%</td>
<td>14%</td>
<td>0.26</td>
</tr>
<tr>
<td>Antibiotics prescribed at the time of clinic visit</td>
<td>39%</td>
<td>64%</td>
<td>0.02</td>
</tr>
<tr>
<td>Erythromycin prescribed at the time of clinic visit</td>
<td>35%</td>
<td>52%</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Fisher's Exact Test*
## CLINICAL CHARACTERISTICS OF COUGH IN STUDENTS WITH COUGH FOR ≥ 6 DAYS (Mink et al. CID. 1992; 14: 464-471)

<table>
<thead>
<tr>
<th>Characteristic of Cough</th>
<th>34 Students with <em>B. pertussis</em> Infection</th>
<th>96 Student without <em>B. pertussis</em> Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration prior to study</td>
<td>21 days</td>
<td>14 days*</td>
</tr>
<tr>
<td>Frequency ≥ 1 episode/hour</td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td>Quality Staccato or paroxysmal</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td>Productive with each episode</td>
<td>3%</td>
<td>21%†</td>
</tr>
<tr>
<td>Severity severe ‡</td>
<td>40%</td>
<td>35%</td>
</tr>
</tbody>
</table>

* p = 0.92  
† p = 0.02  
‡ Definition: required interruption of all activities during episode
Clues in the Clinical Dx of Pertussis in Older Children, Adolescents and Adults

- Lack of fever
- Lack of a truly productive cough
- WBC, ESR and CRP normal
- Feeling of a choking sensation
- Cough worse at night; need to sleep sitting up
- Sweating episodes
- Normal between coughing episodes
Treatment
ANTIMICROBIAL AGENTS FOR THE TREATMENT AND PREVENTION* OF PERTUSSIS

Children

Erythromycin† = 40-50 mg/kg/day for 14 days administered every 6 hours (maximum dose = 2 gms/day)

Azithromycin = 10 mg/kg on day 1 and 5 mg/kg on days 2-5 as a single dose/day (maximum dose = 500 mg on day 1 and 250 mg on days 2-5)

Clarithromycin = 15-20 mg/kg in 2 divided doses for 7 days (maximum dose = 1gm/day)

Trimethoprim-sulfamethoxazole = 8-12 mg of trimethoprim, 40-60 mg of sulfamethoxazole /day in 2 doses for 14 days (maximum dose = 320 mg of trimethoprim)

* Prophylactic dose is the same as the treatment dose
† Recent data suggest that a 7 day treatment course is effective
ANTIMICROBIAL AGENTS FOR THE TREATMENT AND PREVENTION* OF PERTUSSIS

Adults

Azithromycin = 500 mg on day 1 and 250 mg on days 2-5 as a single dose/day

Clarithromycin = 1 gm/day in 2 divided doses for 7 days

Trimethoprim-sulfamethoxazole = 320 mg of trimethoprim, 1.6 gm of sulfamethoxazole/day in 2 doses for 14 days

* Prophylactic dose is the same as the treatment dose
Prophylaxis
Laboratory Diagnosis of *B. pertussis* Infection
Serologic Diagnosis of

*B. pertussis* Infection
When Pertussis Tests are Likely to be Positive in Infected People
Epidemiology
The Epidemiology of Reported Pertussis is Different from the Epidemiology of *B. pertussis* Infection
Pertussis Epidemiology

1) In prevaccine era, pertussis was a universally present disease with cyclic peaks every 2 to 5 years

2) In the prevaccine era > 93% of reported cases occurred in children < 10 years of age

3) In the 1970s 50% of cases were reported in infants

4) Recently about 65% of reported cases are in persons > 10 years of age

5) Immunization changed the rate of reported pertussis in the US from 157 per 100,000, in the prevaccine era, to < 1 per 100,000 in the 1970s

6) Since 1984 there has been a modest increase in reported pertussis (from 1 to 8 cases per 100,000)

7) In the vaccine era the cyclic peaks of reported pertussis still occur at 2 to 5 year intervals
Reported Pertussis Cases -- U.S., 1922-2005*

* 2005 Provisional
Reported Pertussis Cases by Age Group, U.S., 1983-2005

Number of cases

Year

*2005 Provisional
Reported Pertussis

• Pertussis has been and is presently under reported
• Rates of reported pertussis depend upon how carefully cases are looked for
Possible Reasons for the Resurgence of Reported Pertussis

1) Genetic changes in *B. pertussis*
2) Lessened potency of pertussis vaccines
3) Waning of vaccine-induced immunity
4) Greater awareness of pertussis
5) The general availability of better laboratory tests
Reported Pertussis

In spite of the fact that reported pertussis is only the “tip of the iceberg,” it is clear that cyclic disease pattern occurs and that this pattern has continued in the vaccine era.
Measles – United States, 1950-2002*

*2002 provisional data

Vaccine Licensed
Epidemiology of *B. pertussis* Infections

**Issues**

1. Percentage of prolonged cough illnesses in adolescents and adults due to *B. pertussis* infections
2. Rate of *B. pertussis* infections in adolescents and adults
3. Rate of *B. pertussis* cough illnesses in adolescents and adults
## Percentage of Prolonged Cough Illnesses in Adolescents and Adults Due to *B. pertussis* Infections

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Year</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mink et al.</td>
<td>Los Angeles</td>
<td>86-89</td>
<td>13%</td>
</tr>
<tr>
<td>Wright et al.</td>
<td>Nashville</td>
<td>92-94</td>
<td>16%</td>
</tr>
<tr>
<td>Nennig et al.</td>
<td>San Francisco</td>
<td>94-95</td>
<td>12%</td>
</tr>
<tr>
<td>Strebel et al.</td>
<td>Minneapolis/St. Paul</td>
<td>95-96</td>
<td>13%</td>
</tr>
<tr>
<td>Birbeback et al.</td>
<td>Denmark</td>
<td>95-97</td>
<td>17%</td>
</tr>
<tr>
<td>Vincent et al.</td>
<td>Korea</td>
<td>97-98</td>
<td>7%</td>
</tr>
<tr>
<td>Dalby et al.</td>
<td>Denmark</td>
<td>06-08</td>
<td>~10%</td>
</tr>
</tbody>
</table>

* Significant IgA or IgG antibody titer rise or high titer to PT, or culture or PCR positive
**Percentage of Prolonged Cough Illnesses in Adolescents and Adults Due to *B. pertussis*** Infections

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Year</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mink et al.</td>
<td>Los Angeles</td>
<td>86-89</td>
<td>13%</td>
</tr>
<tr>
<td>Wright et al.</td>
<td>Nashville</td>
<td>92-94</td>
<td>16%</td>
</tr>
<tr>
<td>Jansen et al.</td>
<td>San Diego</td>
<td>93-94</td>
<td>1%</td>
</tr>
<tr>
<td>Nennig et al.</td>
<td>San Francisco</td>
<td>94-95</td>
<td>12%</td>
</tr>
<tr>
<td>Strebel et al.</td>
<td>Minneapolis/St. Paul</td>
<td>95-96</td>
<td>13%</td>
</tr>
<tr>
<td>Birbeback et al.</td>
<td>Denmark</td>
<td>95-97</td>
<td>17%</td>
</tr>
<tr>
<td>Vincent et al.</td>
<td>Korea</td>
<td>97-98</td>
<td>7%</td>
</tr>
</tbody>
</table>

* Significant IgA or IgG antibody titer rise or high titer to PT, or culture or PCR positive
# Rate of *B. pertussis* Infection in Adolescents and Adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Year</th>
<th>Annual Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deville et al.*</td>
<td>Los Angeles, CA</td>
<td>84-89</td>
<td>6%</td>
</tr>
<tr>
<td>Cromer et al.*</td>
<td>Columbus, OH</td>
<td>85-90</td>
<td>~1%</td>
</tr>
<tr>
<td>Hodder et al.*</td>
<td>Cleveland, OH</td>
<td>89-92</td>
<td>3%</td>
</tr>
<tr>
<td>Wright et al.*</td>
<td>Nashville, TN</td>
<td>92-94</td>
<td>2.2%</td>
</tr>
<tr>
<td>Ward et al.*</td>
<td>Eight US cities</td>
<td>97-99</td>
<td>1.3%</td>
</tr>
<tr>
<td>de Melker et al. †</td>
<td>Netherlands</td>
<td>95-96</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

* Infections were determined by the demonstration of a significant serum antibody titer rise to PT in successive serum samples

† Infections were determined by demonstration of PT values above their cut off limits
## Rate of *B. pertussis* Cough Illnesses in Adolescents and Adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Year</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strebel et al.</td>
<td>Minneapolis/St Paul</td>
<td>95-96</td>
<td>0.5%</td>
</tr>
<tr>
<td>Ward et al.</td>
<td>Eight Centers, USA</td>
<td>97-99</td>
<td>0.37%</td>
</tr>
<tr>
<td>Hodder et al.</td>
<td>Cleveland</td>
<td>89-92</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
Summary 2011

• *B. pertussis* infections in adolescents and adults are very common and endemic in the present vaccine era
• Data from Germany in the early 1990’s when few children were being immunized and pertussis was epidemic, as well as early observations in the U.S., suggest that infections in adolescents and adults were also common and endemic in the prevaccine era
• Rates of reported pertussis are 40 to 160-fold less common than actual illness rates
• Asymptomatic infections are 4 to 22 times more common than symptomatic infections
• Today symptomatic adolescents and adults are the major source of infection in unvaccinated children
Pertussis Vaccines
Pertussis Vaccines

~1945 DTwP vaccines
~1995 DTaP vaccines
  PT
  PT,FHA
  PT,FHA,PRN
  PT,FHA,PRN,FIM
~2005 Tdap vaccines
  PT,FHA,PRN
  PT,FHA,PRN,FIM 2/3
Virulence factors of *Bordetella pertussis*

**TOXINS:**
- Pertussis toxin
- Adenylate cyclase toxin
- Dermonecrotic Toxin
- Tracheal cytotoxin
- Lipopolysaccharide

**ADHESINS:**
- Filamentous hemagglutinin
- Pertactin, BrkA, Vag8, Tracheal colonization factor
- Fimbriae (or pili)
Antibody To:

- PT-promotes neutrophil chemotaxis; prevents leukocytosis with lymphocytosis; prevents increased insulin secretion
- FHA-may block attachment
- PRN-induces opsonic antibodies which facilitates phagocytosis
- FIM-agglutinates bacteria which blocks attachment
Why Do Pertussis Vaccines Fail?
Possible Reasons Why DTP and DTaP Vaccines Fail

- Over expectation of efficacy due to case definition.
- Over expectation of efficacy due to observer bias.
- Other *Bordetella* sp are the cause of similar cough illnesses
- Decay in antibody over time.
- Incomplete antigen package.
- Genetic changes in *B. pertussis*
Possible Reasons Why DTP and DTaP Vaccines Fail

• Over expectation of efficacy due to case definition.
• Over expectation of efficacy due to observer bias.
• Other *Bordetella* sp are the cause of similar cough illnesses
• Lack of initial potency.
• Decay in antibody over time.
• Incomplete antigen package.
• Incorrect balance of antigens in the vaccine.
• Linked-epitope suppression.
• ELISA values measured are cross reacting antibodies
• Genetic changes in *B.pertussis*
WHY ARE THERE MORE CASES IN PREVIOUS VACCINEES THAN IN NONVACCINEES?

<table>
<thead>
<tr>
<th>Population</th>
<th>1000</th>
<th>90% immunized</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE= 70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attack rate in nonvaccinees 70%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccinees</th>
<th>900</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number susceptible</td>
<td>270</td>
</tr>
<tr>
<td>Number of cases</td>
<td>189</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonvaccinees</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number susceptible</td>
<td>100</td>
</tr>
<tr>
<td>Number of cases</td>
<td>70</td>
</tr>
</tbody>
</table>

\[
\text{VE} = \frac{70 - 21}{70} = .70 \times 100 = 70\%
\]
Over Expectation of Efficacy due to Case Definition.
WHO Pertussis Case Definition
(Geneva January 11, 1991)

≥21 days of paroxysmal cough and one or more of the following:
• Positive culture of B. pertussis
• Titer rise (ELISA) IgG or IgA to PT, FHA or Fim 2-3
• Household contact with culture confirmed case occurring ±28 days of onset in trial child.
## Vaccine Efficacies of Eight Acellular Pertussis Component Vaccines and Two Whole Cell Pertussis Component Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Components</th>
<th>Percent Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amvax</td>
<td>PT</td>
<td>31(-4-59)</td>
</tr>
<tr>
<td>JNIH-7</td>
<td>PT</td>
<td>-6(-49-24)</td>
</tr>
<tr>
<td>JNIH-6</td>
<td>PT, FHA</td>
<td>43(15-61)</td>
</tr>
<tr>
<td>SKB</td>
<td>PT, FHA</td>
<td>42(33-51)</td>
</tr>
<tr>
<td>SKB</td>
<td>PT, FHA, PRN</td>
<td>71(60-78)</td>
</tr>
<tr>
<td>Chiron-Biocine</td>
<td>PT, FHA, PRN</td>
<td>71(61-79)</td>
</tr>
<tr>
<td>Lederle/Takeda</td>
<td>PT, FHA, PRN, FIM-2</td>
<td>62(38-77)</td>
</tr>
<tr>
<td>Connaught (Canada)</td>
<td>PT, FHA, PRN, FIM-2,3</td>
<td></td>
</tr>
<tr>
<td>Wyeth- Lederle</td>
<td>Whole Cell</td>
<td>78(62-88)</td>
</tr>
<tr>
<td>Connaught (USA)</td>
<td>Whole Cell</td>
<td>41(30-51) to 23(1-40)</td>
</tr>
</tbody>
</table>
Over Expectation of Efficacy Due to Observer Bias
The Effect of Investigator Compliance (Observer Bias) on Calculated Efficacy in a Pertussis Vaccine Trial

James D. Cherry, MD, MSc; Ulrich Heininger, MD; Klemens Stehr, MD; and Peter Christenson, PhD
Percent Vaccine Efficacy by Investigator Compliance Category Against Mild and Typical and Typical Pertussis Attributable to *B. pertussis* *

<table>
<thead>
<tr>
<th>Investigator Compliance Category</th>
<th>Mild and Typical Pertussis (95% CI)</th>
<th>Typical Pertussis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTaP</td>
<td>DTP</td>
</tr>
<tr>
<td>High</td>
<td>40 (3-65)</td>
<td>73 (48-86)</td>
</tr>
<tr>
<td>Low</td>
<td>75 (53-87)</td>
<td>85 (68-93)</td>
</tr>
</tbody>
</table>

* Cherry et al., *Pediatrics* 1998; 102: 909-912
Decay of Antibody Over Time
## Geometric Mean Values (EU/ml) Postdose 3, Predose 4, Postdose 4 and Predose 5 *

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>FHA</th>
<th>PRN</th>
<th>FIM 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postdose 3</td>
<td>90</td>
<td>74</td>
<td>36</td>
<td>268</td>
</tr>
<tr>
<td>Predose 4</td>
<td>11</td>
<td>13</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>Postdose 4</td>
<td>174</td>
<td>108</td>
<td>94</td>
<td>553</td>
</tr>
<tr>
<td>Predose 5</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>35</td>
</tr>
</tbody>
</table>

Pertussis cases in children and adolescents aged 0-18 years, by vaccine history -- California, 2010-2010*

*As of 1/6/2011
Other *Bordetella* sp are the Cause of Pertussis

“17% in California in 2010”
Genetic Changes in *B. pertussis*
Genetic Changes in *B. pertussis*-2010

- Vaccine pressure has resulted in changes in PT, PRN and FIM.
- Since DTP vaccines contain multiple antigens these genetic changes are unlikely to lead to vaccine failure.
- Since DTaP and Tdap vaccines contain fewer antigens it seems possible that genetic changes will lead to vaccine failure. Particularly with PT and PT/FHA vaccines.
Summary

• DTP vaccines generally have greater efficacy than DTaP and Tdap vaccines

• All vaccine efficacy has been inflated due to case definition and observer bias

• The main reason for vaccine failure is antibody decay, and perhaps incomplete antigen package, and incorrect antigen balance.
Approach to the Problem

• Recognize that *B. pertussis* is circulating in all age groups and therefore for herd immunity need to universally vaccinate all age groups at frequent intervals

• Develop new vaccines
  1. DTaP vaccines with multiple additional components and minimal PT
  2. “live vaccines”
  3. DTP vaccines with detoxified LPS
CDPH Approach 2010
Pertussis Mitigation

• Promote the use of Tdap - particularly in those who have contact with infants
  – Free vaccine through 12/31/2010 for birth hospitals with postpartum Tdap policies; encourage ED use of Tdap
  – Work with payers re: Tdap reimbursement
  – CDPH expanded Tdap recommendations

• Clinician education
  – CDPH Tdap recommendations
  – Pertussis signs and symptoms
  – Treatment recommendations for infants with severe pertussis
  – Accelerated DTaP schedule for infants

• Public education
  – Vaccination/cocooning
  – Pertussis signs and symptoms
  – Keep ill people away from infants
Immunize pre-teens, teens and adults with Tdap vaccine
- 7-9 year olds who are underimmunized
- those ≥10 years of age who have not yet received Tdap, especially
  - women of childbearing age, preferably before, or else during or immediately after pregnancy
  - others with close contact with young infants
  - includes persons >64 years of age

No minimum interval between Td and Tdap
Tdap for Healthcare Personnel

• Per the CalOSHA aerosol-transmissible disease standard, employees who may be exposed to aerosol-transmissible diseases must be offered Tdap if they haven’t already received it.

• Susceptible employees must also be offered measles, mumps, rubella, and varicella vaccines and all employees must be offered influenza vaccine each year.

• Employees should be offered Tdap unless they can provide written documentation of a prior dose.

• No minimum interval between the last dose of Td per CDPH recommendations.
The Circulation of *B. pertussis*

- It occurs in all ages
- Prevaccine era: Most cases in children 1-5 years old. However, infection in all ages
- 3 dose schedule: Most cases in 3-10 year olds
- 4 dose schedule: Most cases in 5-13 year olds
- 5 dose schedule: Most cases in adolescents
- 6 dose schedule: Most cases in adults
- 6 dose schedule plus cocooning: Prevents infant pertussis
What Can You do?

- Dx and Rx pertussis.
- Educate those who care for adults that pertussis is common in adults, usually misdiagnosed and it can be prevented by Tdap.
- Promote cocooning around infants.
- Fill in the gaps-7 to 9 year olds, DTaP or Tdap; >64 year olds, Tdap.
Pertussis in Adults


Last Paragraph

Pediatricians and others who care for children in the United States have accepted the public health responsibilities of universal immunization. As a result, adult rubella (the cause of congenital rubella) has almost been eliminated, and immunization of infants and children for hepatitis B is expected to eliminate this predominately adult disease. Ifacellular pertussis vaccines prove to be effective in adults, I hope that those who give primary care to adults will accept the public health challenge and effectively carry out universal immunization for this burdensome disease.

James D. Cherry, MD, MSc
University of California, Los Angeles, School of Medicine
Los Angeles, CA 90095
Conclusions

1) *B. pertussis* infections in adolescents and adults are common and endemic.
2) Immunity after infection or vaccination is not long lasting.
3) The outcome of an infection depends upon the time since vaccination or a previous infection.
4) Endemic adolescent and adult disease is responsible for the cyclic pattern in unvaccinated children.
5) *B. pertussis* circulation cannot be controlled by present immunization programs.
6) A universal program with adolescent and adult Tdap boosters would decrease the circulation of *B. pertussis* in these age groups and might lead to the elimination of the organism from the population.
7) Since this is unlikely to occur in the near future the best strategy at present is universal adolescent immunization and vigorous cocooning.

Conclusions

Our number one priority today regarding vaccine preventable diseases should be to find a way to universally vaccinate adults as well as children. We need to find a method to see that all adults get the immunizations they need including protection against *B. pertussis* infection.
Slowly he would cruise the neighborhood, waiting for that occasional careless child who confused him with another vendor.