Pertussis: Clinical Disease, Diagnosis, Treatment, Epidemiology and Prevention 2011

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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".

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A Bit of History

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 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**

Total Duration of Cough in 247 German Children with *B. pertussis* Infections

April 1991-February 1992

Total Days of Cough	No.	%	Cumulative %
1-7	11	4.5	4.4
8-14	28	11.3	15.8
15-21	24	9.7	25.5
22-28	54	21.9	47.4
>28	130	52.6	100.0

Source: Heininger et al. *Pediatr Infect Dis J* 1993; 12: 504-9

Young Infants

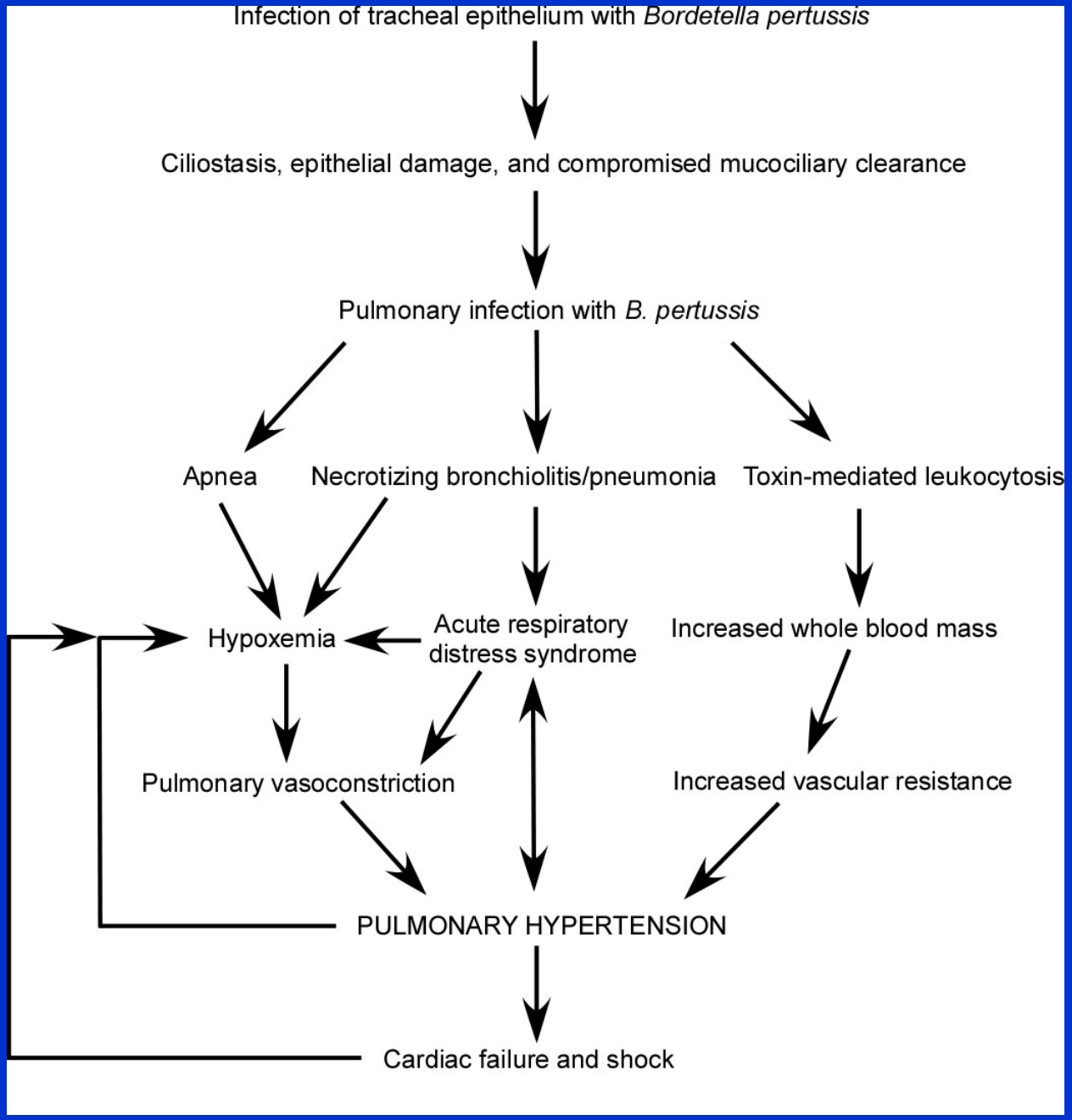
Pertussis in Young Infants

- 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

Pathology and Pathogenesis of Fatal *Bordetella pertussis* Infection in Infants*

Christopher D. Paddock, Gary N. Sanden, James D. Cherry,et al

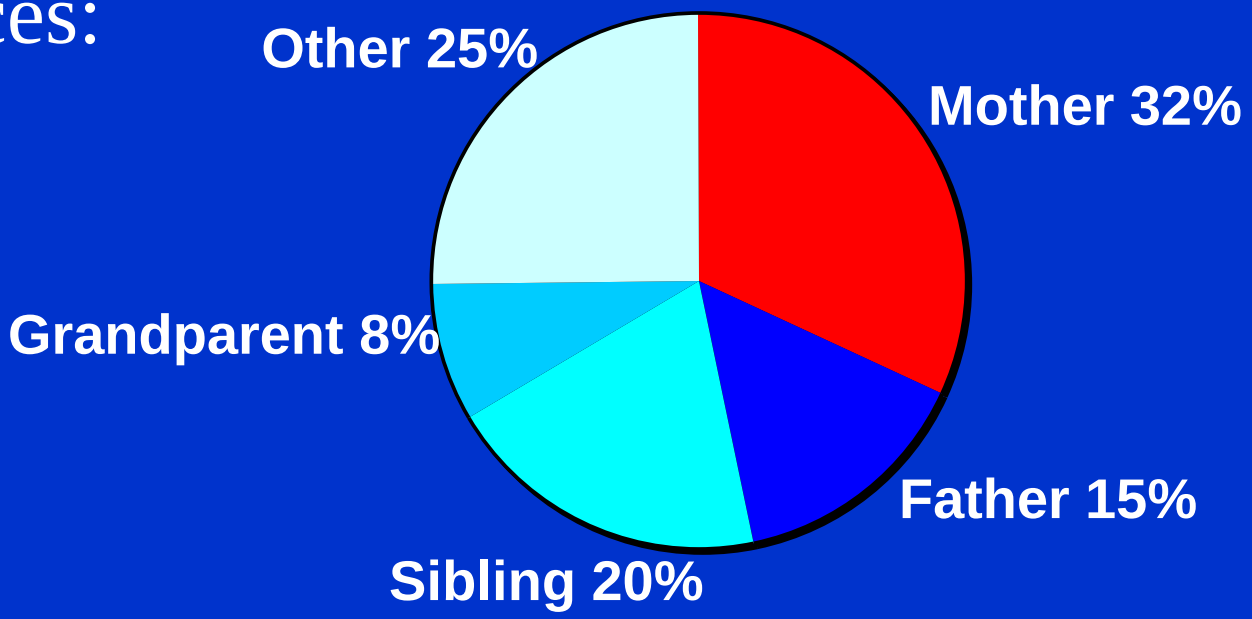
*CID 2008;47:328-338



Source of Pertussis in Infants

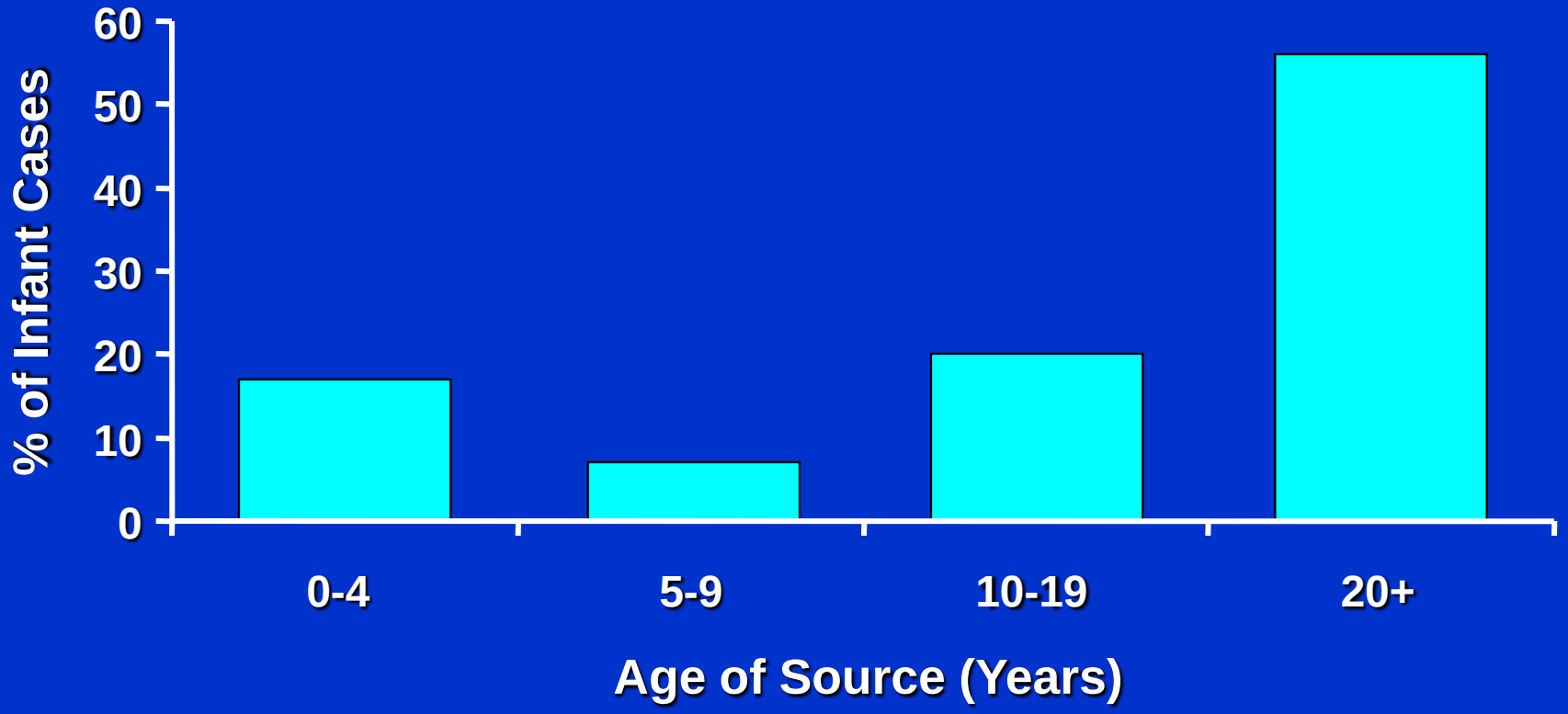
CDC Study – Infant Pertussis: Who Was the Source?

- 774 infant cases from 4 states
- 264 cases had source identified
- Sources:



Bisgard, K. *PIDJ.* 2004;23:985-9.

Age of Pertussis Source* for Infants



*219 source-persons with known age

Bisgard, K. *PIDJ.* 2004;23:985-9.

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%

Transmission of Pertussis to Young Infants

Wendelboe et al PIDJ 2007;26:293-299

Age of 49 source patients

Age in Years	Percent
< 13	14%
13-18	16%
19-39	61%
40-64	8%

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%**

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Adolescents and Adults

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.

*Luttinger P. AJDC. 1916;12:290.

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.
4. Blood count not characteristic.

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.

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 664 ADOLESCENTS AND ADULTS*

Characteristic	Percent
Paroxysms	99
Posttussive apnea	87
Posttussive vomiting	65
Whoop	69
Sweating episode	32

* De Serres et al. JID 2000; 187: 174-9

COMPLICATIONS OF PERTUSSIS IN 664 ADOLESCENTS AND ADULTS*

Characteristic	Percent
Sinusitis	13
Otitis media	4
Urinary incontinence	4
Pneumonia	4
Weight loss	3
Rib Fracture	2
Fainting	2

*De Serres et al. JID 2000; 187: 174-9

An Epidemic of Pertussis Among Elderly People in a Religious Institution in the Netherlands

Eur J Clin Microbiol Infect Dis 1999; 18:242-247

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)

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

CLINICAL CHARACTERISTICS OF COUGH IN STUDENTS WITH COUGH FOR ≥ 6 DAYS (Mink et al.CID.1992;14:464-471)

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

* p = 0.92

† p – 0.02

‡ Definition: required interruption of all activities during episode

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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

Culture

The main reasons for failure to isolate *B. pertussis* from correctly collected and transported specimens are:

1). Bacterial and fungal contamination

2). Lack of fresh media

3). Specimen collected too late in illness

PCR on NP Secretions

1). More sensitive than culture

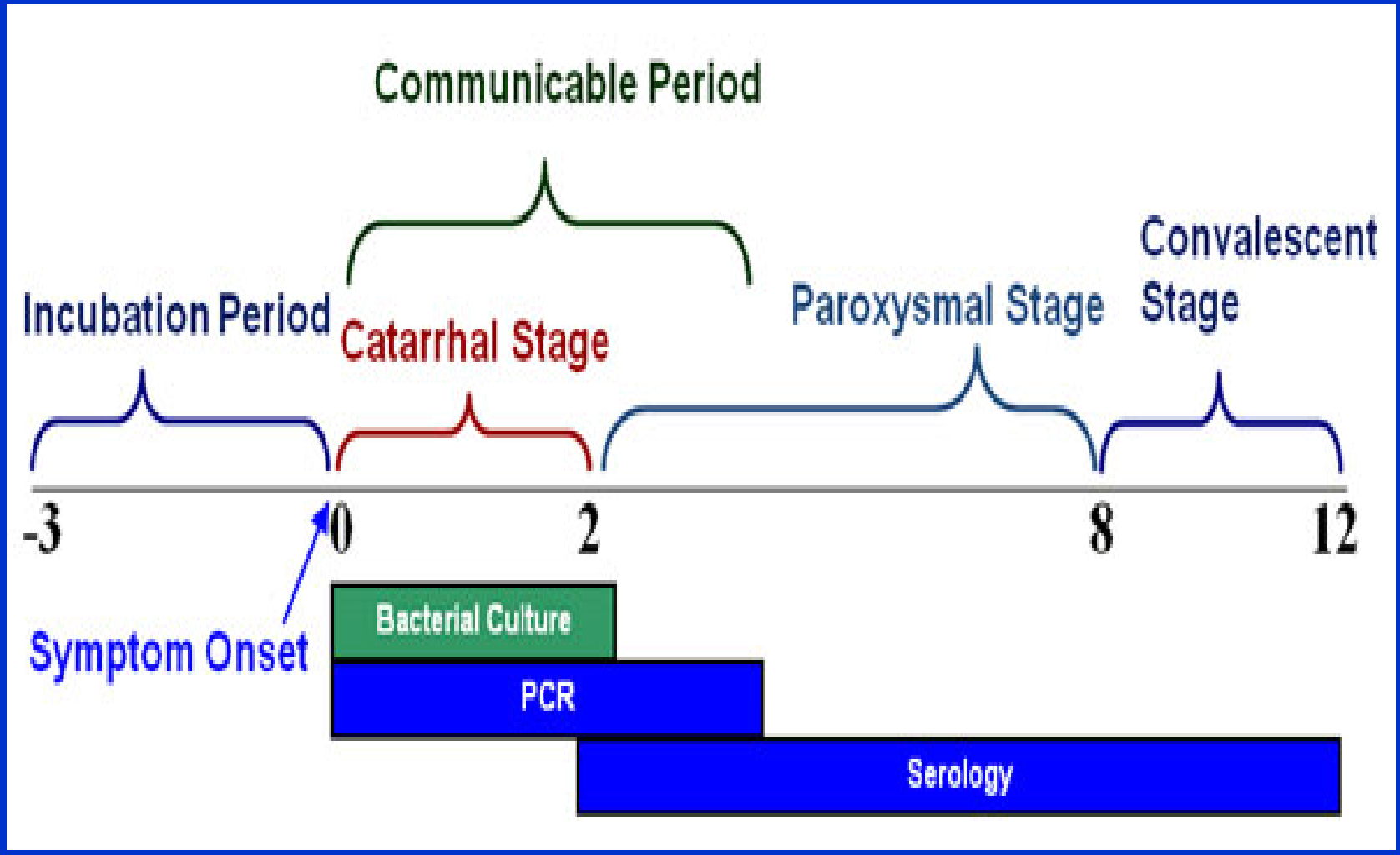
2). With use of multiple primers can identify and separate other *Bordetella* sp

3). False positives are a problem

4). Delay in specimen collection is main reason for negative PCR

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

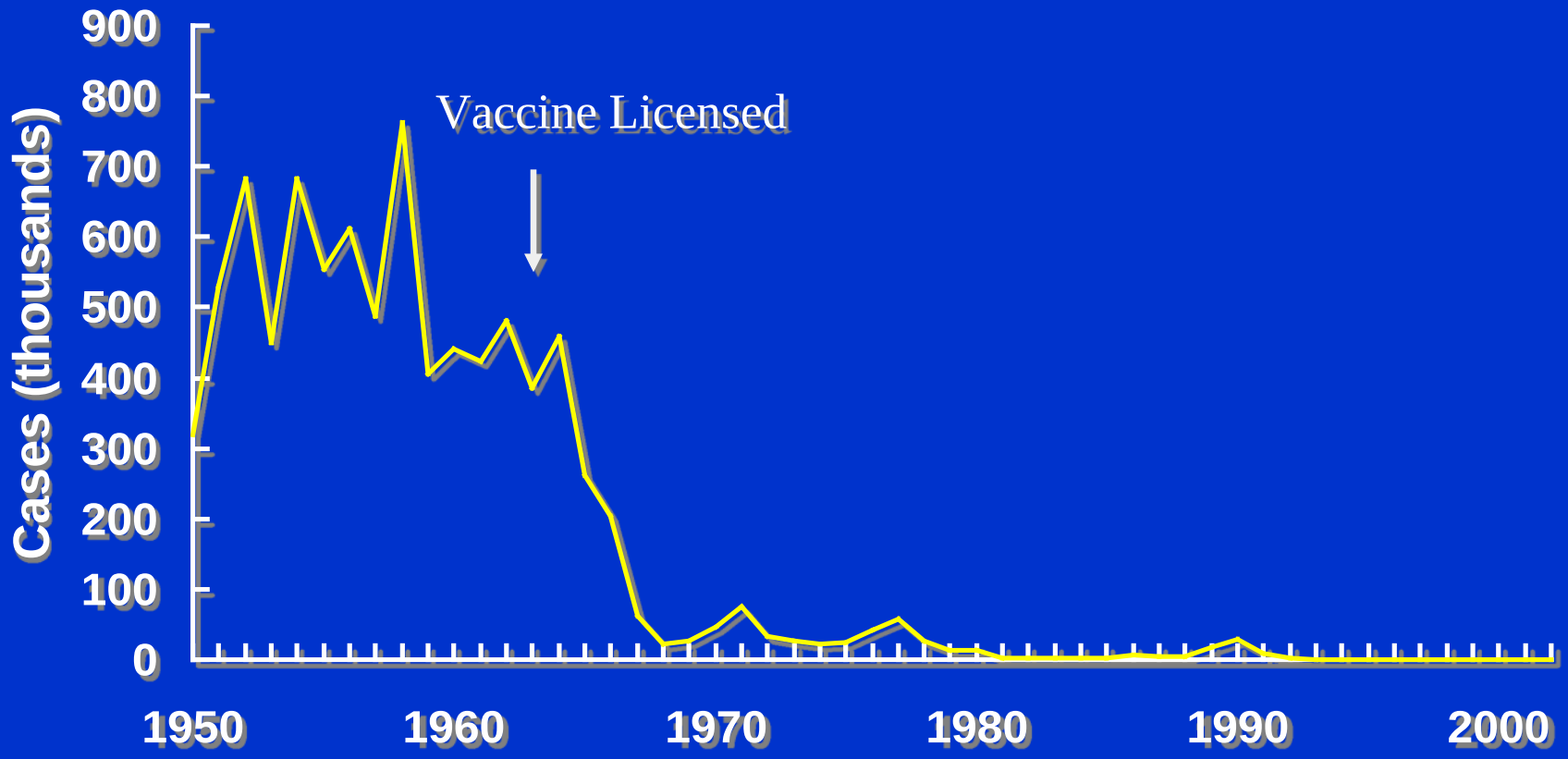
Possible Reasons for the Resurgence of Reported Pertussis

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

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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

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

Rate of *B. pertussis* Infection in Adolescents and Adults

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

* 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

Author	Location	Year	Rate
Strebel et al.	Minneapolis/St Paul	95-96	0.5%
Ward et al.	Eight Centers, USA	97-99	0.37%
Hodder et al.	Cleveland	89-92	1.5%

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 that symptomatic infections
- Today symptomatic adolescents and adults are the major source of infection in unvaccinated children

Pertussis Vaccines

Pertussis Vaccines

~1945 DTwP vaccines

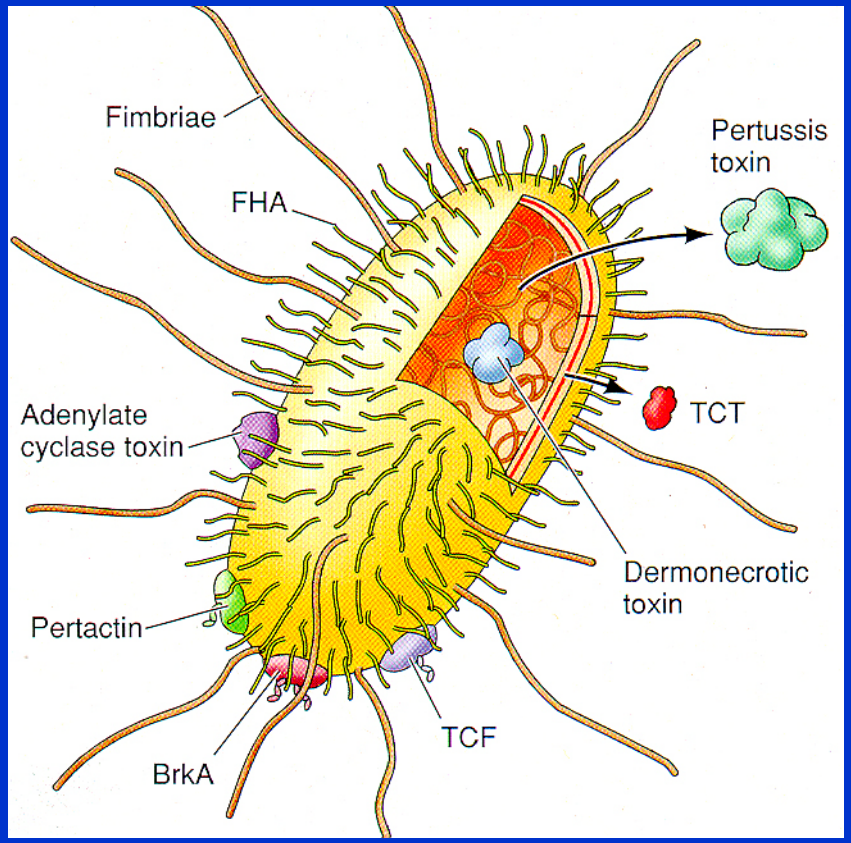
~1995 DTaP vaccines

- 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
- 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?

Population	1000 90% immunized
VE= 70%	
Attack rate in nonvaccinees 70%	

Vaccinees	900
Number susceptible	270
Number of cases	189

Nonvaccinees	100
Number susceptible	100
Number of cases	70

VE = $\frac{70-21}{70}$ = .70 x 100 = 70%

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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

Vaccine	Components	Percent Efficacy (95% CI)
Amvax	PT	31(-4-59)
JNIH-7	PT	-6(-49-24)
JNIH-6	PT, FHA	43(15-61)
SKB	PT, FHA	42(33-51)
SKB	PT, FHA, PRN	71(60-78)
Chiron-Biocine	PT, FHA, PRN	71(61-79)
Lederle/Takeda	PT, FHA, PRN, FIM-2	62(38-77)
Connaught (Canada)	PT, FHA, PRN FIM-2,3	78(73-82)
Wyeth- Lederle	Whole Cell	78(62-88)
Connaught (USA)	Whole Cell	41(30-51) to 23(1-40)

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**

Investigator Compliance Category	Mild and Typical Pertussis (95% CI)		Typical Pertussis (95% CI)	
	DTaP	DTP	DTaP	DTP
High	40 (3-65)	73 (48-86)	69 (41-83)	90 (75-96)
Low	75 (53-87)	85 (68-93)	84 (64-93)	93 (80-98)

* 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 *

	PT	FHA	PRN	FIM 2/3
Postdose 3	90	74	36	268
Predose 4	11	13	6	36
Postdose 4	174	108	94	553
Predose 5	10	8	9	35

* Guerra. Pediatrics. 2009; 123:301-312

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. pertusiss* 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

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.

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.

Cherry JD. *Pediatrics* 2005;115:1422-1427.

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.