Pertussis in California –
The New Normal

Prevention, Diagnosis and Reporting Recommendations for Health Care Providers

July 23, 2015
Overview of Today’s Webinar

• Background and epidemiology of pertussis
• Pertussis: clinical disease, diagnosis, treatment and prevention
• Common pertussis issues encountered by providers
• Conclusions
• Question and Answer
James D. Cherry, MD, MSc
Distinguished Research Professor of Pediatrics
David Geffen School of Medicine at UCLA
Member of Division of Infectious Diseases
Mattel Children’s Hospital, UCLA

Kathleen Winter, MPH
Epidemiologist
Immunization Branch
California Department of Public Health
Commercial Support

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Epidemiology of pertussis in CA

Kathleen Winter, MPH
California Department of Public Health
Pertussis (whooping cough)

- Caused by *Bordetella pertussis*
- “The 100 day cough”: three stage illness (catarrhal, paroxysmal, and convalescent) that lasts typically 4-12 weeks
- Classic presentation: no fever, coryza, paroxysmal cough, posttussive vomiting, posttussive whoop
- *B. pertussis* infections and illness in adolescents and adults are very common but often not diagnosed (both in the pre-vaccine and present eras)
- Most severe disease and death occurs in infants <4 mos of age
- Highly infectious; $R_0$ estimated to be 15-17
- Disease patterns are cyclical and peak every 3-5 years
- Cyclic peaks have been increasing since the 1990s causing major epidemics in recent years
Pertussis vaccines

• Whole-cell pertussis vaccine (DTP)
  – Widely used from 1940-1990s in children <7 years
  – Associated with adverse reactions (real and perceived)
• Acellular (subunit) pertussis vaccines (DTaP & Tdap)
  – Less reactogenic, but less effective and faster waning of immunity than whole cell vaccines
  – DTaP recommended in 1992 for the 4th/5th doses of childhood series and for entire series in 1997
  – Tdap licensed in 2005 for adolescents and adults
  – Recommended schedule:
    • Pediatric: 2m, 4m, 6m, 18m, 4-6y, 11-12y
    • Pregnant women: 27-36 weeks gestation during each pregnancy
    • Adults: once during adulthood
Number and Incidence of reported pertussis cases by year of onset -- California, 1945-2015*

DTP widely used

DTaP widely used

PCR available

*Includes cases reported to CDPH as of 7/7/2015
Current situation in CA - as of 7/7/2015

- 11,203 reported cases with onset in 2014; state rate 29.3 cases/100,000
  - 456 hospitalized; 119 (26%) required intensive care
    - Most (61%) hospitalized were <4 months of age
    - 3 deaths in infants <2 months of age
- 3,150 reported cases with onset in 2015
  - Including 115 hospitalized and one infant death
Why is the incidence of pertussis increasing?

- Increased public health awareness and reporting

- Use of acellular vaccines (DTaP and Tdap), which replaced whole-cell vaccine (DTP) in the 1990s
  - Faster waning immunity than was expected

- PCR more sensitive and widely available

- Possibly due to genetic changes in *B. pertussis*
  - Recent increase in identification of strains in the USA and other countries which no longer express pertactin antigen

Incidence of pediatric pertussis cases by age -- California, 2014*

*Reported to CDPH as of 5/20/2015
Incidence of hospitalized pertussis cases by age -- California, 2014*

*Reported to CDPH as of 5/20/2015
Pertussis among infants in California

• Since 2009, more than 2,400 pertussis cases in infants <4 months of age have been reported in California
  – 1,378 (56%) were hospitalized
    • 38% of those with detailed hospitalization information were admitted to the ICU; 28% of these required intubation
  – 20 (1%) died
California Pertussis Deaths

- All California pertussis deaths since 1998 have been in infants ≤3 months of age
- 83% Hispanic
- Of those with known status, all had pneumonia and pulmonary hypertension
- The median WBC count of fatal cases in 1998-2014 was 77,000 (range 15,000-148,000)
- Only 1 had received any doses of DTaP vaccine; this child was premature with bronchopulmonary dysplasia
Risk factors for death among infants

- In small study of infants admitted to an ICU, more severe cases had higher WBC counts, higher heart rates and respiratory rates and more likely to develop pneumonia\(^1\)

- In a larger case-control study comparing fatal and non-fatal hospitalized cases\(^2\)
  - Younger infants and those with a low birth weight have higher odds of death; LBW <2800g a predictor of death
  - Elevated WBC, particularly >46K was important predictor of death
  - All fatal cases required intubation
  - DTaP protective against high WBC counts and death

2. Winter et al. CID. 2015
Pertussis cases, hospitalizations and deaths in infants, by age in weeks at time of disease onset -- California, 2009-2015*

*reported to CDPH as of 5/20/2015

Gap in protection
Maternal Tdap in pregnancy

- ACIP, AAFP and ACOG recommend that all pregnant women receive Tdap vaccine during each pregnancy between 27-36 weeks gestation, regardless of her Tdap vaccination history
  - Antibodies to pertussis are actively transported across the placenta to the baby¹,²
- UK Tdap program for pregnant women estimates 90% reduction in disease in infants <2 months of age³
- However, uptake of Tdap among pregnant women in CA is improving but still low and many barriers are reported
  - CDPH convenience survey of L&D hospitals: 44% in 2014; 22% in 2013
  - N. CA Kaiser: >80% in 2015; 15-30% in 2010-2012

Accelerating first dose of DTaP from 8 weeks to 6 weeks

- AAP recommends that when pertussis is present in a community, DTaP can be started as early as 6 weeks\(^1\)
- Among infants in the U.S. aged \(>42\) days, one dose of DTaP protected against death, hospitalization and pneumonia (aORs 0.28, 0.69 and 0.80, respectively)\(^2\)
- Acceleration of DTaP to 6 weeks estimated to reduce average notifications, hospitalizations, and hospital bed-days by 8%, 9%, and 2%, respectively in Australia\(^3\)
- Similarly in the U.S., acceleration from 2 months to 6 weeks was predicted to prevent 1236 cases of pertussis, 898 hospitalizations, and 7 deaths per year\(^4\)

Pertussis in older children and adolescents

• In 2014, the largest burden of disease occurred in adolescents/teenagers 10-16 years of age; many middle and high school outbreaks reported statewide
  – Nearly all cases had been previously immunized with pertussis vaccines
  – Most cases did not have severe disease and very few required hospitalization

• A recent study in San Diego of pertussis cases 13-17 years of age found that students (Varan et al. 2015, manuscript in preparation)
  – Missed an average of 5.4 days of school and 15.4 days of sports activities during their illness.
  – Nearly all (96%) had received their Tdap booster; median time from vaccination to illness was 3.3 years
Vaccine effectiveness and waning immunity for DTaP and Tdap

- Recent studies indicate that immunity from DTaP vaccine is high immediately following receipt but quickly wanes within a few years\(^1-^3\).
- Tdap effectiveness similarly shows moderate short-term protection (53-75%) and rapid waning of immunity 2-4 years after receipt\(^4-^6\).
- Three studies also suggest that immunity wanes faster in children and adolescents born in 1998 and later who have only received acellular pertussis vaccines (DTaP and Tdap)\(^7-^9\) (i.e., no doses of whole-cell vaccine).

8. Sheridan et al. JAMA. 2012
What about additional doses of Tdap?

- Safe and provide short-term immunity
- Only currently recommended for pregnant women
  - Not considered cost-effective on a population level due to short duration of immunity
  - Limited/no data on effectiveness of Tdap for “cocooning” – may be beneficial on an individual basis, but no longer seen as a public health priority
- Highest burden of disease is in adolescents and teens; very few have known complications
  - <1% hospitalized among 10-17 age group
- Repeated doses of Tdap doses can be given and would likely provide short-term protection
  - May not be covered by insurance
Pertussis: Clinical Disease, Diagnosis, Treatment and Prevention

James D. Cherry, MD, MSc
Pertussis Fact #1

The rate of reported pertussis today is ~20 fold less than in the pre-vaccine era. This fact is often overlooked today when experts and the media discuss the resurgence of pertussis.
Pertussis Fact #2

Illness in DTaP vaccine failures is less severe than illness in similar aged unvaccinated children
Pertussis in Adolescents and Adults

• Many believe that adolescent and adult pertussis is a relatively new phenomenon
  – This is incorrect
• Pertussis was common in adolescents and adults in the pre-vaccine era
• Vaccine use may have changed the clinical expression rate
Clinical Illness
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
Pertussis in Young Infants
Clinical Presentation in 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
  - Pneumonia
  - Pulmonary hypertension
  - Adenovirus or RSV coinfection can confuse the picture
2010 Pertussis Death

• Pertussis Case: April 2010
  – Previously healthy, Hispanic female
  – Lived with mom, dad, sister – no daycare
  – Father had cough illness for several weeks
  – Cough onset at age 5 weeks, one week prior to admission
  – Seen in ER 4 days prior to admission with cough, post-tussive vomiting and cyanosis; pertussis not considered - discharged home
  – Seen in ER 4 days later and admitted
  – Hospitalized in children’s hospital for one week before transfer to PICU and intubation
  – WBC 80,000; pulmonary HTN - single volume exchange transfusion done
  – Transferred to second children’s hospital PICU for ECMO, but not done due to multi-organ failure
Pertussis in Adolescents and Adults
Clinical Pertussis in Adolescents and Adults

• It is an afebrile illness unless there is a concomitant or secondary infection
• The severity of illness is variable but virtually all will have a paroxysmal cough
• The cough is non-productive
• The onset is insidious; medical care is usually not sought until the 3\textsuperscript{rd} or 4\textsuperscript{th} week
• The duration is 2 weeks to 4 months; there is memory for the cough - it may reoccur with a URI
### 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
Clinical Diagnoses Assigned by the Primary Care Providers and Antibiotic Therapy in Students with Cough \(\geq 6\) Days (Mink et al. CID. 1992;14:464-471)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Subjects with (B.) \textit{pertussis} infection ((n = 31))</th>
<th>Subjects without (B.) \textit{pertussis} 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 B. pertussis Infection</th>
<th>96 Student without B. pertussis 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
Diagnosis
Clues in the Clinical Dx of Pertussis in Young Infants

- They have a cough illness without fever
- They don’t have wheezing unless there is a concomitant viral infection
- They have a rapidly rising WBC count with a lymphocytosis. Therefore do a WBC count on all infants with a new afebrile cough illness
- Most often there is an adult family member with an afebrile cough illness
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
Laboratory Diagnosis
Collection of Specimens

- NP wire with dacron swab
- NP aspirate with plastic catheter and specimen trap.
Culture of NP Secretions

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) Delay in specimen collection is main reason for negative PCR
Serologic Dx of Pertussis
ELISA

Diagnosis is made on the basis of high single serum IgG and/or IgA titer to PT. It is a practical and reasonably sensitive and specific test.
When Pertussis Tests are Likely to be Positive in Infected People
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
† Data suggest that a 7 day treatment course is effective
Treatment in Young Infants

*** Neonates should be treated with Azithromycin and not Erythromycin because of the risk of pyloric stenosis

*** Treat with Azithromycin immediately; do not wait for PCR/culture
Treatment in Young Infants

• Nearly all infants < 4 months of age should be admitted to a hospital with a PICU and seen by a PID MD

• Risk factors for death in infants < 4 months of age are: WBC count > 46,000; rapid pulse rate; rapid resp. rate; pneumonia
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
Who Should Receive Prophylaxis?

- Restrict to high risk situations (young infants, NICUs)
- Focus on high risk persons (e.g., pregnant women, caregivers of young infants) in low risk settings such as classrooms, schools, and workplaces
- It is better to do post-exposure surveillance and Rx early onset cases than to provide prophylaxis to large population groups
Summary

- The hallmark of pertussis is paroxysmal cough and the cause of this unique cough is not known.
- Clinical manifestations vary by age.
- Pertussis is common and occurs in all age groups (this is not new).
- Infants get pertussis from adolescents and adults.
- Deaths in young infants are caused by PT.
- Method of laboratory Dx depends upon stage of illness.
- Antimicrobial Rx can shorten the illness course and prophylaxis is highly effective.
Common Pertussis Issues Encountered by Medical Providers
Diagnosing Pertussis: Does prior vaccination rule out pertussis?

Without indication of a prior pertussis exposure to the patient, consider pertussis as a differential diagnosis in patients with...

- Afebrile paroxysmal cough illness (with or without whoop or post-tussive vomiting)
- Apnea (for young infants)

...regardless of vaccination status and duration since most recent dose.
Reporting Pertussis: Do providers need to report if the lab is reporting?

YES! Medical providers are legally required to report patients suspected of having pertussis to the Los Angeles County Department of Public Health within 1 working day of identification.¹

*Do not wait for lab confirmation*

*Do not assume that the lab will send the report to the Health Department*

¹. California Code of Regulations. Title 17, Sections 2500 and 2505
Pertussis Treatment: Clearing patients to return to activities

Prescribe azithromycin, erythromycin, trimethoprim-sulfamethoxazole (TMP-SMX), or clarithromycin for your symptomatic patients and their contacts

Inform symptomatic patients that they must complete 5 days (of an appropriate antibiotic therapy) before returning to school or work
Asymptomatic Pertussis Contacts: what should you do if they present at your clinic?

1. Do NOT perform a test for pertussis in an asymptomatic patient/contact who was exposed to a person with pertussis

2. Household/day care contacts: If the asymptomatic patient lives in the household or attends daycare with a person with pertussis, provide antibiotic prophylaxis regardless of vaccination status.
Asymptomatic Pertussis Contacts: what should you do if they present at your clinic?

3. **School contacts:** If the asymptomatic patient was exposed at school to a person with pertussis, only provide antibiotic prophylaxis to high risk contacts (i.e., immunocompromised, pregnant, unvaccinated/under-vaccinated).

4. **All unvaccinated and under-vaccinated contacts to a person with pertussis should be immunized right away.**
Summary: Checklist when a patient presents to you with possible pertussis:

1. **Consider pertussis** in your differential diagnosis if a paroxysmal cough of any duration is mentioned or observed (regardless of the patient’s vaccination status)

2. **Test for pertussis**: nasopharyngeal swab for *Bordetella pertussis* PCR, ideally within 3 weeks of cough onset *(preferred)*

3. **Treat for pertussis**: prescribe an appropriate antibiotic
Summary: Checklist when a patient presents to you with possible pertussis:

4. Return to work/school: the patient can return after completing the 5th day of an appropriate antibiotic.

5. Provide antibiotic prophylaxis: if possible, provide antibiotic prophylaxis to all household contacts when a pertussis diagnosis is confirmed.

6. Consult with and/or report the suspect pertussis case to the Los Angeles County Department of Public Health (report within 1 working day).
Conclusions

• Increased incidence is the new normal, especially among acellular vaccine recipients
• In spite of less efficacious vaccines, incidence is still lower than in the pre-vaccine era
• Illness in vaccine failures is less severe
• Public health focus has changed from reducing overall morbidity to targeting those at highest risk of severe disease and death
Conclusions

• Key strategies to reducing severe disease are prompt infant immunization with the primary series and prenatal vaccination with Tdap during the 3\textsuperscript{rd} trimester.

• Lowering the start age of immunization to 6 weeks and the immunization of all pregnant women (each pregnancy) is likely to prevent virtually all infant deaths due to pertussis.
Pertussis Resources

✓ Reporting pertussis cases to the Los Angeles County Department of Public Health:

✓ Pertussis Laboratory Testing Guidelines:

✓ Recommended pertussis treatment and post-exposure prophylaxis information:
Pertussis Resources

✓ General Pertussis and Pertussis Vaccination Information
  www.publichealth.lacounty.gov/ip/DiseaseSpecific/Pertussis.htm
  www.cdc.gov/vaccines/vpd-vac/pertussis/default.htm
  www.cdph.ca.gov/healthinfo/discond/pages/pertussis.aspx

✓ Downloadable Educational Materials:
  www.eziz.org/resources/
Thank you for attending the pertussis webinar

To view a recording of this webinar, download handouts or request CME/certificates of attendance visit

publichealth.lacounty.gov/ip/PertussisWebinar.htm
AAFP  American Academy of Family Physicians
AAP   American Academy of Pediatrics
ACIP  Advisory Committee on Immunization Practices
ACOG American Congress of Obstetricians and Gynecologists
aOR  Adjusted Odds Ratio
CI    Confidence Interval
CRP  C-Reactive Protein
DTaP  Diphtheria, Tetanus, & acellular Pertussis
DTP  Diphtheria, Tetanus, Pertussis
DTwP Diphtheria, Tetanus, & whole-cell Pertussis
Dx   Diagnosis
ECMO Extracorporeal Membrane Oxygenation
ELISA Enzyme-Linked Immunosorbent Assay
ER   Emergency Room
ESR  Erythrocyte Sedimentation Rate
HTN  Hypertension
ICU  Intensive Care Unit
IgA  Immunoglobulin A
IgG  Immunoglobulin G
Acronym & Abbreviation Guide (L-Z)

**LBW**  Low Birth Weight

**LPS**  Lipopolysaccharide

**NIAID**  National Institute of Allergy & Infectious Diseases

**NICU**  Neonatal Intensive Care Unit

**NIH**  National Institutes of Health

**NP**  Nasopharyngeal

**OR**  Odds Ratio

**PCR**  Polymerase Chain Reaction

**PICU**  Pediatric Intensive Care Unit

**PID**  Pediatric Infectious Diseases

**PT**  Pertussis Toxin

**R_0**  Number of persons infected by single disease source

**RSV**  Respiratory Syncytial Virus

**Rx**  Prescription

**Tdap**  Tetanus, diphtheria, & acellular pertussis

**URI**  Upper Respiratory Infection

**WBC**  White Blood Cell

**WHO**  World Health Organization