2010 California Pertussis Epidemic and Risk Factors for Death

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California Overview

- 2010 population: 37,253,956
- Persons under 5/18 years (2009): 7.5/25.5%
- Language other than English spoken at home: 42.2%
- Births 2009: 526,774
  - 51% Hispanic
California Overview

- 2010 race/ethnicity:
  - White/non-Hispanic 40.1%
  - Hispanic 37.6%
  - Asian/Pacific Islander 13.4%
  - Black 6.2%
  - American Indian 1.0%
Early Warning of the 2010 Epidemic

In early April 2010, the California Department of Public Health (CDPH) was notified by the Children’s Hospital of Central California of an increase in pertussis cases similar to that seen in early 2005, the last peak year for pertussis.
Pertussis Mitigation

- After the notification, CDPH queried local health departments and hospitals about pertussis cases - many reported increases in cases; CDC alerted

- Mitigation efforts began immediately; the primary goal was to prevent infant deaths

- Unlike prior epidemic years, Tdap was available as a control measure, however, barriers to use were identified so CDPH made additional Tdap recommendations

- Intensive efforts to educate providers and public
  - Early diagnosis and treatment
  - Treatment recommendations for infants with severe disease
  - Immunization, especially cocooning
Pertussis Mitigation – Public Education

- Vaccination/cocooning
- Pertussis signs and symptoms
- Infants at greatest risk - keep ill people away from infants

父母：

Is it just a cough?

Or is it whooping cough?
Pertussis Mitigation – Provider Education

• Provider education
  ▪ Clinical recognition – pertussis signs and symptoms
  ▪ Specimen collection and laboratory testing
  ▪ Treatment recommendations, including for severely ill infants
Pertussis Cases by Year of Onset
California, 1947-2011*

Previous peak in 1947
number of cases: 9,394

Previous peak in 1958
incidence: 26.0/100,000

DTP widely used

DTaP licensed

PCR available

Tdap licensed

*As of 8/10/2011
2010-2011 California Pertussis Summary

- **2010**: 9,158 confirmed, probable or suspect cases of pertussis were reported for 2010; **23.4 cases/100,000**
  - This was the most reported cases in 63 years when 9,394 cases were reported in 1947, a peak year, and the highest incidence since 1958 when there were 26 cases/100,000 population

- **2011** (as of 15 August): 2,182 cases; no deaths
  - The number of cases in the early months of 2011 was higher than the number of reported cases during the peak months of 2005
California Pertussis Hospitalizations, 2010-2011*

- 943 (9%) cases were known to have been hospitalized
  - Most (655/69%) hospitalized cases were infants <6 months of age; 466 (49%) were <3 months of age
  - 62% of infants <3 months of age were hospitalized

- 492 (79%) of the hospitalized infants <6 months of age with known ethnicity were Hispanic
  - 51% of the annual California birth cohort of ~530,000 is Hispanic

- Some infants had co-infections, e.g., RSV

Includes cases reported to CDPH through 8/15/2011
Pertussis Cases and Hospitalizations Among Infants <6 Months of Age, by Month of Onset
California, 2010-2011*

*Includes cases reported to CDPH by 8/15/2011
Pertussis Rates by Age and Race/Ethnicity
California, 2010

- White
- Hispanic
- API
- Black
- All race/ethnicities

Overall rate per 100,000
Rate by race/ethnicity per 100,000

Age group:
- <6 mos
- 6 mos-6 years
- 7-9 years
- 10-18 years
- 19-64 years
- 65+ years

Graph showing pertussis rates by age and race/ethnicity.
Why are Hispanic infants over-represented among infant cases?

- Increased incidence in Hispanic infants <6 months has been noted in other U.S. states as well.
- Higher mortality rates have been estimated in the U.S. for Hispanic vs. non-Hispanic infants since the 1990s.
- The reason is unclear, but Hispanics have larger average household sizes than other racial/ethnic groups and may also have cultural practices that increase the number of people in contact with infants, i.e., more contacts = more potential for exposure to people with pertussis.
- In 2010, the over-representation of California Hispanic infants among cases disappeared by age two years.

California Pertussis Deaths 1998-2010

- All 52 reported California pertussis deaths since 1998 have been in infants ≤3 months of age
- 80% Hispanic
- Of those with known status, all had pneumonia and pulmonary hypertension
- Pertussis toxin elicits a dose-dependent leukocytosis
  - Mean WBC of fatal cases in 1998-2009 was 75,000 (range 15,000-148,000)
  - Lymphocyte count also elevated - absolute lymphocyte count more important than percentage
- Increases in leukocyte mass can diminish blood flow by increasing vascular resistance; some experts recommend exchange transfusion to lower the WBC
Exchange Transfusion for Pertussis: Dr. Jim Cherry’s Thoughts

- In addition to lowering WBC, exchange transfusion may also be helpful because it reduces circulating pertussis toxin, which affects G proteins.

- Watch slope of WBC carefully, if ≥ 20,000 assess infant’s status for pneumonia and pulse rate ≥ 180:
  - If infant looks good and no pneumonia or tachycardia - check WBC in 24 hours
  - If infant has pneumonia or tachycardia - check WBC in six hours
  - If WBC is not leveling off at ~30,000, be prepared to do the exchange transfusion.

- Do exchange transfusion sooner rather than later and be more aggressive the younger the infant is.
Pertussis Cases and Hospitalizations in Infants <4 Months of Age -- California, 2004-2010

Cases

Year

2004
2005
2006
2007
2008
2009
2010

Outpatient cases <4 months
Hospitalized cases <4 months
Hospitalization rate
Deaths

Hospitalization rate
2010 California Pertussis Deaths

- 10 deaths; 9 Hispanic infants, 1 White (in 1950, 30 deaths among 6,613 reported cases); 50% female; case fatality rate among infant cases <3 months of age = 1.3%
- Nine were infants <2 months of age at time of disease onset who had not received any doses of pertussis-containing vaccine
- One death occurred in a former premature infant who received the first dose of DTaP at 2 months of age, 15 days prior to disease onset, and had 3 older siblings with cough illness
- Many of the fatal cases had multiple contacts with healthcare providers before pertussis was diagnosed, several had family members with cough illness
Fatal Pertussis Risk Factor Study

• Compare fatal infant pertussis cases identified in 1998-2010 with four nonfatal hospitalized cases <4 months of age from the same year and county; identify modifiable (i.e., treatment) and non-modifiable risk factors

• Potential risk factors evaluated include:
  ▪ Clinical: WBC/lymphocytes, pulse, CXR, pulmonary hypertension
  ▪ Treatment: timing and type of antibiotic therapy, PICU, intubation/ventilation, ECMO, exchange transfusion
  ▪ Possible health disparity markers: time from symptom onset to first presentation for care, time from first presentation for care until diagnosis/treatment/admit, number of clinician visits before diagnosis/admit, language spoken at home, race/ethnicity
  ▪ Other: breastfeeding, maternal age/smoking/education, gestational age/birthweight, household size, underlying conditions, DTaP
Very Preliminary Results

- 18 deaths, 48 non-deaths; final study will include 52 deaths and ~200 non-deaths
- Fatal cases were characterized by markers of severe disease:
  - More likely to receive ECMO, exchange transfusion, intubation, or be admitted to the PICU
  - More likely to be diagnosed with pneumonia
  - More likely to have a higher pulse rate and higher WBC count (lower lymphocyte %)
- Fatal cases less likely to be vaccinated but were also younger than non-deaths at onset of earliest noted pertussis symptom
- Fatal cases less likely to have received macrolide antibiotics
- No significant differences between fatal and nonfatal cases in:
  - Time from earliest noted symptom onset to hospital admission
  - Current breastfeeding
  - Sex
Are all pertussis deaths identified?

• Probably not...
  ▪ Studies have demonstrated that not all infant deaths due to pertussis are recognized as such; infant postmortem exams in the U.S. do not routinely include pertussis testing
  ▪ Many infant pertussis deaths do not meet the U.S. case definition for pertussis (cough ≥ 2 weeks) and may not be counted because they died < 2 weeks after cough onset; all laboratory-confirmed deaths in California have been counted since 2005
  ▪ CDPH is currently attempting to identify possibly unrecognized pertussis deaths since 2005 and test any lung, trachea, or bronchi tissue for pertussis by immunohistochemistry (IHC) and PCR
Postmortem Diagnosis of Pertussis

Immunohistochemistry (IHC)

Tracheal epithelium of an infant with fatal pertussis
Death Certificate Data for Reported Fatal Pertussis Cases -- California, 1998-2008

- Primary cause of death, 1998-2008 (n=39)
  - 23/39 (59%) – Whooping cough
  - 7/39 (18%) – Pneumonia (unspecified, congenital, and RSV)
  - 2/39 – Primary pulmonary hypertension
  - 2/39 – Other specified infections specific to the perinatal period
  - 5/39 – Acute myocardial infarction, other viral infections, streptococcal infection, congenital malformation of the heart, and respiratory distress syndrome of newborns

- Primary + contributing cause of death, 1998-2004 (n=23)
  - 19/23 (83%) – Whooping cough somewhere on death certificate
  - 3 of the 4 deaths not noted as whooping cough were in 1998
  - Have things improved?
Why has there been a U.S. pertussis resurgence since the 1990s?

- Acellular vaccines, which were recommended in the U.S. in 1992 for the 4th/5th doses and the entire series in 1996 are less reactogenic, but less effective than whole cell vaccines.
- General availability of more sensitive laboratory tests (PCR).
- More rapid waning of vaccine-induced immunity from acellular vaccines?
- Genetic changes in *B. pertussis*?
Proportion of Pertussis Cases Diagnosed by Culture and PCR -- California, 1990-2010

- Culture positive
- PCR positive
- % PCR
- % Culture
Preliminary PCR Analysis Results
California Pertussis Cases, 2010

1,294 PCR IS \textit{481} Ct results from California residents provided by a large commercial laboratory.

Ct values are inversely related to DNA amount:
- What influences Ct values?
- Are higher Ct values more likely to represent false positives?

1,008/1,294 were identified in our pertussis surveillance database.

The following were associated with higher Ct values (less DNA):
- Any previous vaccination
- Collection of a nasal swab compared with a nasal aspirate
- Receipt of antibiotics prior to specimen collection
- Delay in time from symptom onset to testing
- Older age at specimen collection; those <6 months of age had significantly lower Ct values (also more likely to have a nasal aspirate collected)
Pertussis Cases in Children and Adolescents Aged 0-18 years, by Vaccine History -- California, 2010
### Interim Analysis* DTaP Vaccine Effectiveness Estimates, by Age Group

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<tr>
<th>Model**</th>
<th>Case (n)</th>
<th>Control (n)</th>
<th>VE, %</th>
<th>95% CI</th>
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<td>19</td>
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<tr>
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<tr>
<td>5 doses</td>
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<td>820</td>
<td>81.1</td>
<td>60.8 - 91.0</td>
</tr>
</tbody>
</table>

* VE estimates are preliminary and based on interim data.
** Adjusted for county and provider clustering.
Possible Genetic Changes in *Bordetella pertussis*

- It has been postulated that after introduction of acellular pertussis vaccines, strain replacement with more virulent *B. pertussis* strains occurred.

- To evaluate genotype/phenotype relationships, CDPH is collaborating with researchers at the University of California – Los Angeles to conduct molecular studies.

- Historic and current *B. pertussis* isolates from California infants, stratified by severity of illness, will be genotyped for ptxP3 and a subset will undergo whole genome sequencing.

Why did the 2010 California epidemic happen?

- The last peak year was 2005; a sufficient number of susceptible people accumulated in the population via:
  - Large birth cohort of unvaccinated infants
  - Previously vaccinated people with waning immunity
  - Previously vaccinated people with vaccine failure
  - People who had previous disease with waning immunity (less chance for boosting opportunities)
  - Parental choice not to vaccinate children

- Once the epidemic was recognized, testing increased
Bordetella pertussis PCR Percent Positive by Week
Large California Health Maintenance Organization
July - December 2010
Scientific Gaps

- Other methods to better protect newborns
  - Tdap during pregnancy (now recommended in U.S.)
    - Need for pertussis vaccine during every pregnancy?
    - Possible blunting of infant DTaP immune response?
  - Vaccination of newborns
    - Need for single antigen vaccine?
- DTaP and Tdap vaccine effectiveness
- Tdap booster interval needed
- Efficacy of cocooning
- Community vaccination as a control measure and way to protect infants
- Appropriate postexposure prophylaxis
Questions?

- Compared to the 1980s, the incidence of pertussis in the 1990s increased by 40% among infants <4 months of age and by 49% among infants <2 months of age.

- 103 deaths occurred; a disproportionate number were associated with pulmonary hypertension, Hispanic ethnicity and birth <37 weeks gestation.

- 82% of fatal cases were <4 months of age, median WBC=62,000, median lymphocyte percentage=49%.

- Most cases in summer, most deaths in winter months, 25% had co-infections with other viruses or bacteria.


- 91 infant deaths; all <7 months of age, 58% <2 months
- Average annual infant pertussis mortality rate was 3.8 per 1 million live births, and 13.1 per 1 million live births for infants <2 months of age
- Infant pertussis deaths showed an independent association with birthweight <2500 g, female sex, Apgar score <8, and mother with <12 years education
- The mortality rate among Hispanic infants <2 months of age was 2.6 times greater than among non-Hispanic infants of similar age

2010-2011 ACIP Pertussis Recommendations

- **October 2010**
  - No interval necessary between Td and Tdap
  - Tdap for adults 65 years of age and older with infant contact
  - One dose of Tdap for un- and under-immunized children 7-10 years of age

- **February 2011**
  - All healthcare personnel (HCP) who have not received Tdap should receive it as soon as possible
  - Healthcare facilities should take steps to encourage Tdap, including providing it at no cost
  - Postexposure prophylaxis recommended for all HCP exposed to pertussis who are likely to expose high-risk patients (infants and pregnant women), regardless of vaccination status
Pertussis Diagnostics

- Culture: Labs should maintain capability; cultures should be used to confirm outbreaks and are needed for antibiotic susceptibility testing.

- PCR: Adoption of multi-target R-PCR methods will allow for confirmation and speciation among *Bordetella* spp; Ct cut off values are important; contamination of NP swabs with pertussis vaccine DNA can lead to false positives.*

- Serology: An ELISA-like test that quantitatively measures IgG and IgA antibody to pertussis toxin appears to be a useful diagnostic method, especially in adults and in the later stages of the disease; CSTE/CDC is likely to include serologic evidence of infection in the next update of the pertussis case definition (lab pos + cough of any duration).

When Pertussis Tests are Likely to be Positive in Infected People
CDPH/CDC DTaP Vaccine Effectiveness Assessment

• Objectives:
  - Assess overall VE of DTaP following the 5 dose series
  - Determine duration of protection at specific time points after vaccination - is vaccine waning earlier than expected?
  - Evaluate the impact of the timing of administration of 5th dose (can be given from age 4 though age 6)
  - Evaluate effect of vaccine product on VE and duration of protection (two manufacturers of DTaP and vaccine formulations are different)

• Methods:
  - ~1000 2010 pertussis cases in 15 CA counties and ~3000 unmatched controls aged 4-10 years with same providers
  - In-person collection of vaccine history data
Pertussis in Young Infants

- Infant initially looks deceptively well; coryza, no or minimal fever, mild or no apparent cough
- Leukocytosis with lymphocytosis
- Cyanosis (parents may report red or purple face)
- Gagging, gasping
- Apneic episodes
- Posttussive emesis
- Seizures
- Respiratory distress
- Pneumonia
Pneumonia in Young Infant with Pertussis

Top chest radiograph taken at admission shows central peribronchial thickening only (arrows)

Bottom chest radiograph shows widespread consolidation (confirmed by ultrasound) less than 24 hours later

Pertussis Cases and Fatality Rates in Infants <4 Months of Age -- California, 1988-2010
2010 Pertussis Deaths

- **Case 1: February 2010**
  - Previously healthy, Hispanic female, Los Angeles County
  - Household members with cough illness, however, mom stated they became ill after infant became ill
  - Lived with mother, father, 3 siblings, uncles, aunts, and 2 cousins
  - Symptom onset age 3 weeks
  - Seen by healthcare provider 3 times in 3 days prior to admit; pertussis not considered by provider
  - Admitted from ER after 3 day history of fever, cough, and respiratory distress
  - Transferred from community hospital to children’s hospital PICU for intubation
  - WBC 47,500; 65% lymphocytes
  - Pulmonary HTN, partial exchange transfusion, ECMO
2010 Pertussis Deaths, continued

• Case 2: April 2010

- Previously healthy, Hispanic female, San Bernadino County
- Lived with mother, brother, sister (grandmother babysat)
- Symptom onset age 12 days; mother URI/cough 1 week prior
- Seen in community hospital ER 5 days later, post-tussive vomiting noted, but diagnosed with viral URI and discharged home – pertussis not considered
- Seen in community hospital ER one week later after developing apnea and cyanosis; transferred from ER to children’s hospital PICU; intubation, ECMO
- Admission WBC 33,900
- Pulmonary HTN, renal failure
- Intracranial hemorrhage on day 30 of ECMO → ECMO discontinued → seizures → hemodynamic instability → death
Case 3: April 2010

- Previously healthy, Hispanic female, Fresno County
- 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 multiorgan failure
2010 Pertussis Deaths, continued

- Case 4: May 2010
  - Hispanic male, Stanislaus County
  - Lived with father, mother, 3 siblings – no daycare
  - Mother had history of cough
  - At age 6 days, hospitalized x 24 hours for hyperbilirubinemia; cough onset day after discharge
  - 10 days later, admitted from ER to community hospital where pertussis was not considered at time of admit; condition worsened shortly after admission → transferred after admission to children’s hospital PICU for intubation and ECMO x 7 days
  - Initial WBC 69,000 with 34% lymphocytes; second WBC 90,700 with 26% lymphocytes
  - Pulmonary HTN, disseminated intravascular coagulation, multiorgan failure
2010 Pertussis Deaths, continued

Case 5: May 2010

- Previously healthy, Hispanic male, LA County
- Lived with mother, 2 siblings (grandmother babysat)
- No identified ill contacts
- Cough onset at age 7 weeks, 2 days prior to admit from ER, pertussis not considered at time of admit; transferred from floor to PICU on day of admit after condition worsened
- Admission WBC 33,420; 58% lymphocytes → WBC 100,540; 25% lymphocytes → had two single volume exchange transfusions
- Pulmonary HTN, profound hypoxemia and hypotension from myocardial suppression and ARDS with acute renal failure
Case 6: July 2010

- Previously healthy, Hispanic female, LA County
- Lived with mother, father, MGM, and two siblings
- No identified ill contacts
- Cough onset at age 6 weeks; during the next 8 days until her death, she was seen by her primary care provider x 3 and in an ER x 1 before the second ER visit that led to her admission – pertussis was not considered; she was almost immediately transferred to a PICU after admission and died the next day
- WBC 131,000 with 35% lymphocytes
2010 Pertussis Deaths, continued

- Case 7: July 2010
  - Hispanic male, San Diego County
  - Lived with mother and vaccinated 7 year old sibling
  - No identified ill contacts (mother with cough?)
  - Taken to community clinic for “stuffy nose” and told to use saline nose drops
  - Cough onset at 19 days of age; one week history of mild cough, URI symptoms PTA
  - Circumoral cyanosis, increasing respiratory rate and work of breathing on day of admission
  - Seen in community hospital ER (O2 sat 86%); transferred to children’s hospital and admitted; initial diagnosis bronchiolitis, but pertussis in the differential
  - ECMO → intracranial hemorrhage → death 8 days after admission
2010 Pertussis Deaths, continued

- Case 8: July 2010
  - Former 28 week preemie, LA County
  - Hispanic male, lived with father, mother, and four siblings
  - Three siblings aged 10, 12, and 15 years with cough illness – 7 years old sister asymptomatic (missed opportunity for NICU to assess family immunization status)
  - Received DTaP at 2 months of age, symptom onset 15 days later at ~2½ months of age
  - Seen in clinic on day 4 after symptom onset, one day after cough onset; diagnosed with URI but warned about pertussis and given strict return instructions
  - Admitted from ED 3 days later → respiratory failure → intubation → death <3 days of admission
  - WBC=14.9 with 67% lymphocytes (lower WBC possibly due to receipt of DTaP?)
Case 9: August 2010

- Previously healthy White male, San Bernadino County
- Lived with father, mother, and three siblings
- Mother, father and nine year old sib had cough illness (4 and 5 year old sibs asymptomatic)
- Four year old sib had received four doses of DTaP, fourth dose given in 2010; five year old sib had received five doses of DTaP, fifth dose given in 2009; nine year old sib had received five doses of DTaP, fifth dose given in 2006
- Illness onset at age 20 days, admitted at age 25 days
- Day of admit, seen in clinic with immediate transfer to community hospital and then transferred again to tertiary care hospital – pertussis considered immediately
- Admission WBC=41.9
- Pulmonary HTN, ECMO – death 20 days after admission secondary to cerebral infarction
Case 10: October 2010

- Former 33/34 week Hispanic female; spent two weeks in NICU after birth
- San Diego County resident, age six weeks
- Cough started approximately 2 weeks prior to admission, progressing to post-tussive vomiting
- Two symptomatic contacts - mother’s boyfriend and 4 year old brother
- Evaluated at community hospital ED and transferred to a children’s hospital for admission
- Respiratory failure → intubation
- WBC=40,000-60,000
- Exchange transfusion, death before cannulation for ECMO
U.S. pertussis cases typically peak in the summer - are pertussis deaths seasonal?

Case-Count of Pertussis Cases and Fatalities, 2000-2008

- Pertussis Fatalities
- Pertussis Cases