Coughing up the Facts on Pertussis

Stacey W. Martin, MSc
Meningitis and Vaccine Preventable Diseases Branch
Centers for Disease Control and Prevention

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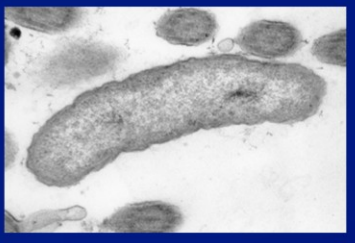
Division of Bacterial Diseases

Presentation Outline

- Background and Clinical Characteristics
- Laboratory Testing Challenges
- Epidemiology and Vaccination
- 2012 Pertussis Activity
- Protecting Infants
- Communications



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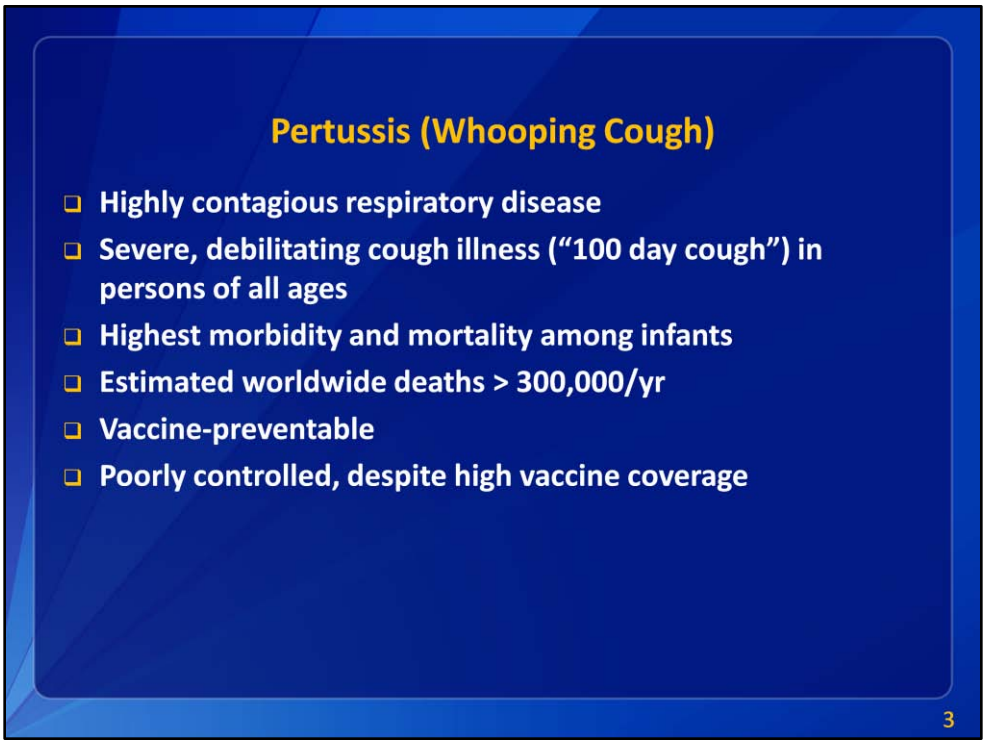
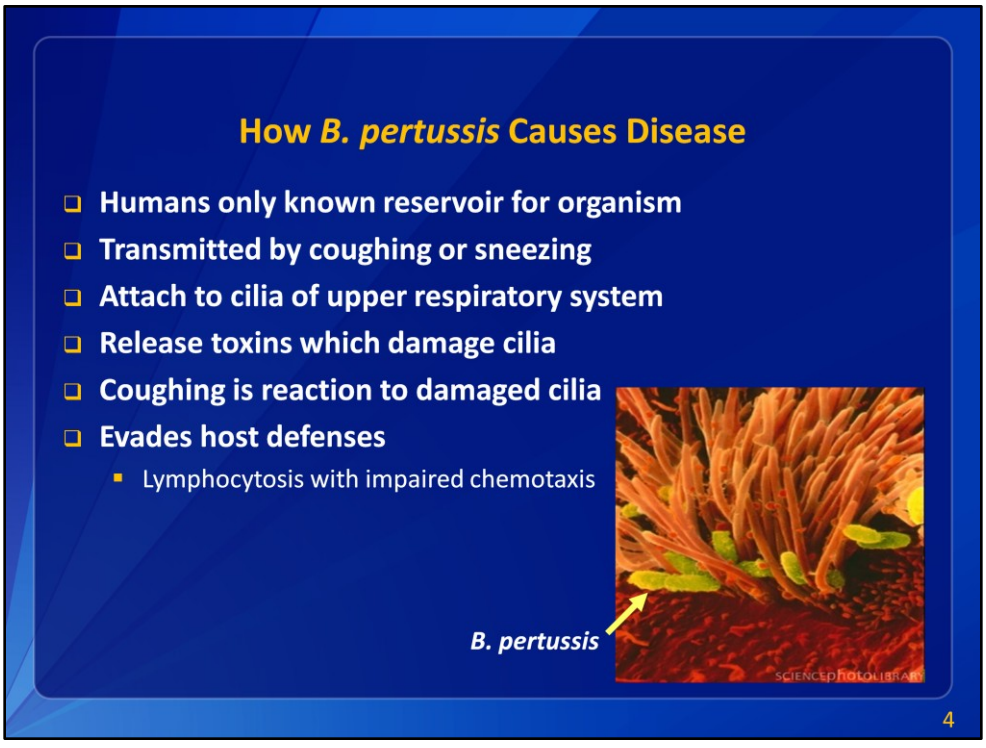
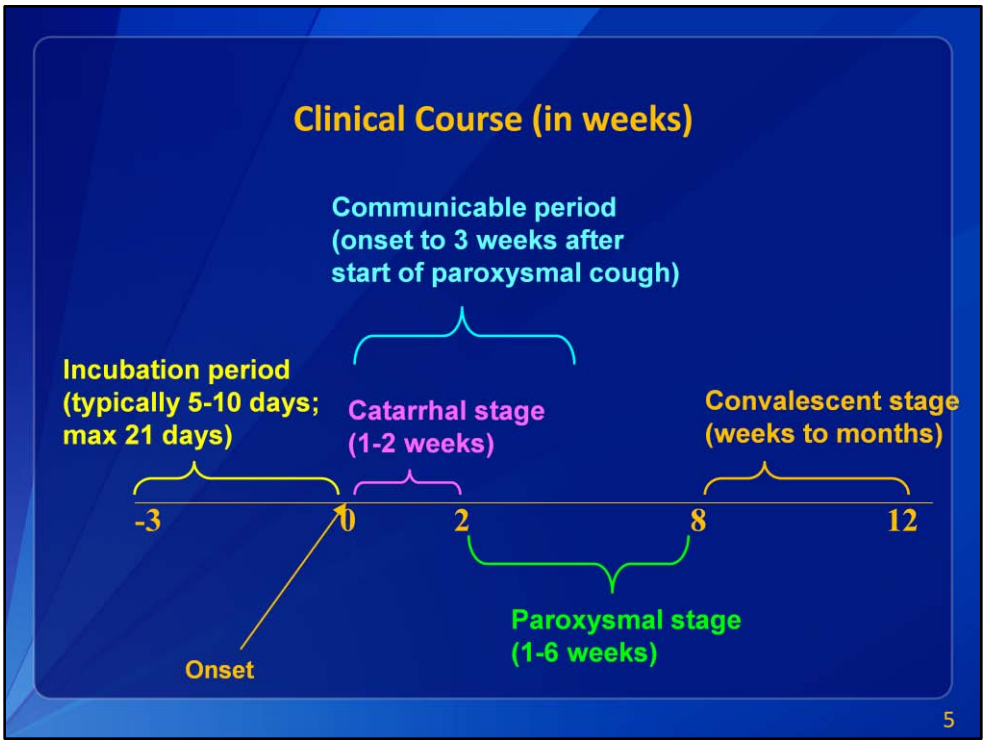
During my talk I will be covering some background and clinical information about pertussis and the unique challenges associated with diagnosis. I will highlight some of the changing epidemiology and look at the impact of our vaccine program on this epidemiology. Since our primary goal is to prevent infant deaths, we will cover new ACIP recommendations that are intended to protect infants too young to be vaccinated and we will end by highlighting some of the communication and educational materials that are available to you.



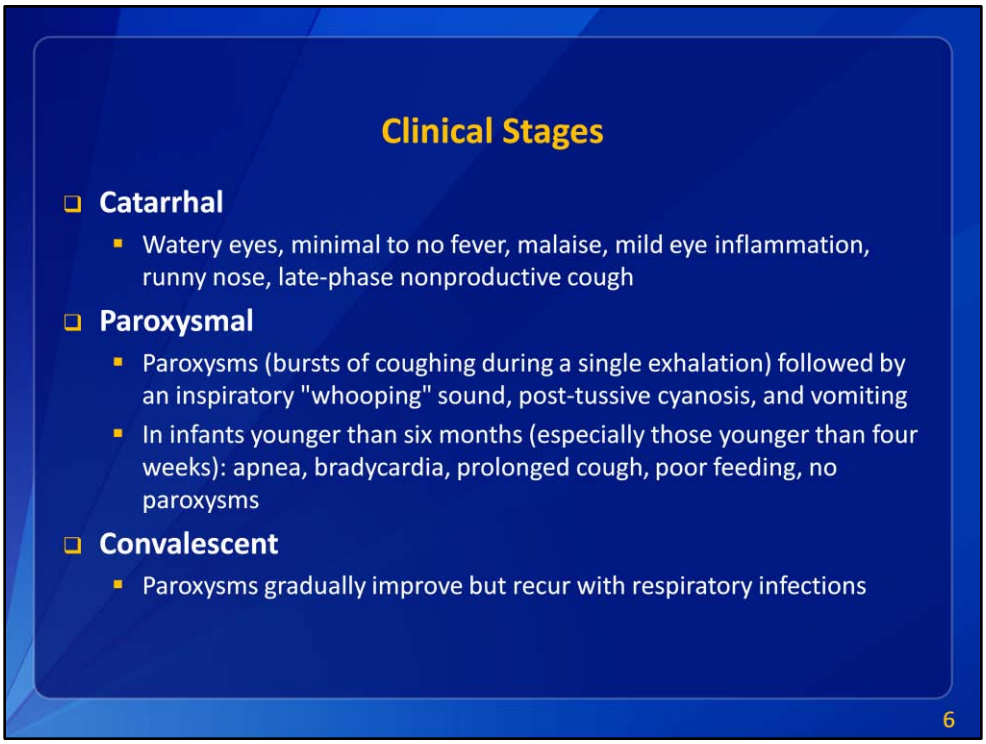
Pertussis is a highly contagious respiratory disease with secondary attack rates as high as 80% in susceptible individuals. It can cause severe debilitating disease in person of all ages, but can be less severe with the typical "whoop" absent in children, adolescents, and adults who have been previously vaccinated. Infants are at greatest risk for disease and death, especially during the first few months of life when they are too young to be protected by vaccination. It is estimated that worldwide, pertussis causes over three hundred thousand deaths per year. Pertussis is a vaccine-preventable disease, but it is poorly controlled despite excellent coverage with the childhood series.



Humans are the only known reservoir for *B. pertussis*. The organisms attach to the cilia of the upper respiratory system and are transmitted through coughing and sneezing. After attachment, the organisms release toxins which damage the cilia and cause them to stop moving. Coughing is the body's reaction to the damaged cilia and may continue for weeks after the organism is gone. The bacterium is very adept at evading the host defenses, for example the classic lymphocytosis with impaired chemotaxis.

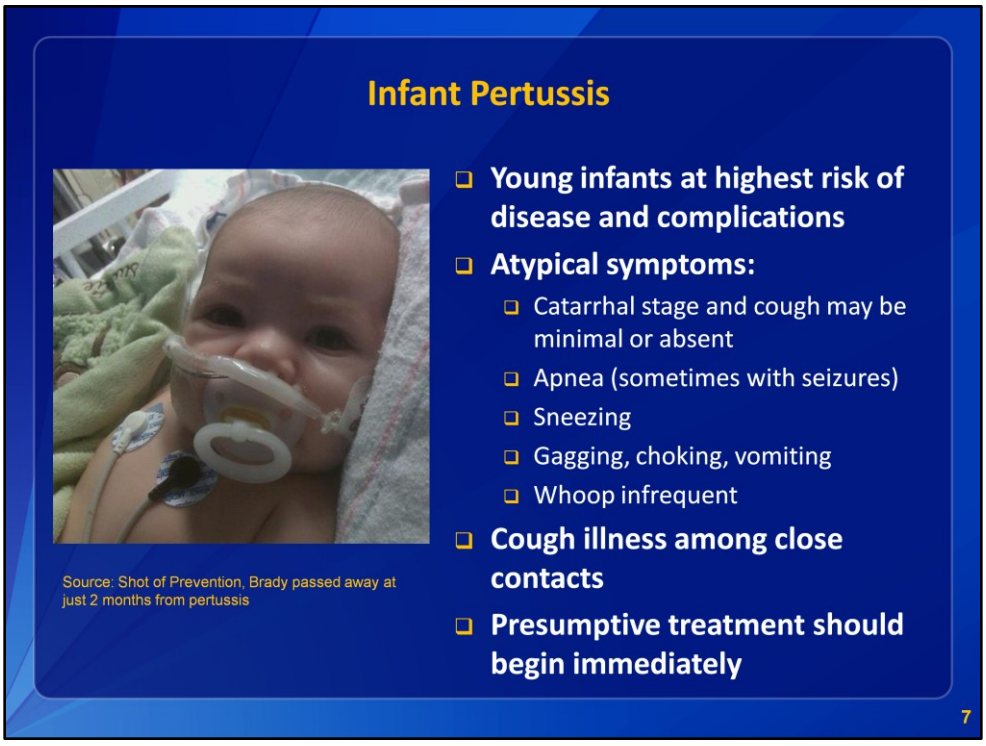


The timeline shows the typical clinical course of pertussis in weeks. The incubation period usually lasts from 5 to 10 days, but can last as long as 21 days. Following onset, the catarrhal stage can last anywhere from 1 to 2 weeks. During the late phase catarrhal stage a cough starts that becomes paroxysmal which marks the beginning of the paroxysmal stage that can last anywhere from 1 to 6 weeks. The paroxysmal stage is followed by the convalescent stage which can last from a week or two, to months in duration. The communicable period begins at symptom onset and lasts until 3 weeks after the paroxysmal cough begins.

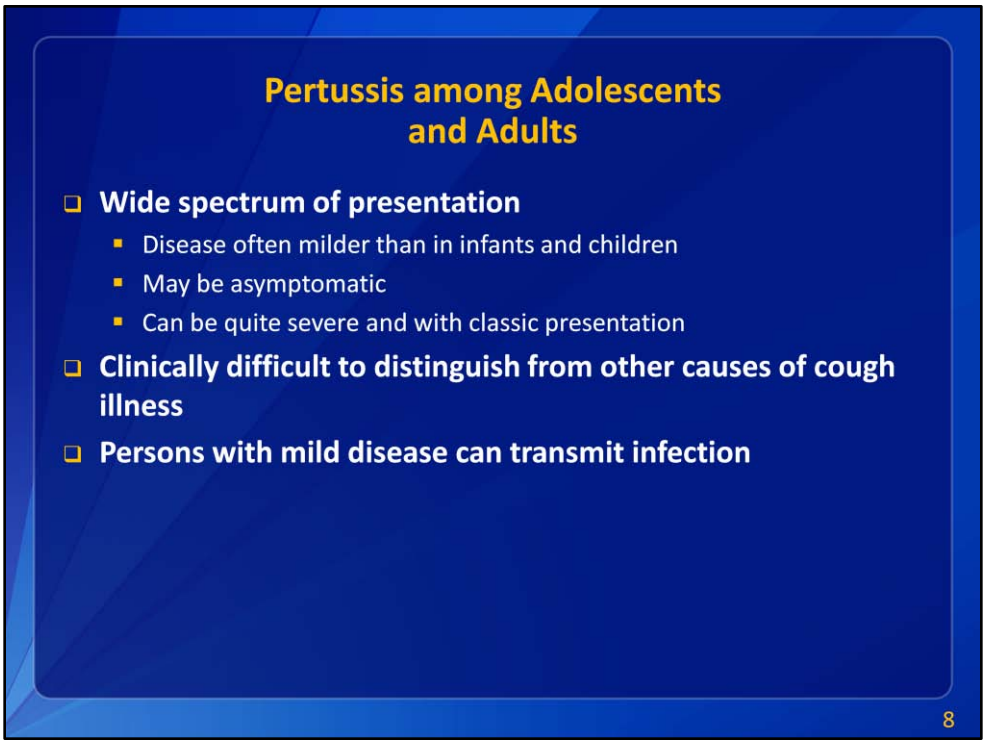


The clinical features of each stage are distinctly different. The catarrhal phase is insidious, in that it often looks like the common cold. It is characterized by watery eyes, no or a low-grade fever, general malaise, mild eye inflammation, runny nose and a late-phase nonproductive cough. As I mentioned on the last slide, the next stage is characterized by paroxysms which are followed by the classic whoop. Post-tussive cyanosis and vomiting also occur. Infants younger than six months can present atypically with apnea, bradycardia, prolonged cough, poor feeding and may not have paroxysms or whoop. During the convalescent stage the paroxysms gradually improve, but can recur with respiratory infections.

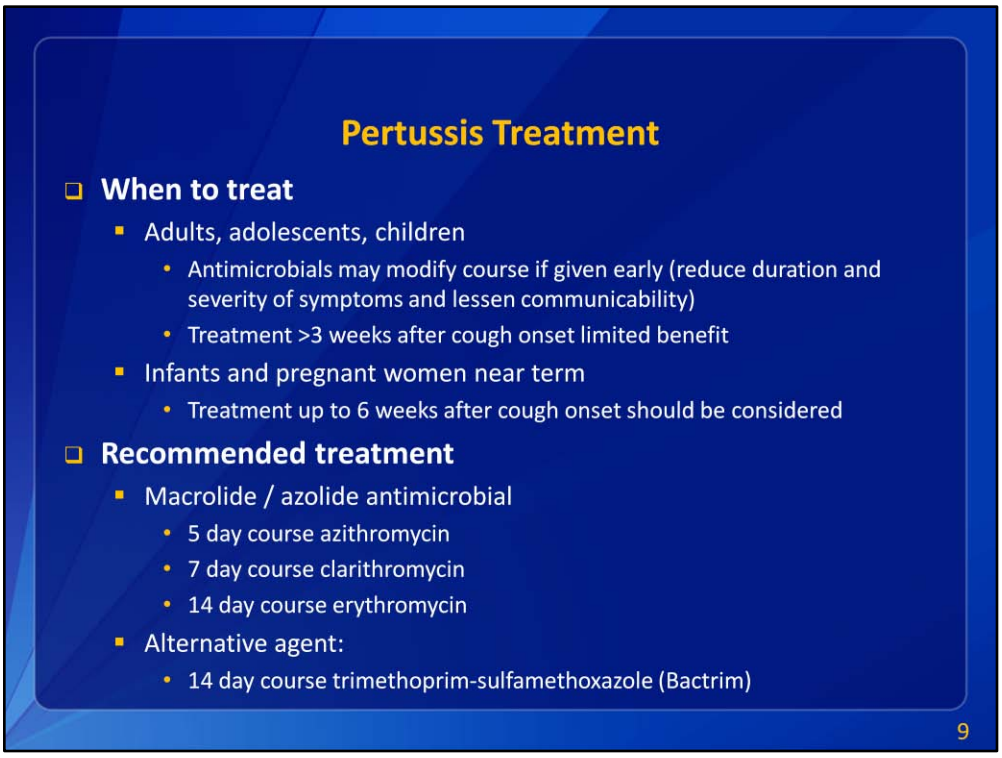
Clinical features that help distinguish pertussis from other causes of cough illness are: minimal to no fever, worsening but nonproductive cough and the characteristic lymphocytosis.



Young infants have the highest rates of disease and serious pertussis-related complications. Making early diagnosis challenging, is the fact they often present with atypical symptoms. The catarrhal stage and cough may be minimal or completely absent. Apnea is a common symptom in very young infants, along with sneezing, gagging, choking, and vomiting. The classic whoop is infrequent. Often cough will be reported among close contacts and because of the increased risk of severe disease in very young infants, presumptive treatment should begin immediately.



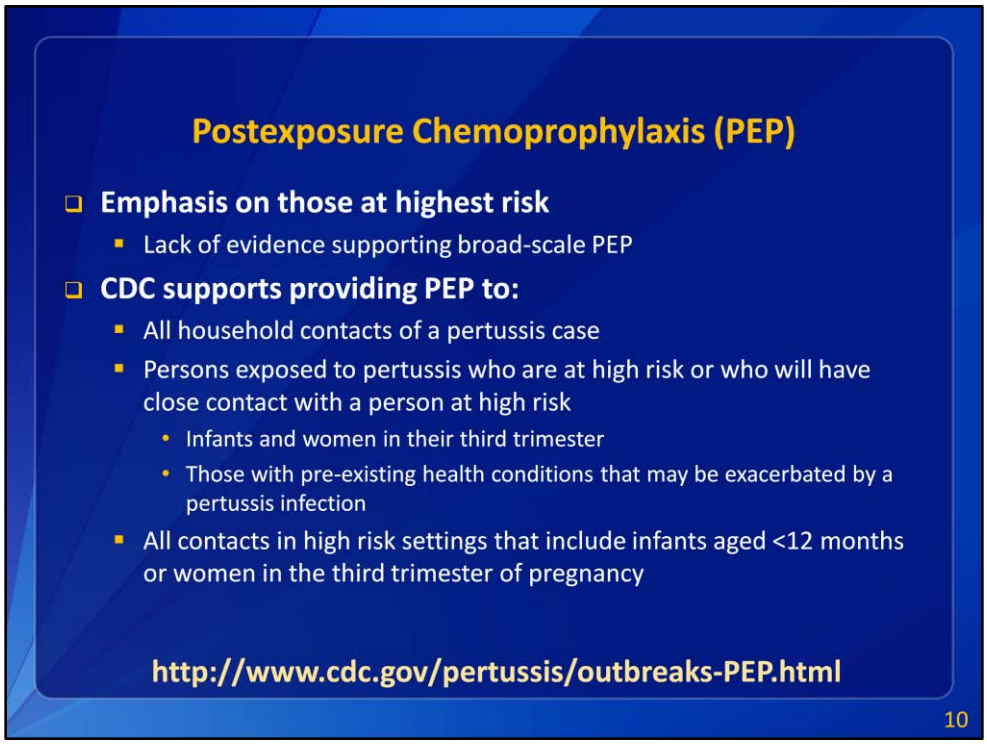
Pertussis illness among adolescents and adults has a wide spectrum of presentation. Disease is often milder than in infants and children and asymptomatic infections are not uncommon. However, you can see adults with severe illness and classic presentation. It is difficult to diagnose in this age group because it is difficult to distinguish from other causes of cough illness and patients often present late in their course of illness when PCR, the most commonly used diagnostic test, is less sensitive. It is important to note that persons with mild disease can transmit infection and are often the source of infection for very young infants too young to have started their vaccination series.



Antibiotics administered early in the course of illness may reduce the duration and severity of symptoms and lesson the period of communicability. However, treatment given more than 3 weeks after cough onset is of limited benefit.

Because of the longer period of infectivity sometimes seen in infants and because of the greater degree of morbidity and mortality seen among infants, treatment up to 6 weeks after cough onset should be considered for infants and pregnant women, especially those in their 3rd trimester.

Macrolides are the recommended choice for treatment of pertussis. While a 14-day course of erythromycin has always been the antimicrobial of choice, the length of treatment and side effects often result in poor adherence. Therefore, azithromycin and clarithromycin are more attractive options. A 14-day course of trimethoprim-sulfa may be used as an alternative agent.

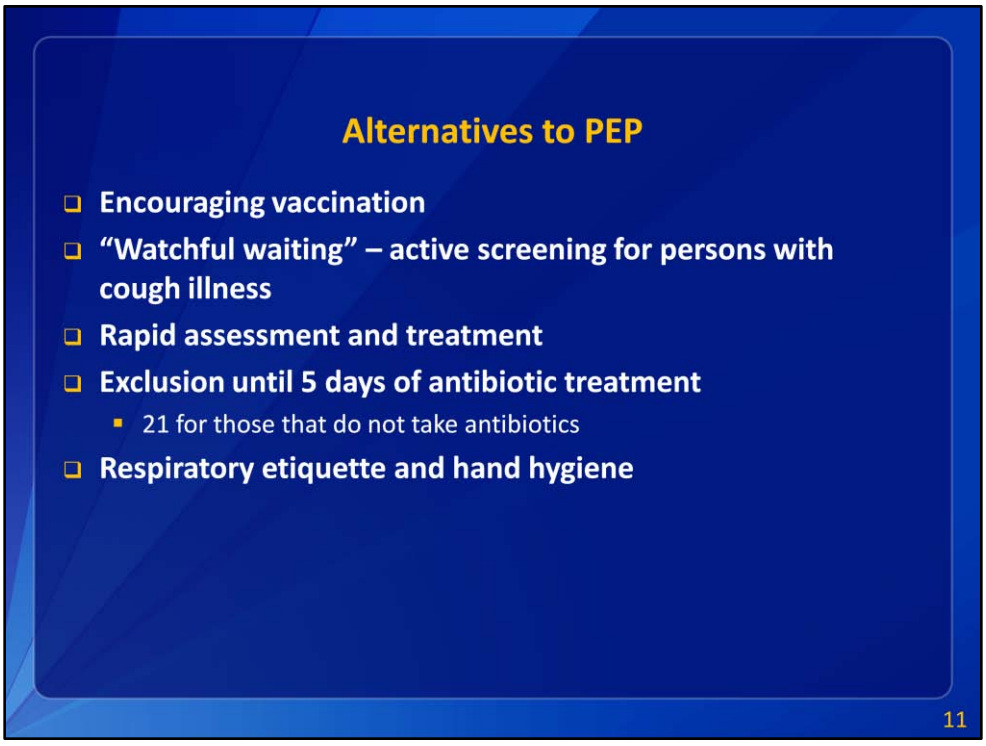


The primary objective of postexposure chemoprophylaxis is to prevent death and serious disease in those at highest risk. Evidence is lacking on the effectiveness of broad-scale prophylaxis and CDC also supports judicious use of antibiotics to prevent antibiotic resistance.

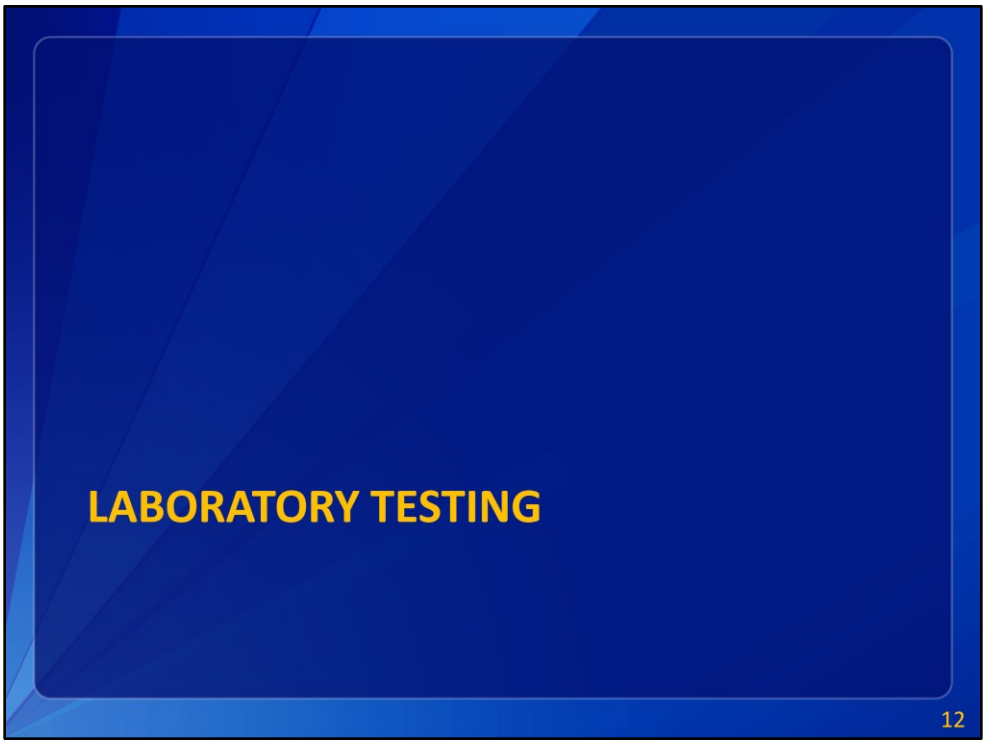
PEP should be provided to all household contacts of a pertussis case. Within families, secondary attack rates are high, even when household contacts are current with immunizations. Administration of antimicrobial prophylaxis to asymptomatic household contacts may prevent disease.

Any exposed infants should receive PEP. Since women in their third trimester of pregnancy may be a source of pertussis to their newborn, it is important that they also receive PEP. Any exposed person that will have contact with an infant or pregnant woman should also receive PEP.

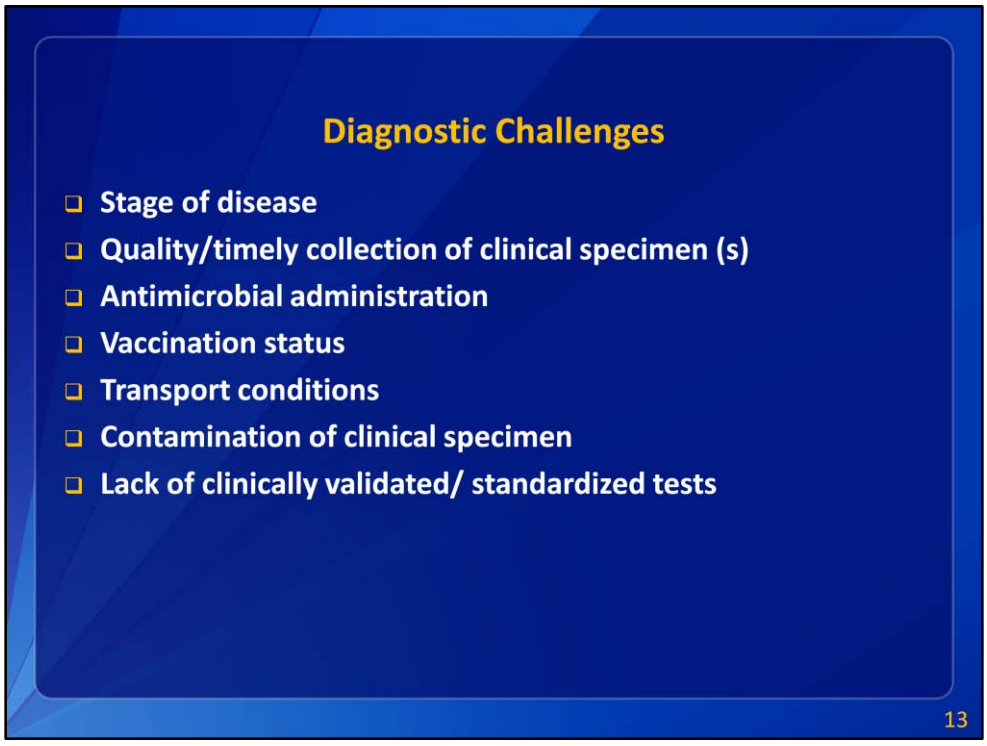
Although risk factors for severe pertussis are not well defined, any exposed person with a pre-existing health condition that may be worsened by a pertussis infection should receive PEP.
And finally all contacts in high risk settings that include infants or pregnant women in their 3rd trimester should receive PEP following an exposure.
Specific details are available at the website shown on the slide.



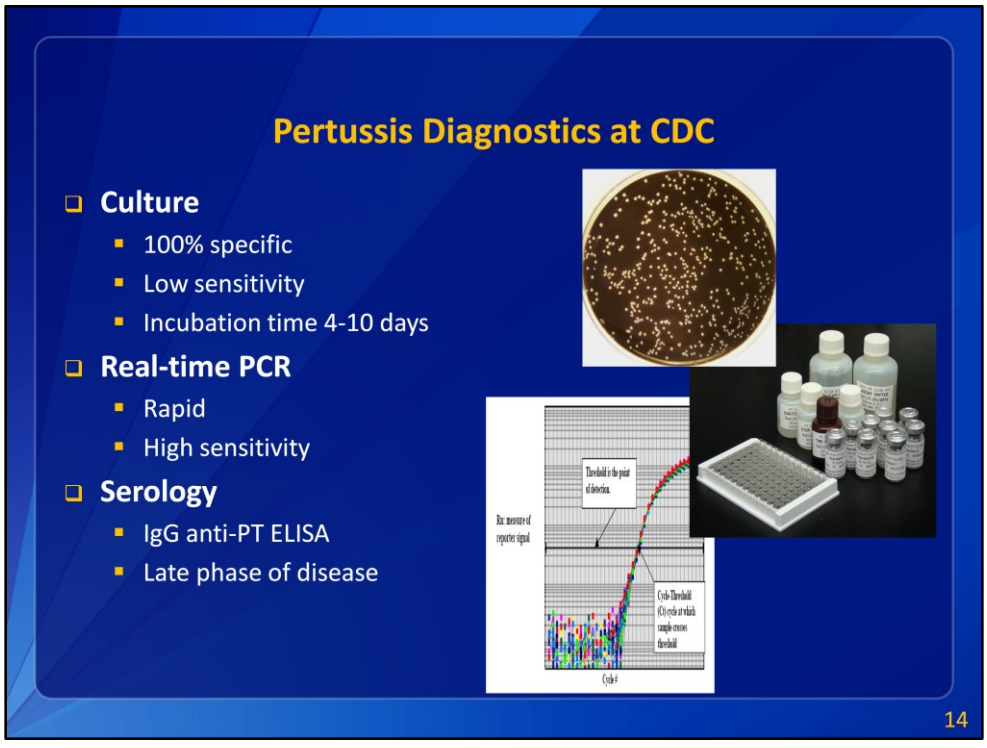
There are some alternatives to broad-scale use of antibiotics. Vaccination should be encouraged at all times and especially when ongoing transmission within communities is evident. In schools or other closed settings, non-pharmaceutical alternatives to prophylaxis, such as watchful waiting, rapid assessment and treatment and exclusion may limit secondary transmission of pertussis. Respiratory etiquette and hand hygiene should be routinely encouraged.



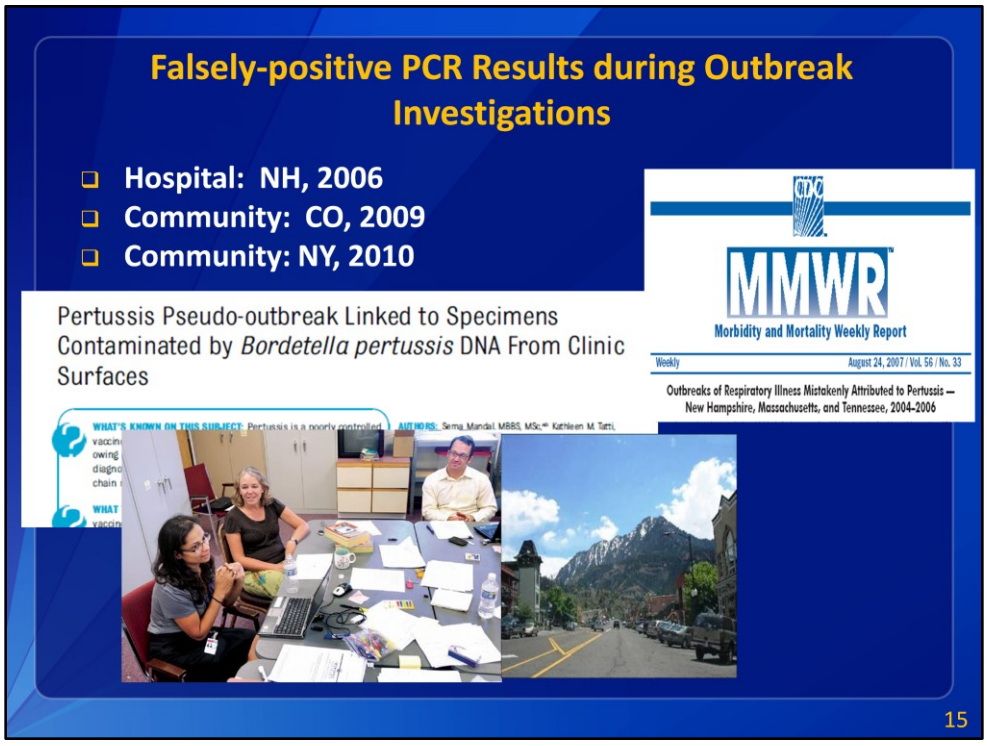
I will now discuss diagnostic testing for pertussis and its associated challenges.



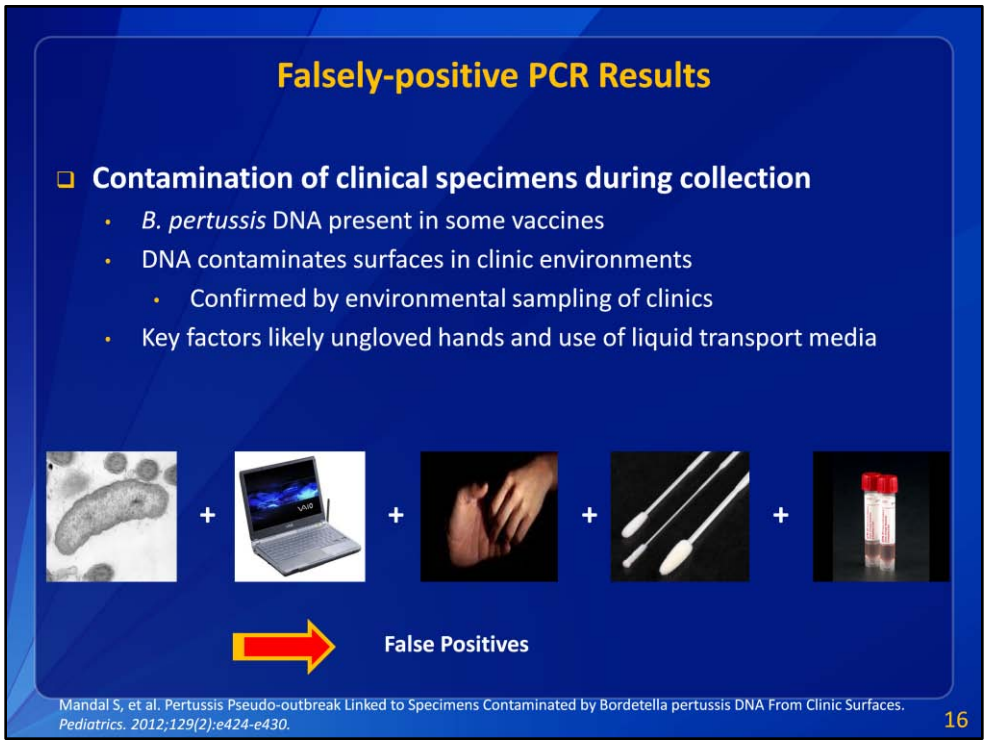
Laboratory confirmation of pertussis can be very challenging. The stage of disease is an important factor impacting the accuracy of diagnostic tests. Individuals with pertussis may not seek treatment immediately and the organism may not be viable in specimens collected late in the course of illness. Specimens collected incorrectly may contain inadequate organisms for culture or PCR. Antibiotic treatment prior to specimen collection and vaccination status influence test results as well. Culture is fastidious requires special media containing cephalexin. The amount of time between specimen collection and culture will also greatly affect whether or not *B. pertussis* is isolated. Contamination of clinical specimens is a concern with PCR and we will discuss this in more detail in a few slides. Adding to the challenges are the lack of clinically validated and standardized tests.



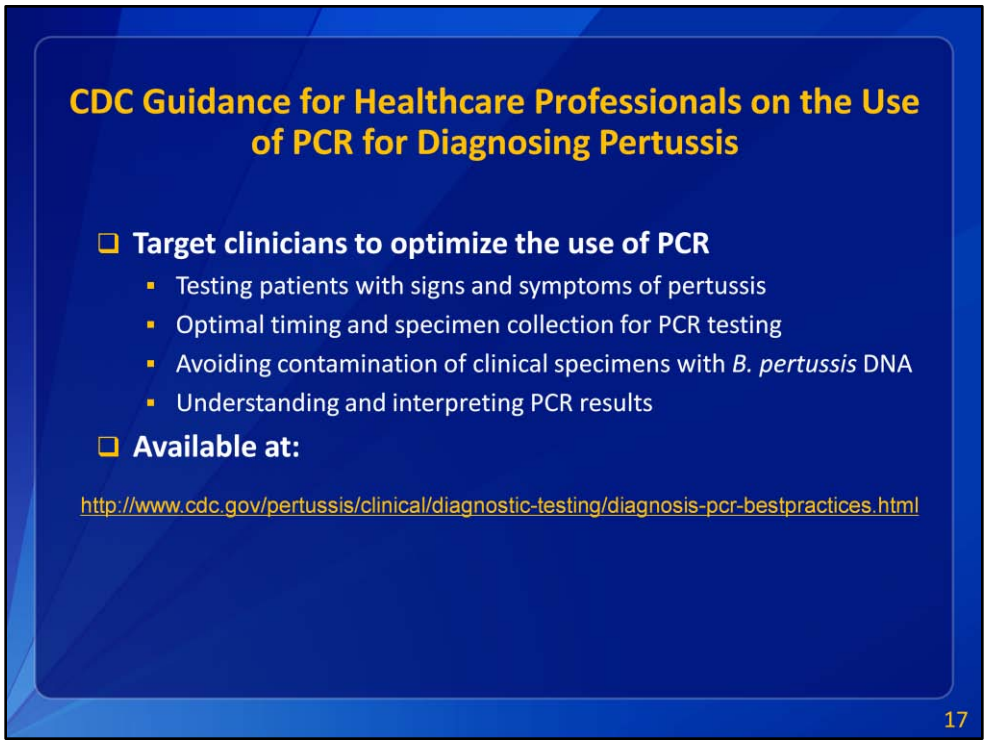
To diagnosis pertussis CDC uses culture and real-time PCR in the early phase of disease and serology in the later phases of disease. Culture is 100% specific but suffers from low sensitivity and can take up to 10 days. PCR is fast and has good sensitivity and usually good specificity. CDC's serology kit is useful for confirming diagnosis during outbreaks, particularly when culture was not performed. While several health departments have adopted the CDC serology assay, it is not commercially available. Commercially available kits are not standardized and have unknown clinical accuracy. We are working at CDC to better understand the clinical usefulness of commercially available serology kits.



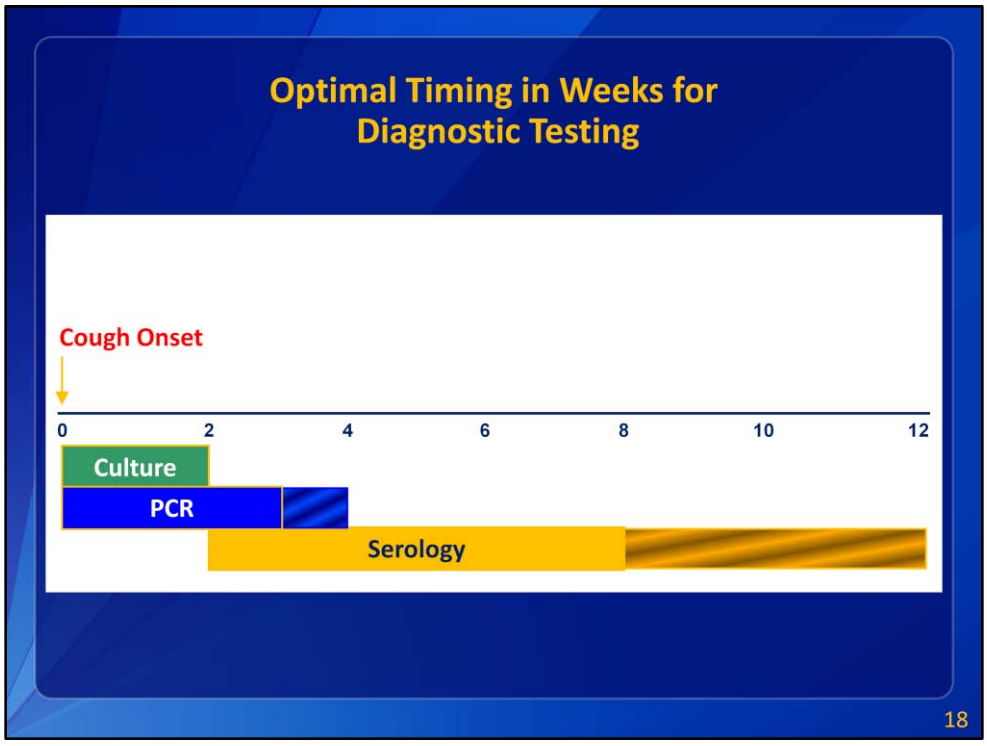
PCR is the most commonly used diagnosed test. And while very sensitive, there can be issues with specificity in certain settings. A number of pseudo outbreaks have been described as a result of falsely-positive PCR results, including a hospital outbreak in New Hampshire in 2006, and more recently community outbreaks in Jefferson County, NY and Durango, Colorado.



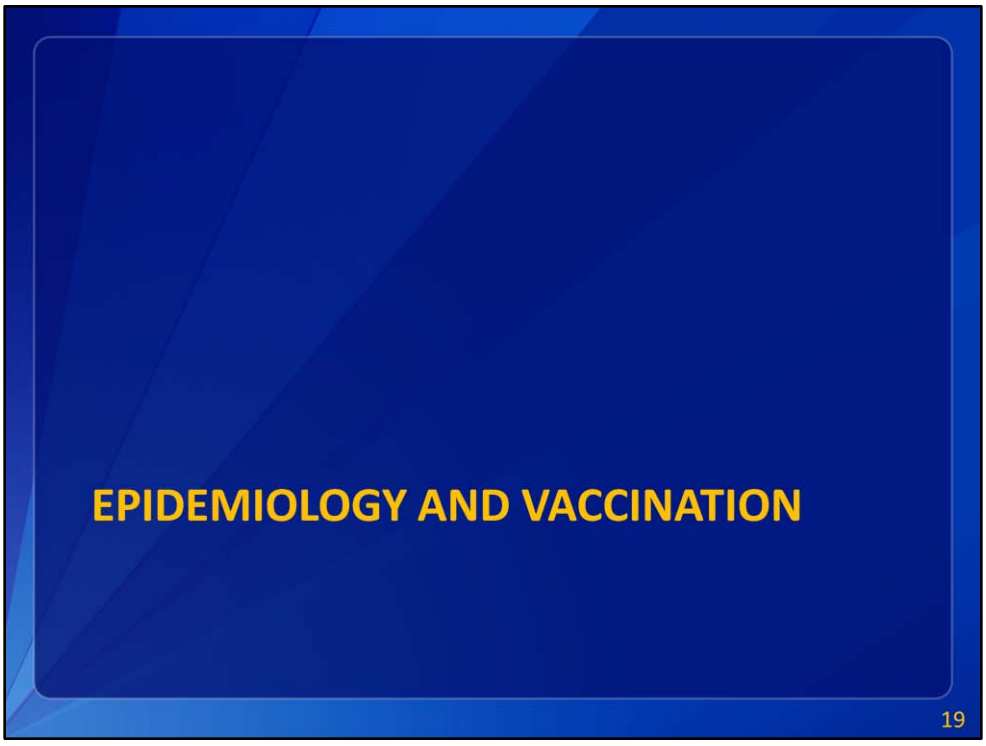
What we found during these investigations is that contamination of clinical specimens during the collection process may result in falsely-positive PCR results. Some pertussis vaccines have been found to contain large amounts of PCR-detectable B. pertussis DNA and environmental sampling has identified the presence of this DNA in clinic environments. Door knobs, computer key boards, sink areas, and vaccine preparation areas are locations within clinic offices that have had DNA contamination. Accidental transfer of the DNA from clinic environmental surfaces to clinical specimens can result in contamination and falsely-positive PCR results. Key factors likely contributing to falsely-positive PCR results in the setting of clinic contamination are ungloved hands and use of liquid transport media. Any contaminant DNA on an ungloved hand can end up on a swab stick. If this swab is then placed in a liquid transport media, the DNA may be washed off into the liquid that is used for PCR testing.



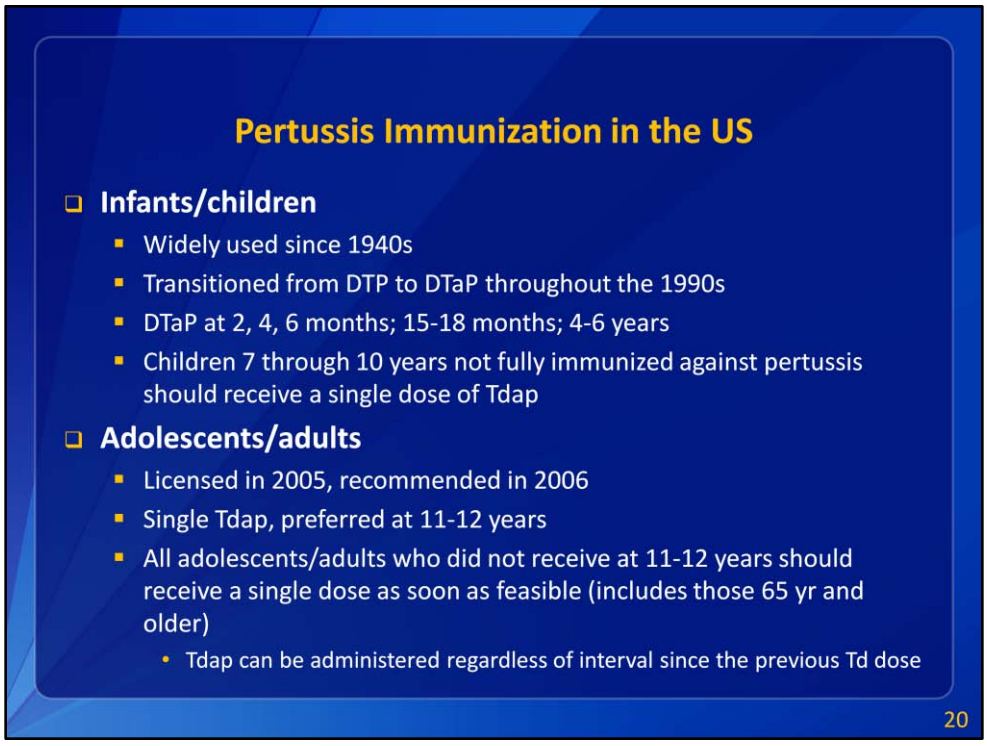
In response to these pseudo-outbreaks, CDC developed a guidance for healthcare professionals on the use of PCR for diagnosing pertussis. The guidance discusses the importance of limiting testing to symptomatic patients, optimal collection techniques, ways to avoid contamination, and correct interpretation of PCR results. This is a long web address, but the guidance is easily located on the CDC pertussis website.



Our diagnostic take-home message is “No single laboratory test can stand alone for diagnosing pertussis”. This illustration shows how culture, PCR and serology can be used in a complementary way to diagnose pertussis. It is critical that the correct specimen be collected properly at the optimal time. Culture must be taken from nasopharyngeal specimens collected between 0 to 2 weeks post cough onset. PCR can be tested from NP specimens taken at a longer time period of 0 to 4 weeks. For the CDC serology kit, the optimal timing for testing is at 2 to 8 weeks where the antibody titers are at their highest, but can continue to 12 weeks post cough onset.

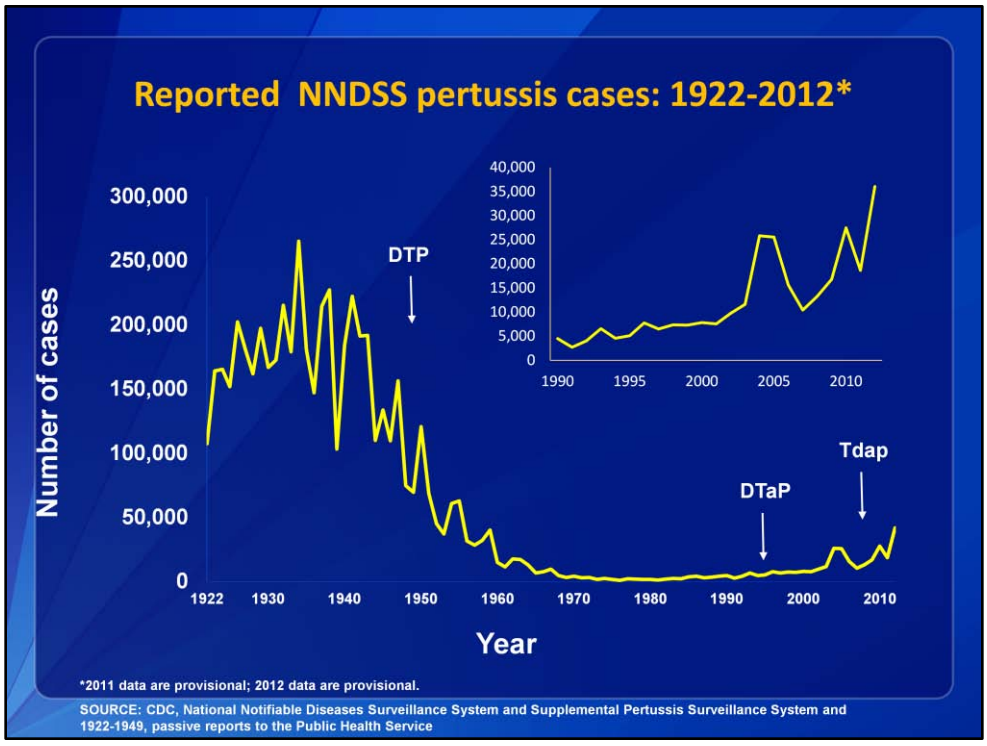


Now I would like to cover epidemiology and vaccination impact.

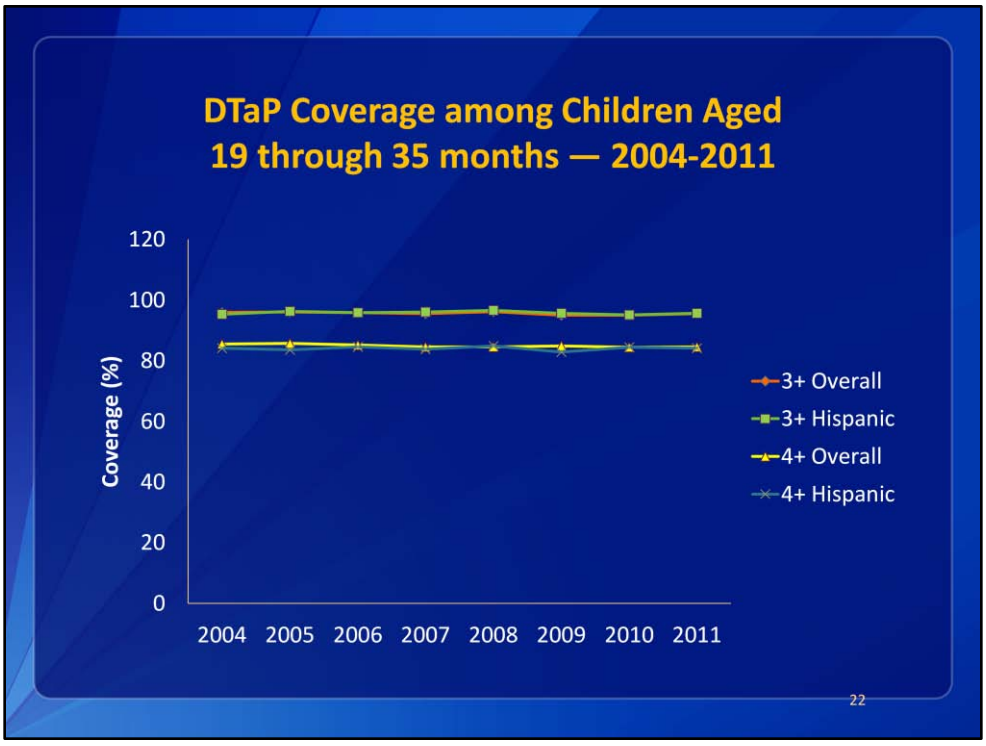


Starting in the late 1940s the US began vaccinating with whole cell pertussis vaccines. In the 1990s a safer version, called an "acellular" vaccine became available in the US to replace the whole-cell vaccine. It is a purified version of the whole-cell vaccine that has fewer components of the inactivated bacteria. In 1992 acellular vaccines were recommended for the 4th and 5th doses given at 15 to 18 months and 4 to 6 years respectively. In 1997, DTaP was recommended for all 5 doses, including the priming doses given at 2, 4, and 6 months.

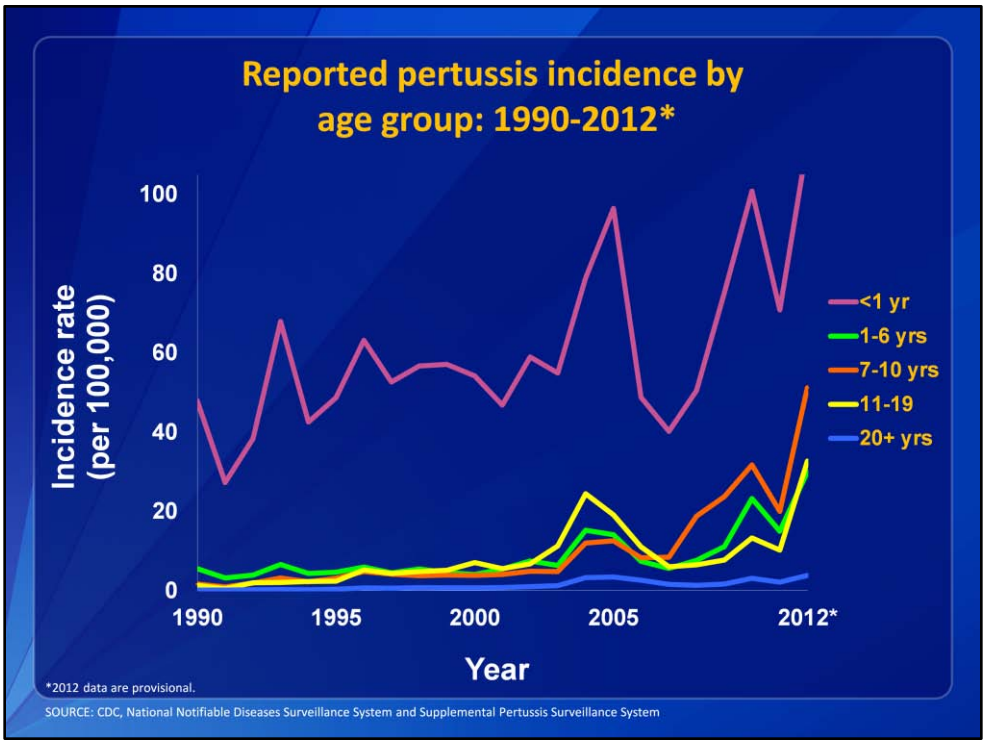
In 2005, two tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines were licensed in the US for adolescents and adults. The preferred administration is at 11-12 years. All adolescents and adults who did not receive Tdap should receive a dose as soon as feasible. Tdap can be administered regardless of the interval since the last dose of Td. If Tdap vaccination status cannot be confirmed, the patient is considered unvaccinated and is therefore eligible to be vaccinated. Additionally, children 7 to 10 years of age that are not fully immunized should now receive a single dose of Tdap.



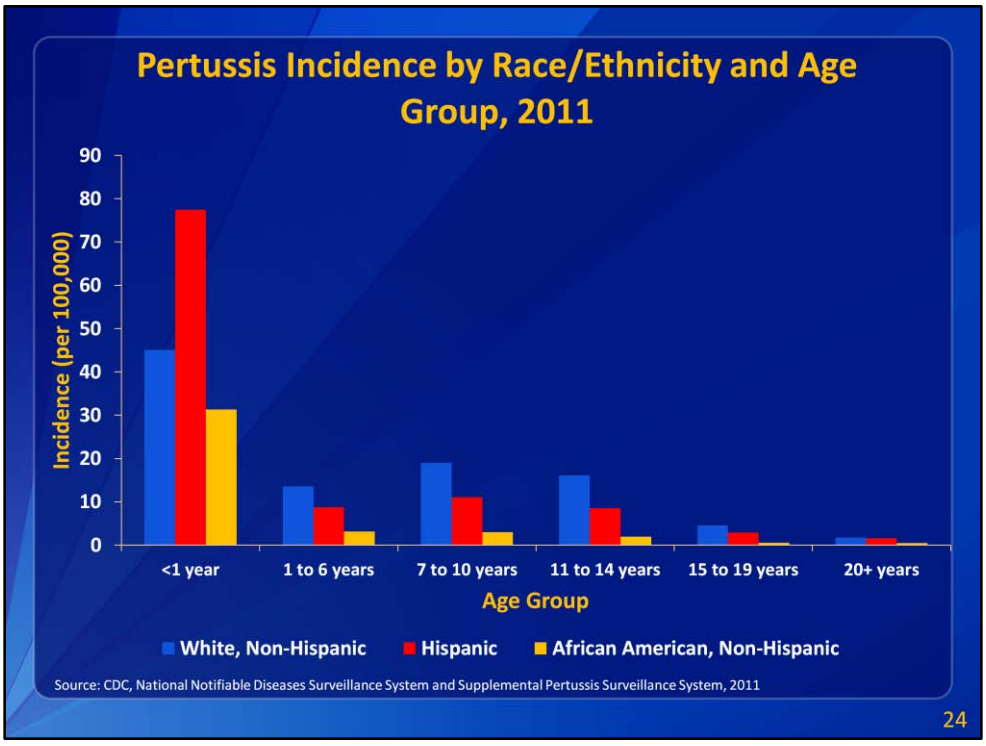
Here you can see the dramatic decline in reported cases following the introduction of whole-cell vaccines and the gradual increase in disease since the nadir in 1976. You can also see the cyclical nature of pertussis with peaks in disease occurring every 3 to 5 years. The increases in reported pertussis cases over the last two decades are likely the result of a number of factors, including improved surveillance capacity, changes in diagnostic testing, increased public and provider awareness, and waning protection from vaccines.



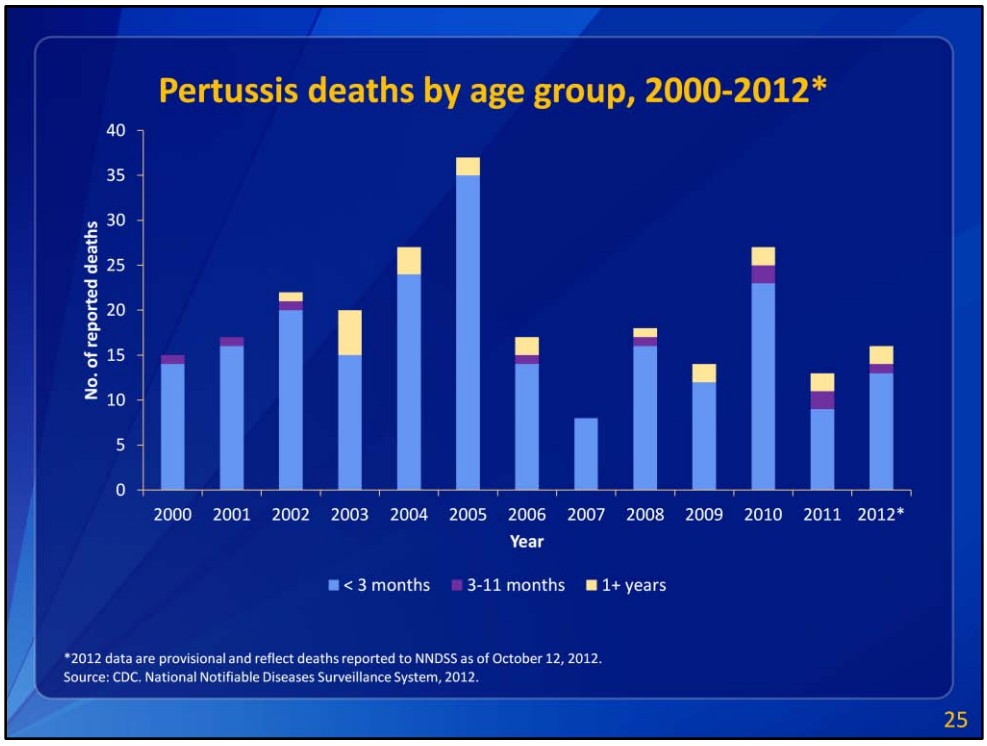
Coverage from the National Immunization Survey shows good DTaP coverage in 19 through 35 month olds with little variability since 2004. Coverage for 3 or more doses is approximately 95% both overall and for Hispanics only. There are no differences in coverage for the pertussis childhood schedule between Hispanics and Non-Hispanics.



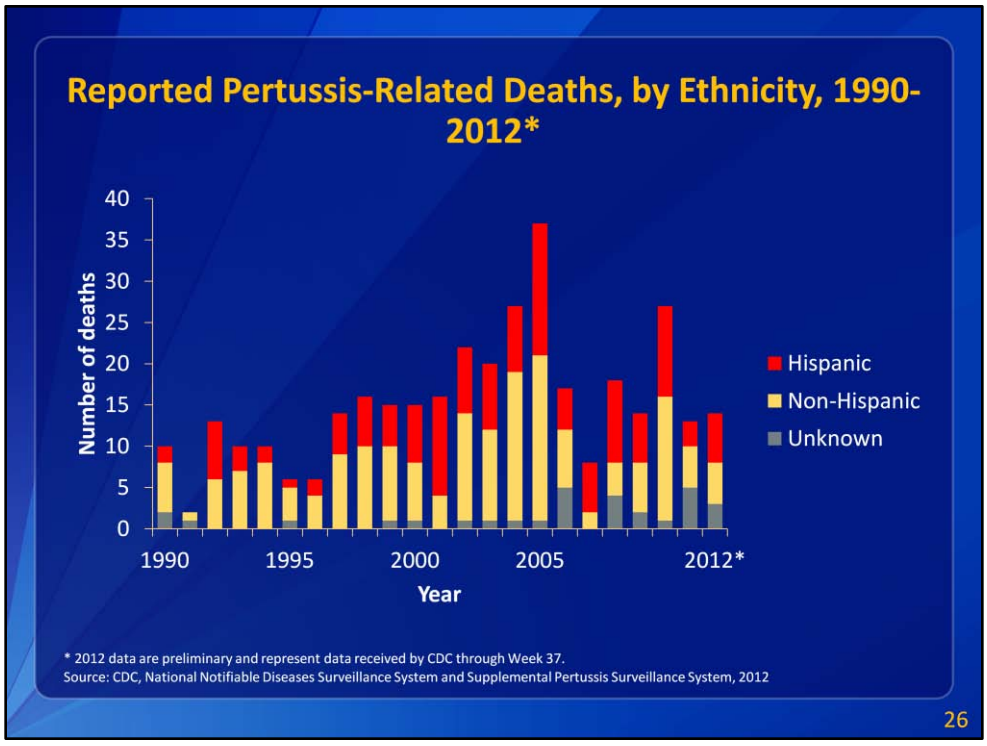
Looking at reported pertussis by age group we see that infants continue to have the highest incidence of disease. In the mid 2000s we saw a shift in the epidemiology where now the 7 to 10 year olds have the 2nd highest incidence of disease. Another notable change is that we saw an increase in teens during 2012. We will discuss these new trends in greater detail in a few slides.



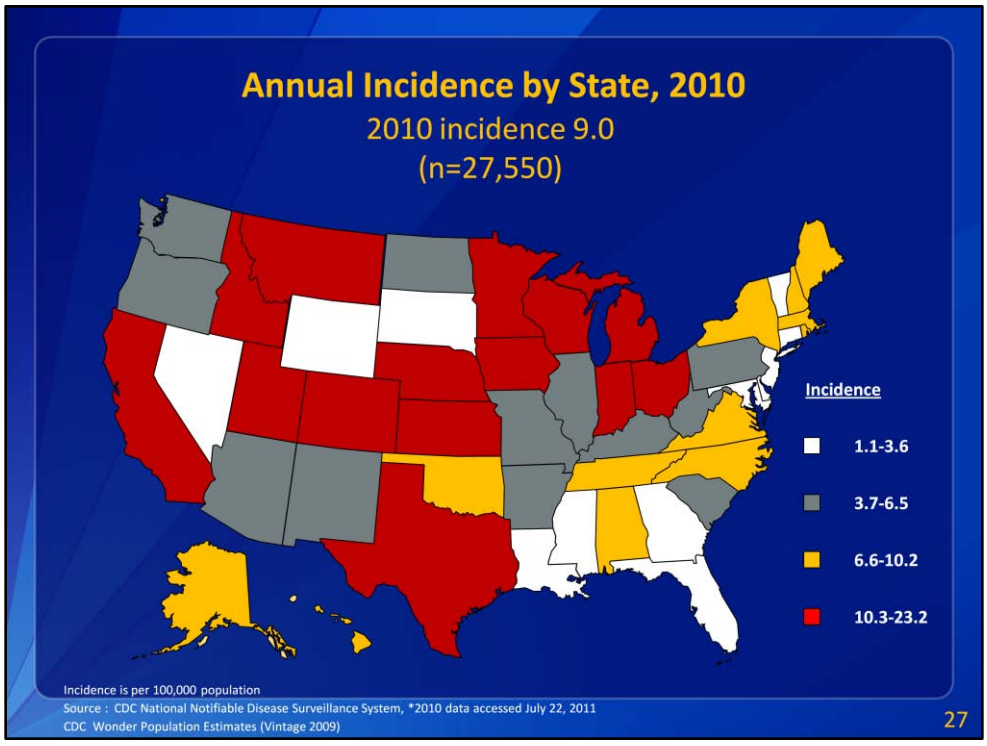
This slide shoes pertussis incidence by race and ethnicity by age group. While whites, shown in blue, have the highest reported rates after infancy, Hispanics, shown in red, have the highest rate in the age group that has the highest occurrence of severe disease and death, those less than 1 year of age. This disparity is not fully understood, but some studies suggest household member size may be a contributing factor. Hispanic infants may tend to have more close contacts putting them at increased risk for pertussis.



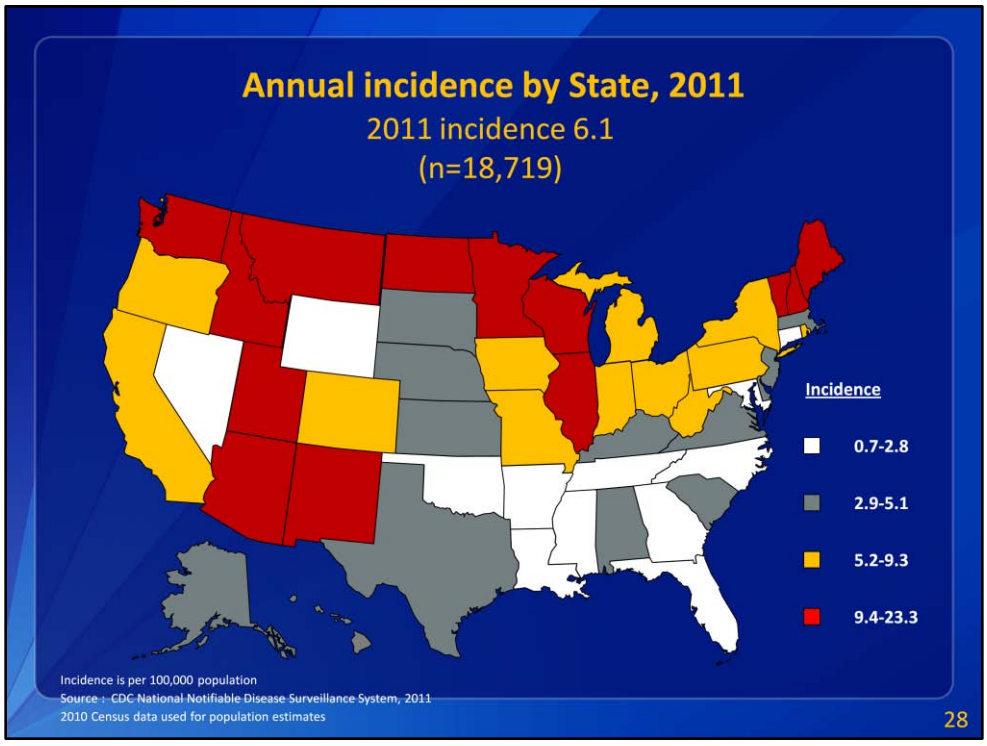
Infants less than 3 months account for the greatest number of reported deaths from pertussis. This age group is too young to have received the full benefit of vaccination.



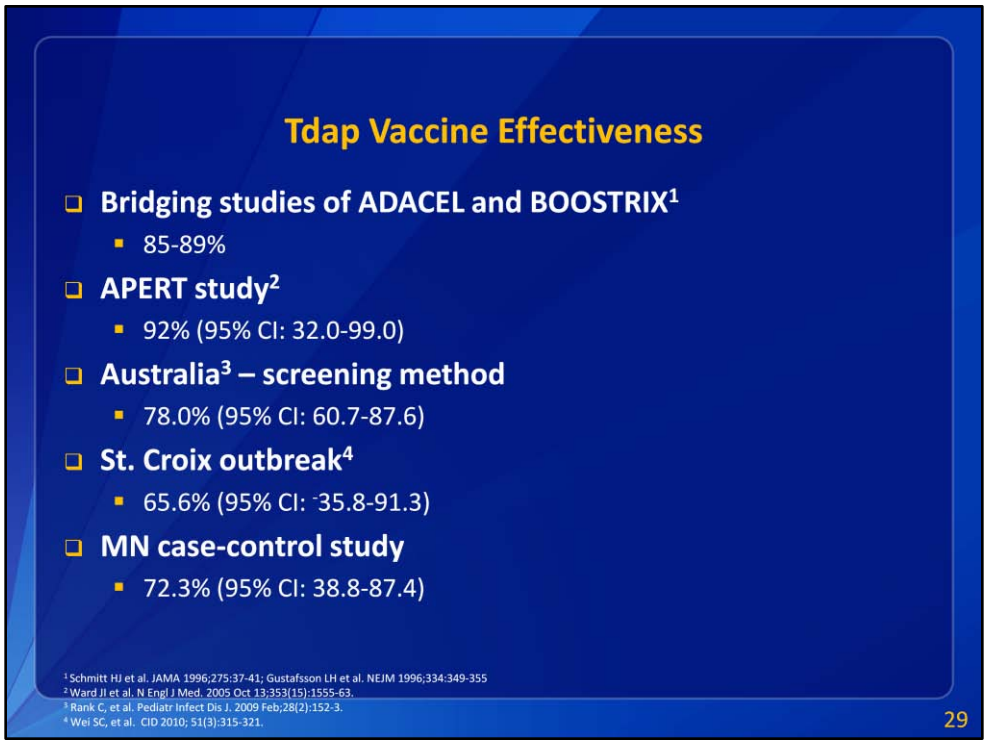
This slide shows that Hispanic infants, shown in red, account for a disproportionate number of deaths from pertussis each year.



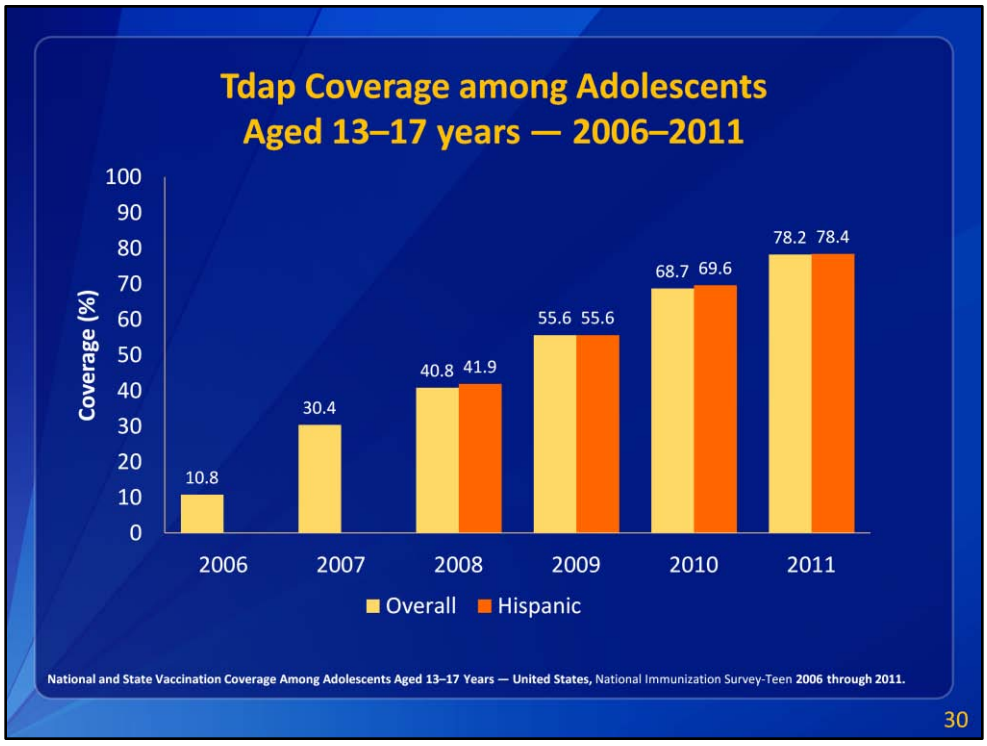
In 2010, California made news by declaring an epidemic of pertussis. They experienced the greatest number of cases in 60 years with over 9,000 cases reported and 10 deaths, 9 of these unfortunate deaths were Hispanic infants. Surprisingly, Minnesota and Iowa reported higher incidence in 2010, but California's large population resulted in a significantly greater number of cases. This slide emphasizes that there is significant geographic variability in the incidence of disease. Some of this is driven by differences in case recognition and reporting, but we know that there is variability in when states experience peaks.



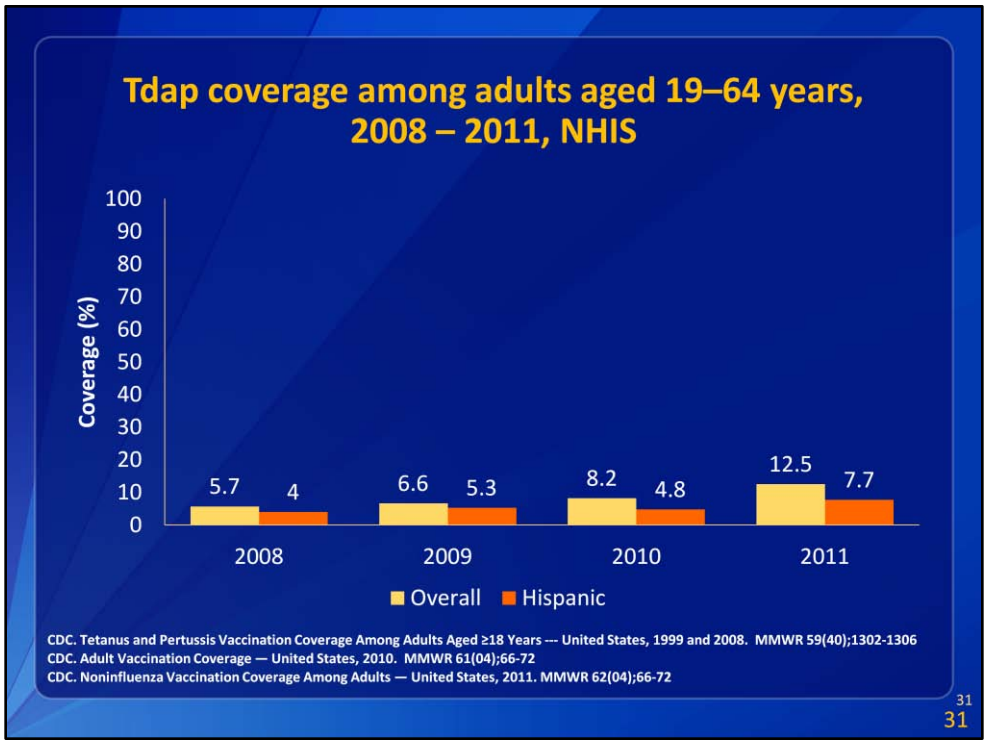
In 2011 states in the Northeast and Pacific Northwest started to see increasing numbers of cases. I will give an update on 2012 pertussis activity in just a moment.



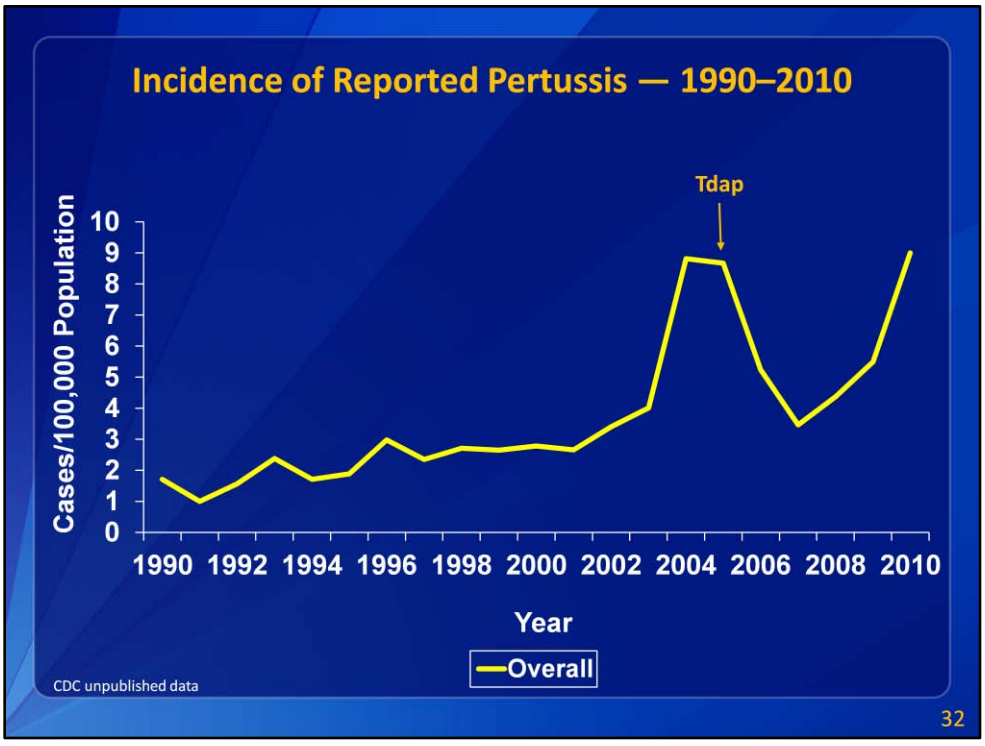
Tdap was licensed and recommended in 2005 for adolescents and adults. At the time of licensure, Tdap efficacy was based on sero-bridging studies from infant efficacy studies. Immune response to Tdap was noninferior to the immune response of infants receiving DTaP. From the adult pertussis trial, overall vaccine efficacy of an acellular pertussis vaccine was 92%. Recent post-licensure studies of Tdap show vaccine field effectiveness at roughly 70%.



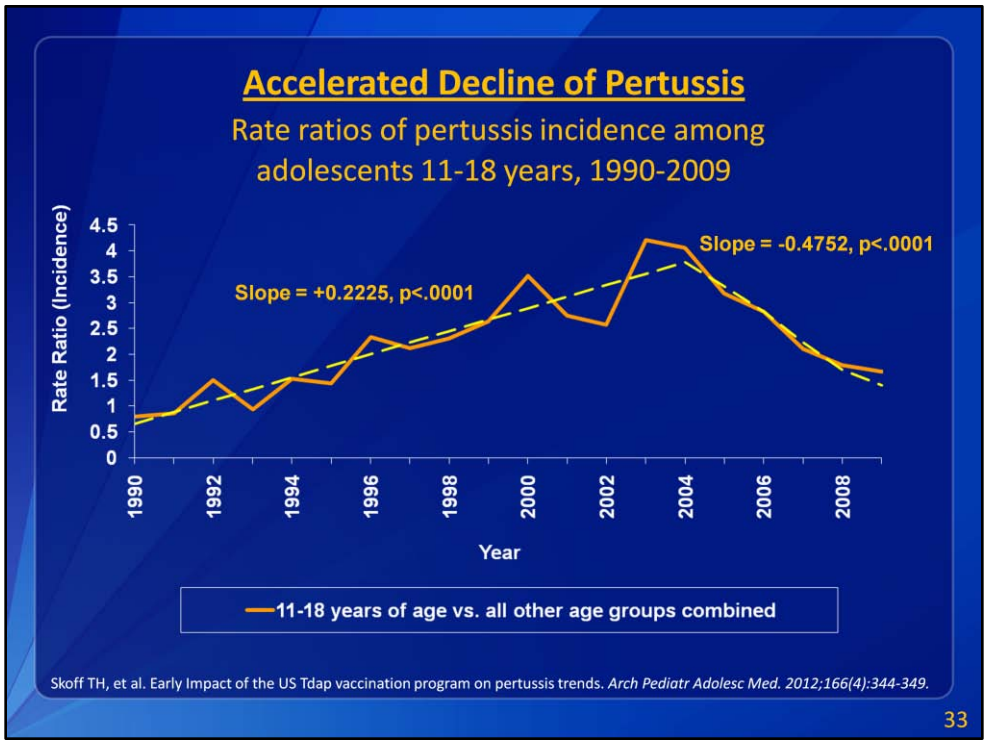
Coverage with Tdap has been slowly increasing since introduction and now is approximately 78% in adolescents. Adolescent Hispanics have Tdap coverage comparable to the overall population, as shown in orange.



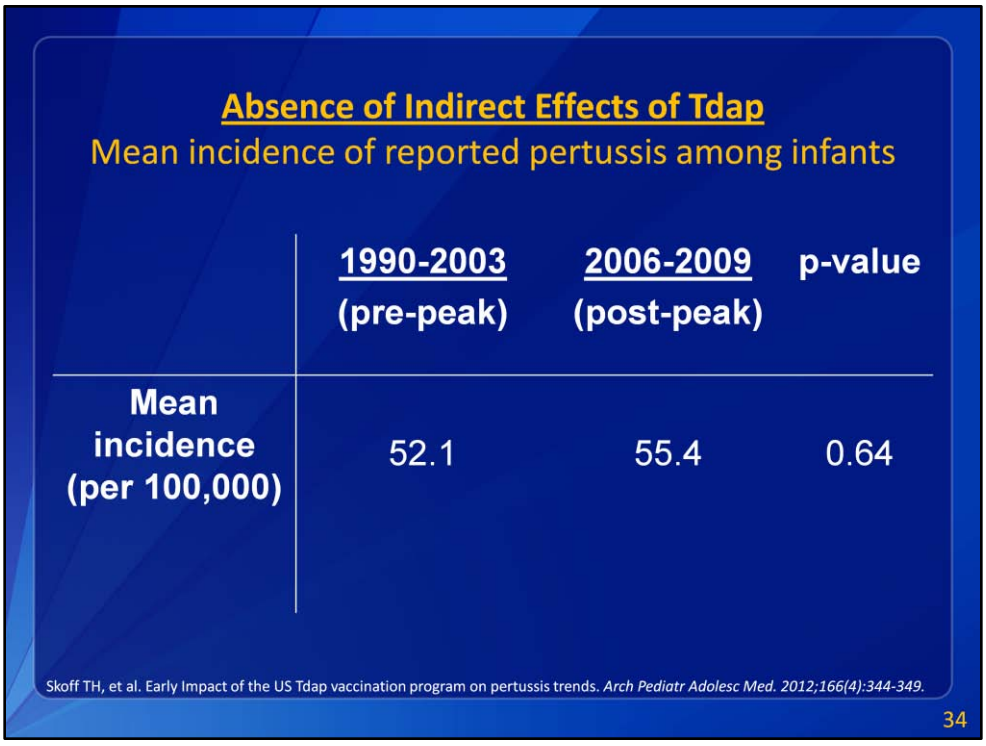
Coverage in adults is still very low. In 2011 it was estimated at approximately 12 percent. Coverage in Hispanic adults is lower than the overall population at only 7.7%.



Now before we look into the potential impact of Tdap, remember, rates of pertussis increased gradually in the US between 1990 and 2003, before reaching a peak of 8.8 cases per 100 thousand population in 2004. The introduction of Tdap in 2005 occurred at the height of this peak when rates of disease in the US were significantly elevated. Following the introduction of Tdap we experienced a decline in incidence only to be followed by a larger peak in 2010, but does this mean the program hasn't been successful? To answer this we need to look more closely at the data.

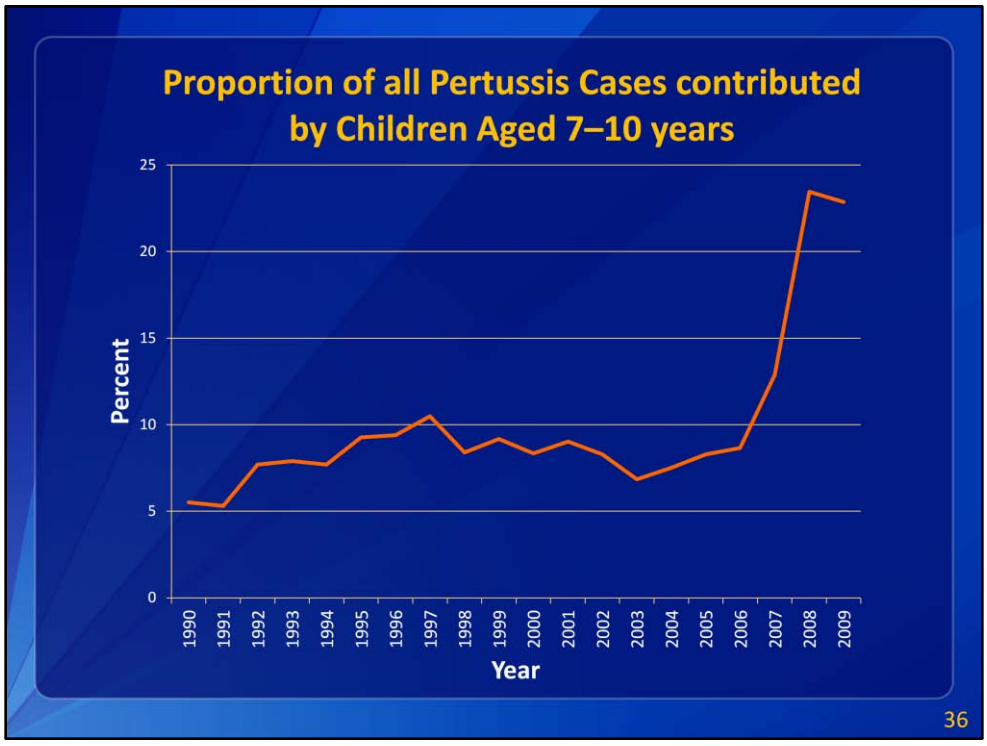


This graph is a little complicated, so let me walk you through it. We calculated rate ratios by dividing the incidence of pertussis among adolescents 11-18 years of age, by the incidence of disease in all other age groups combined. We then modeled the rate ratios to evaluate the impact of Tdap vaccination over time. For our model, we defined 1990-2004 as the pre-Tdap period, and 2005-2009 as the post-Tdap period. We observed a steady increase in rate ratios during the pre-Tdap period and then a reversal to a significant decreasing trend post-Tdap. So this tells us that there has been a significant decrease in the relative contribution of adolescent disease to the total overall burden of pertussis following the introduction of vaccine in 2005. While overall incidence appears to be increasing since 2007, our analysis revealed a divergence between 11- to 18-year-olds and other age groups, suggesting that the targeted use of Tdap among adolescents reduced disease preferentially in this age group.

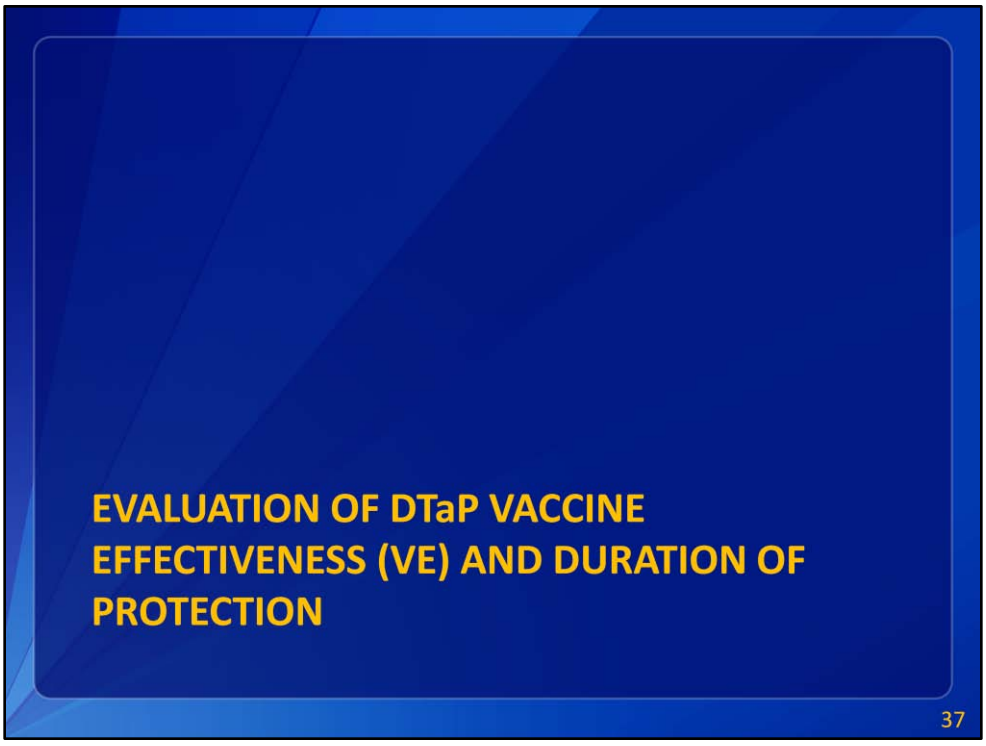


When we looked to see if Tdap was having any indirect effects in infants we didn't find any. Mean incidence was 52.1 before the introduction and 55.4 after the introduction and did not change significantly between the two periods. Adult coverage rates were likely still too low to see an impact. I would like to point out that this analysis is currently being updated with current data. Unfortunately, more recent epidemiologic trends which we will cover in a moment, suggest the impact of Tdap in adolescents may be diminishing somewhat.

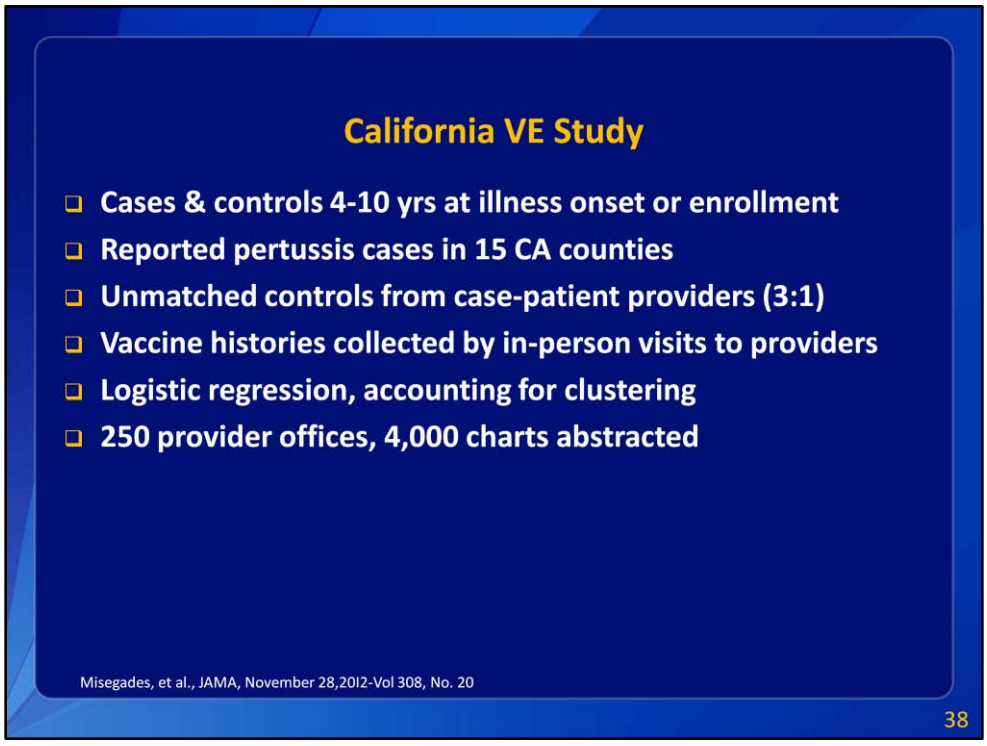
Now, let's examine this recent trend of emerging disease in 7 to 10 year olds.



The trend is easily seen when you graph the proportion of all pertussis cases contributed by children aged 7 to 10. Beginning in 2007 you can see a dramatic shift upwards.

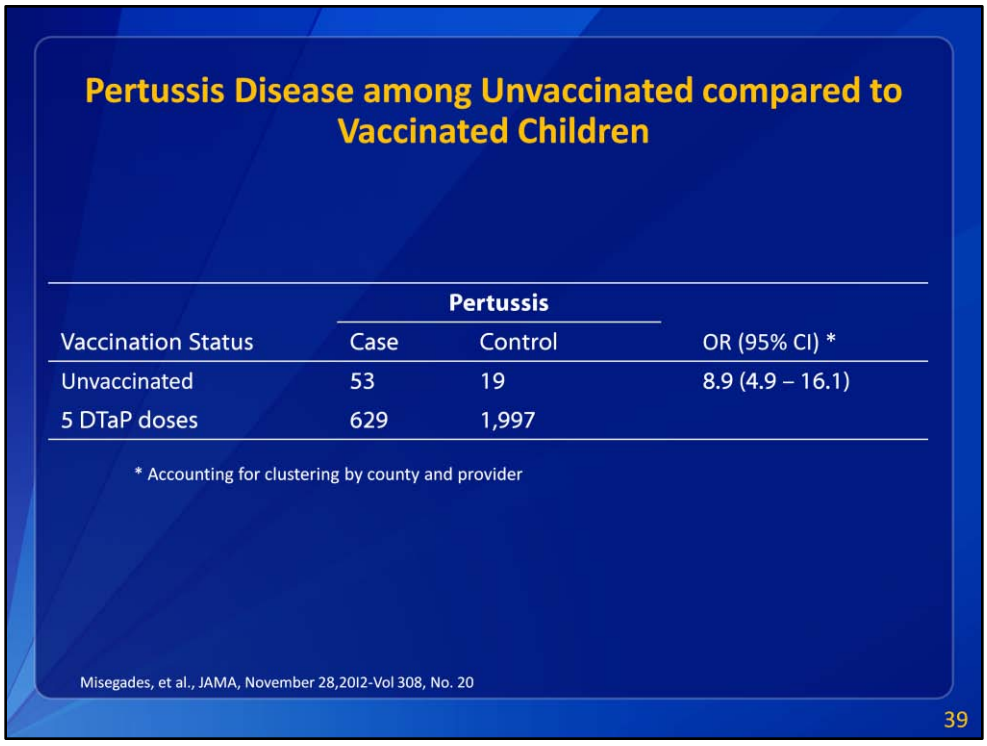


This disconcerting trend of increasing cases in 7 to 10 years old who were the first to receive all acellular vaccines prompted us to evaluate the effectiveness and duration of protection afforded by acellular pertussis vaccines.



California's 2010 epidemic offered an opportunity to conduct a large-scale vaccine effectiveness study. In collaboration with the California Department of Public Health, we enrolled cases and controls 4 to 10 years of age at illness onset or enrollment from 15 counties in California. These counties make up 40% of California's population. Vaccine histories were collected by in-person visits to providers and logistic regression was used accounting for clustering by county and provider.

The results from this study were published in JAMA late last year.



Unvaccinated children had 8.9 times the odds of becoming a pertussis case as children who had received all 5 doses of DTaP. This represents substantially greater risk.

Overall VE & Duration of Protection Estimates

Model *	Case (n)	Control (n)	VE, %	95% CI
Overall VE, All Ages				
0 dose	53	19	Ref	--
5 doses	629	1,997	88.7	79.4 – 93.8
Time since 5th dose				
0 doses	53	19	Ref	--
< 12 months	19	354	98.1	96.1 – 99.1
12 – 23 months	51	391	95.3	91.2 – 97.5
24 – 35 months	79	366	92.3	86.6 – 95.5
36 – 47 months	108	304	87.3	76.2 – 93.2
48 – 59 months	141	294	82.8	68.7 – 90.6
60+ months	231	288	71.2	45.8 – 84.8

* Accounting for clustering by county and provider

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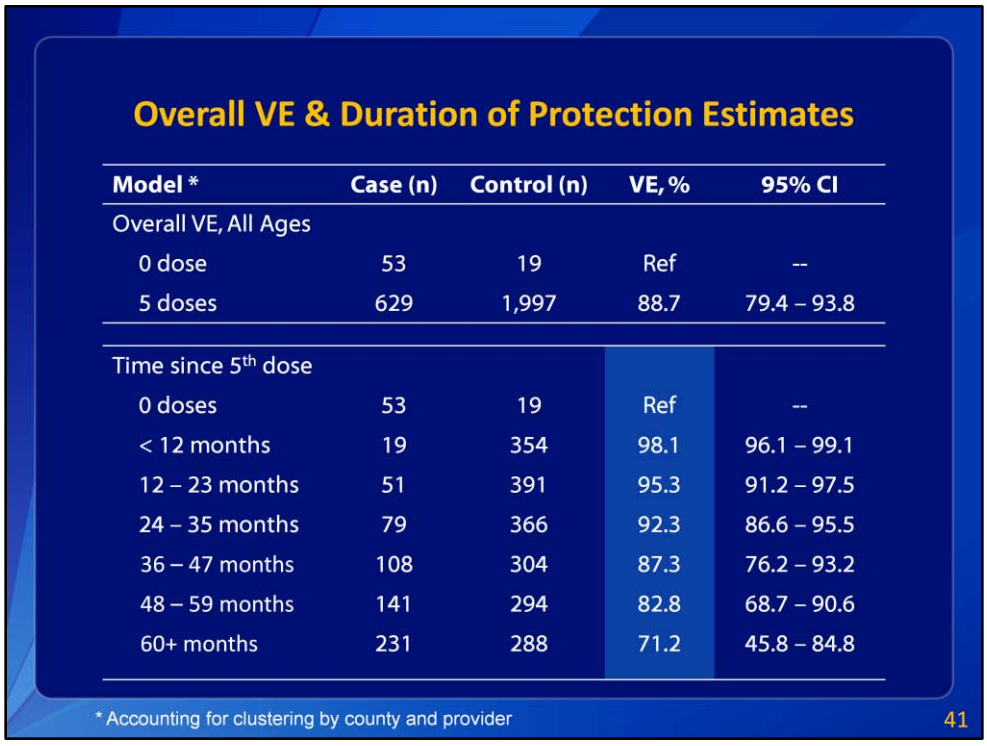
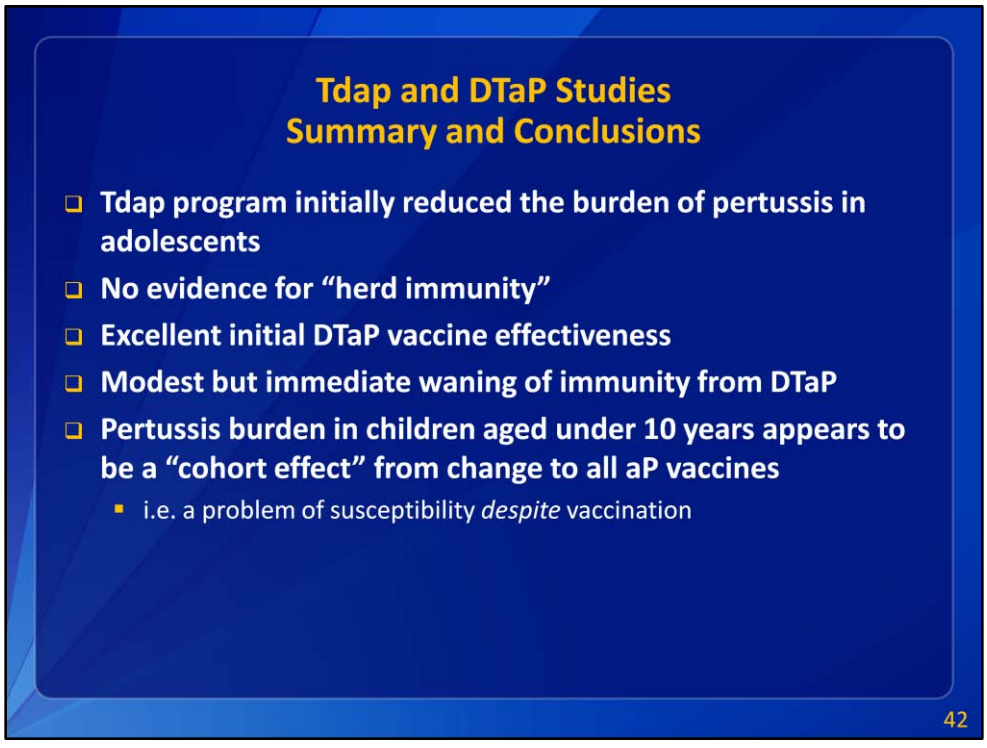
Overall VE was found to be 88.7%. This is the overall or essentially "average" vaccine effectiveness over the period kids are 4 to 10 years of age. This is consistent with the estimates from pre-licensure trials of the currently used vaccines.

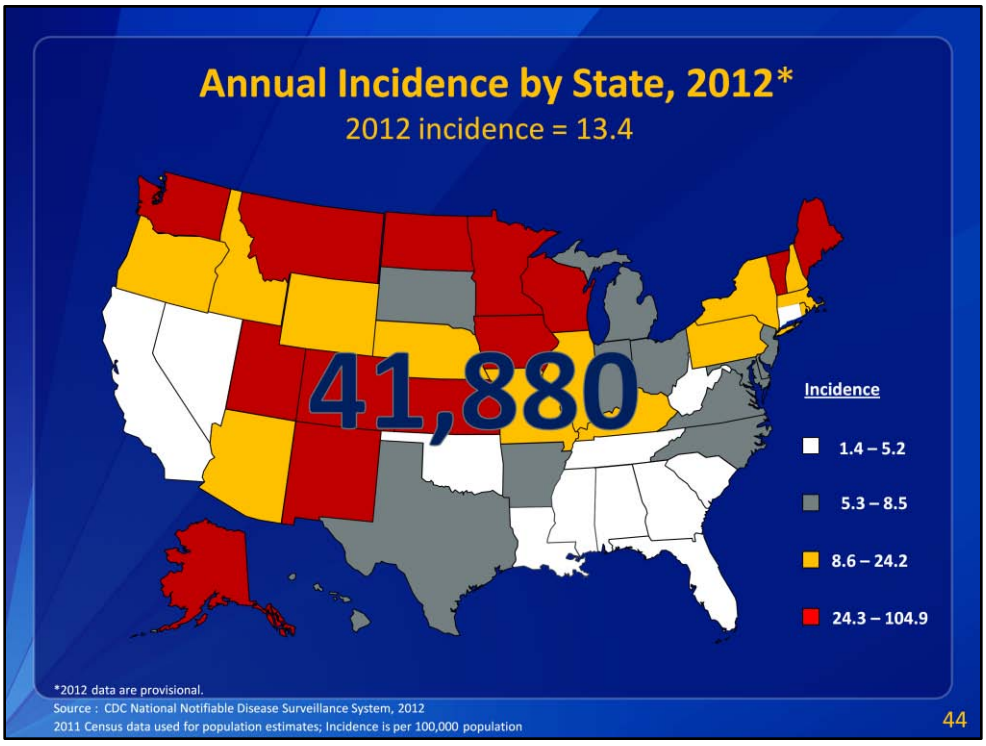


But we found that VE did wane over time. VE was 98% during the first year following the 5th dose. Each year out resulted in a modest decrease in VE and by 5 or more years from the 5th dose, VE had fallen to 71%. This represents a 27% decline in vaccine effectiveness.



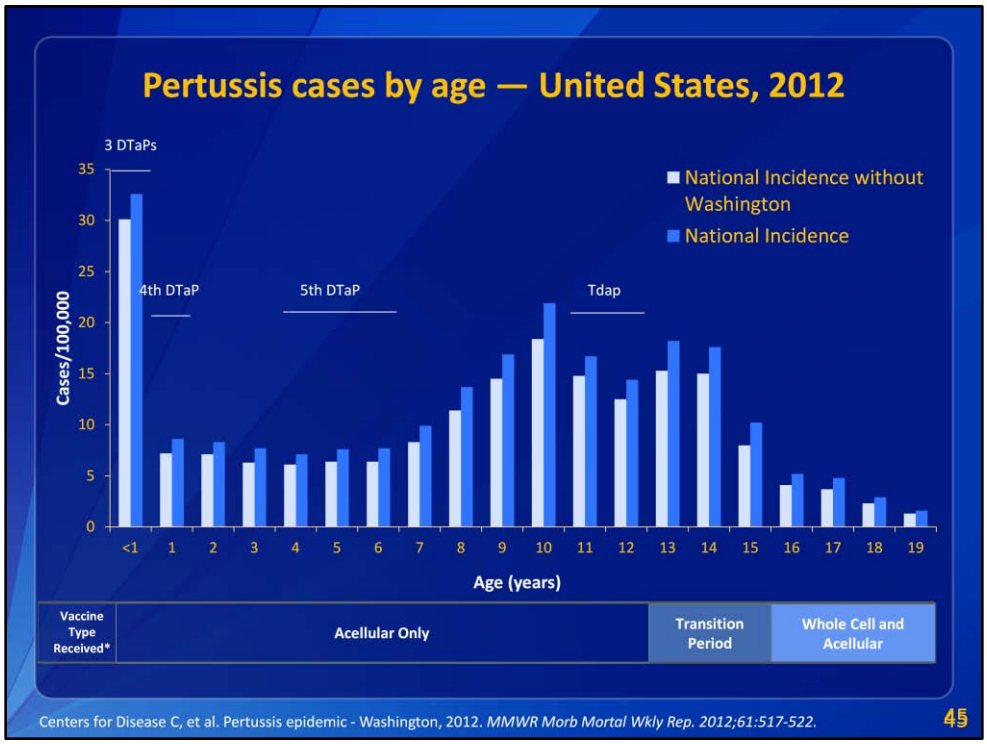
So what have we learned from these studies? The Tdap program initially reduced the burden of pertussis in adolescents, but we have no evidence of "herd immunity". DTaP offers excellent initial vaccine effectiveness, but it is followed by modest waning of immunity each year. The pertussis burden in children aged less than 10 years appears to be a "cohort effect" from a change to all acellular vaccines leading to a problem of susceptibility despite vaccination.

As I'm sure you're aware, 2012 was a very active year for pertussis across the U.S. And we continue to see changes in the epidemiology of disease.

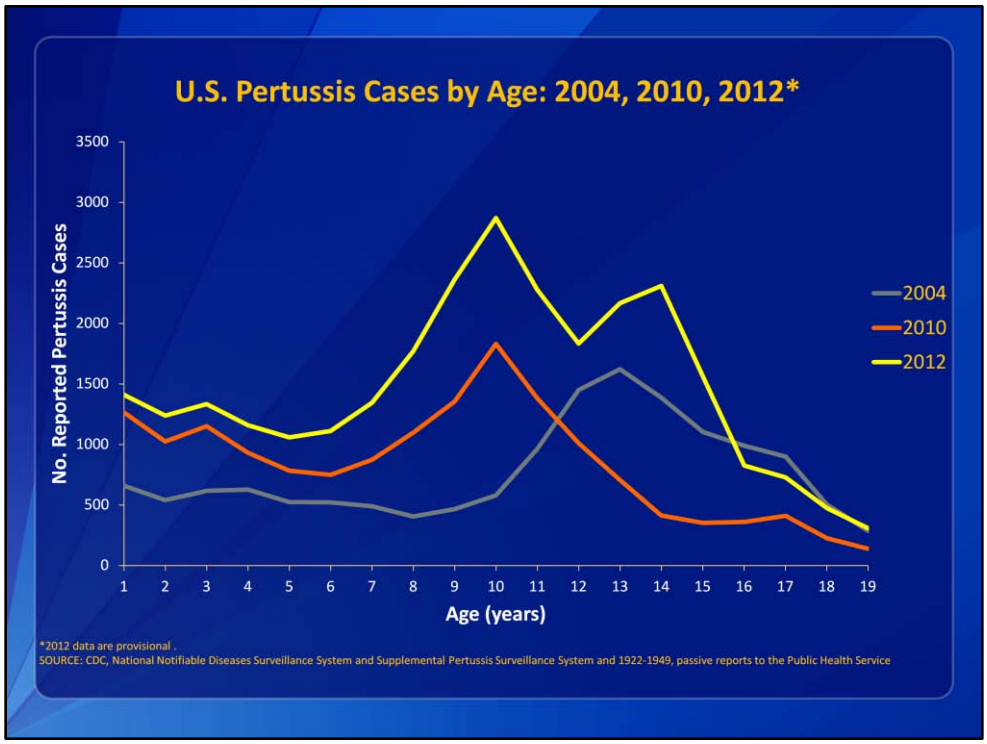


The provisional count for 2012 is over 41,000 cases reported to CDC, which exceeded the total number of cases reported during all of 2010, our last major peak in disease. In fact it is the highest number of reported cases since 1955.

Several states reported epidemic levels of pertussis disease in 2102 including Washington State.



In response to the historic number of cases, the Washington State Department of Health and CDC worked together this past year to analyze the pertussis activity in Washington. One new thing that emerged was a peak in disease reporting among 13 and 14 year olds (a high proportion of whom had received Tdap). When we looked at the national data, we saw a similar trend.



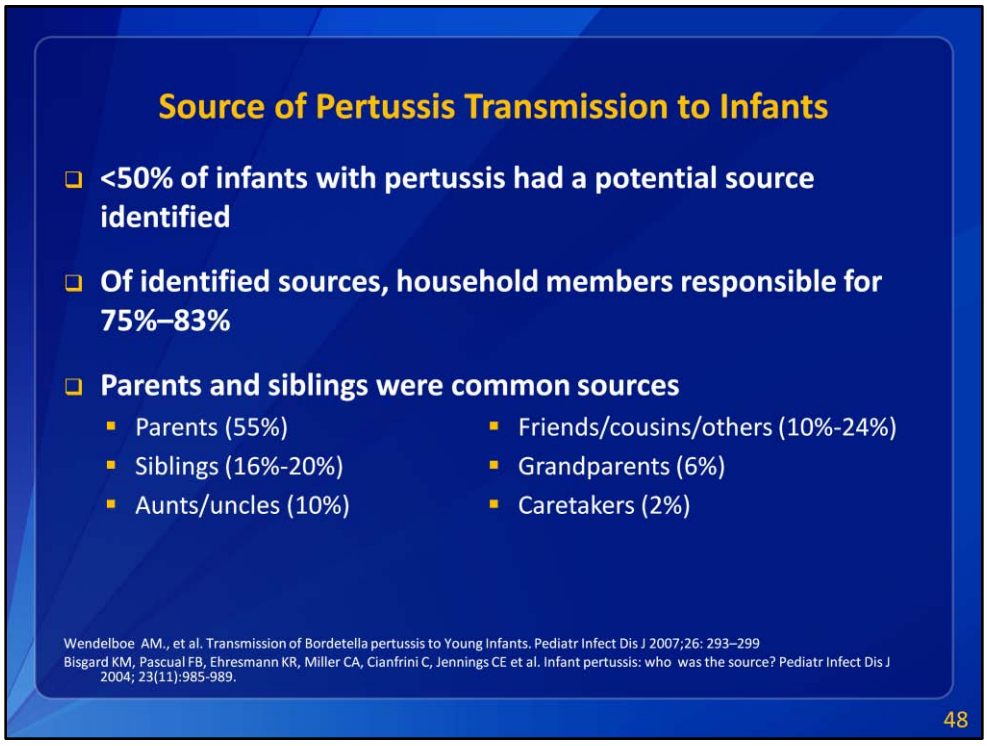
On this graph you can see reported U.S. pertussis cases by age and year during the last three national peaks (2004 in grey, 2010 in orange and 2010 in yellow).

In 2004 adolescents made up a large proportion of the reported cases nationwide. As you already heard, in response to this adolescent disease burden the Tdap booster was recommended for all adolescents and adults. Following the introduction of Tdap we saw a decline in adolescent cases, but an unexpected increase in 7 to 10 year old children who were the first to receive all acellular vaccines for their childhood series. During the 2010 peak, these 7 to 10 years olds had the highest reported case counts.

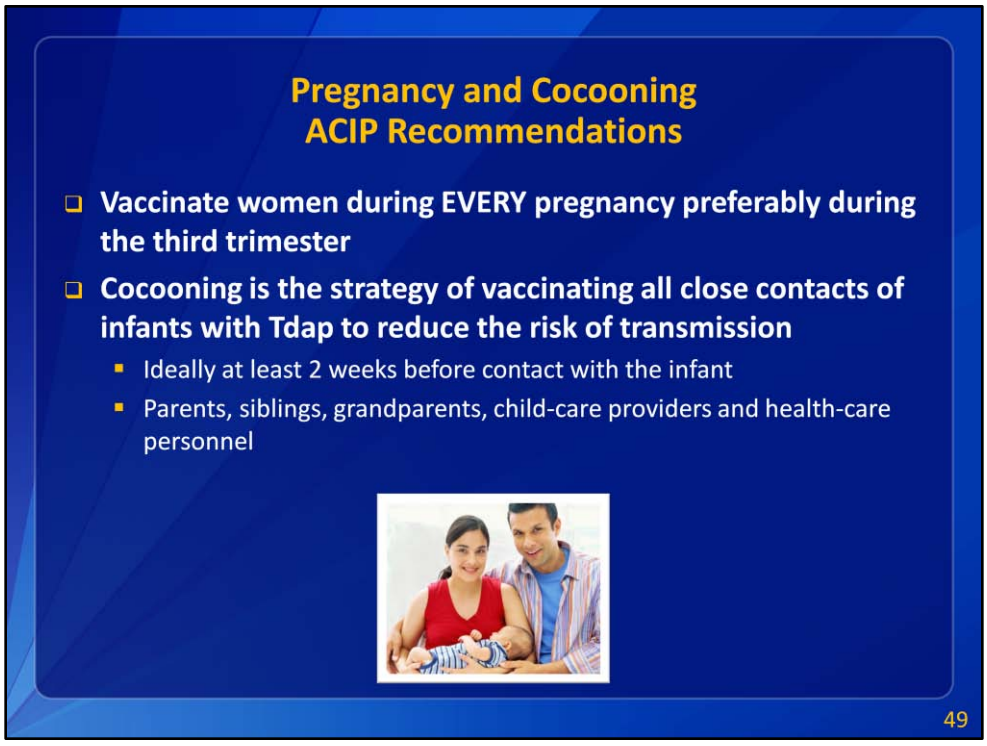
Now in 2012, case counts continued to be elevated among children 7-10 years, but now we see elevated numbers among adolescents aged 13 and 14, which has not been observed since the introduction of Tdap.

Emergence of disease among 13 and 14 year olds, many that did receive Tdap, emphasizes the importance of better understanding the effectiveness of Tdap, especially among children who were primed with acellular pertussis vaccines. CDC is currently working with Washington State Department of Health to assess how long Tdap is protecting adolescents following vaccination.

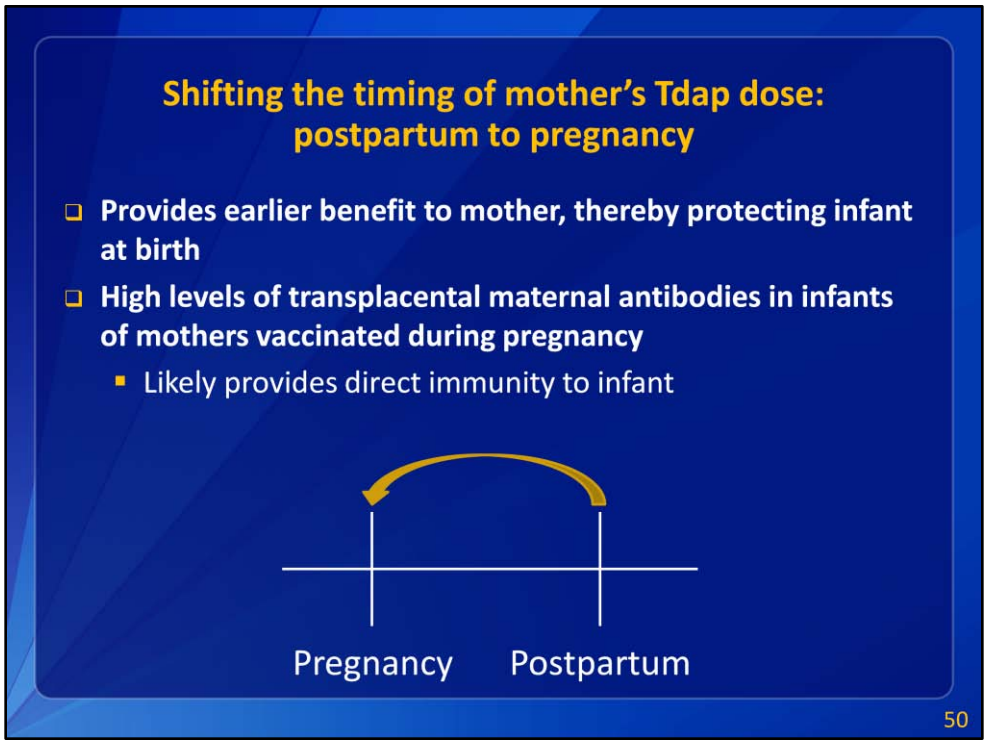
I want to highlight the importance of protecting infants.
90% of pertussis deaths occur in infants too young to be vaccinated; this is why it is so important to focus our prevention efforts on protecting infants.



Numerous studies have evaluated the source of pertussis transmission to infants. Of identified sources, household members were the source for 75% to 83% of the infant cases. Parents were most frequently identified, followed by siblings and other close relatives.



To protect infants, the Advisory Committee on Immunization Practices recommended cocooning in 2005 and vaccination of pregnant women in 2011. In Oct of 2102 , ACIP voted in favor of vaccination during every pregnancy. Pregnant women should be vaccinated with Tdap preferable during the third trimester.
Cocooning is the strategy of vaccinating all close contacts of infants with Tdap to reduce the risk of transmission. Ideally a close contact should be vaccinated at least 2 weeks before contact with the infant. The cocoon should include parents, siblings, grandparents, childcare providers and healthcare personnel.



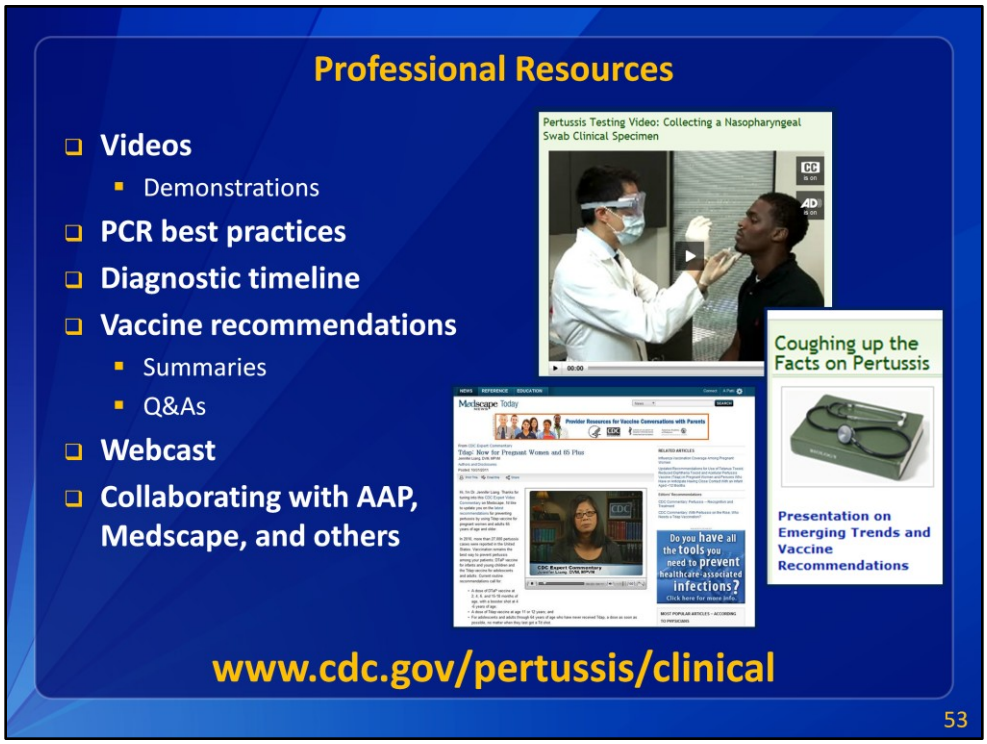
Vaccination during pregnancy is believed to be the most effective means of protecting infants during the most critical first few months of life. Firstly, vaccinating before infant birth provides earlier benefit to the mother, thereby indirectly protecting her infant at birth. Secondly, mothers vaccinated during pregnancy will provide high levels of transplacental maternal antibodies to her infant. These antibodies will likely provide direct immunity to the infant.

New data just released from a study in Australia found a 50% reduction in risk to the infant when mom was vaccinated during pregnancy.

Before I end I would like to highlight some of our communication efforts at CDC and point you to resources that are available for health providers and the public.

Our goals are to raise awareness among both providers and the general public about:
-- How serious and life-threatening pertussis can be in infants and the need to seek urgent medical care
-- The importance of getting vaccinated
-- And recognizing signs and symptoms

We want to encourage all providers to consider pertussis in the differential diagnosis of cough illness and make use of tests like PCR to help confirm results. Providers should remember to ask patients about infant encounters and recommend vaccination to every patient. Especially if they will have contact with an infant under 1 year of age.



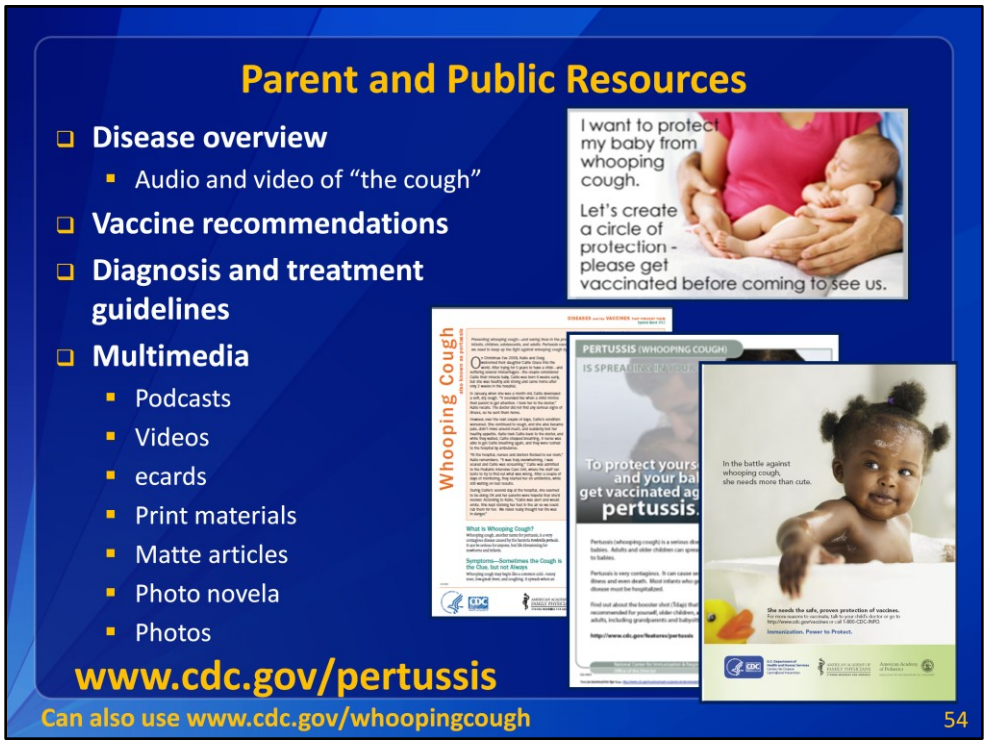
To support clinicians as pertussis re-emerges in the US, we have created a variety of materials.

This section on our website provides a detailed clinical overview of pertussis. Since proper specimen collection is necessary for testing, we've provided a section on those techniques and have swab and aspirate video demonstrations. As you have already heard, there's a best practices document to aid in avoiding contamination issues with specimen collection.

Since there are so many ACIP statements for pertussis vaccines, we've created a simplified chart covering the recommendations. There's also a Q&A for providers about implementing the maternal vaccination recommendation – going over timing, safety, breastfeeding and other questions.

We used an existing partnership with Medscape to tape a series of video commentaries reviewing vaccine recommendations, diagnostic challenges and recognition and treatment.

Lastly, we have a CDC webcast on pertussis and CE credits are available.



To help with outreach, we wanted to be sure you're aware of the variety of downloadable resources CDC has available for parents and the public. Partners can tailor these pieces for local distribution. There's a page housing a variety of multimedia tools, ranging from podcasts and ecards to posters and formatted articles. Print materials include in-depth and basic fact sheets on pertussis and posters. Lastly, there are some powerful photos of an infant being treated for pertussis.

Many of these materials are available for download in Spanish.

Web Resources

- **Provider Resources for Vaccine Conversations with Parents**
  - www.cdc.gov/vaccines/conversations
  - Materials created by CDC, AAP, and AAFP
- **Features/Syndicate**
  - www.cdc.gov/features/pertussis
  - www.cdc.gov/espanol/tosferina

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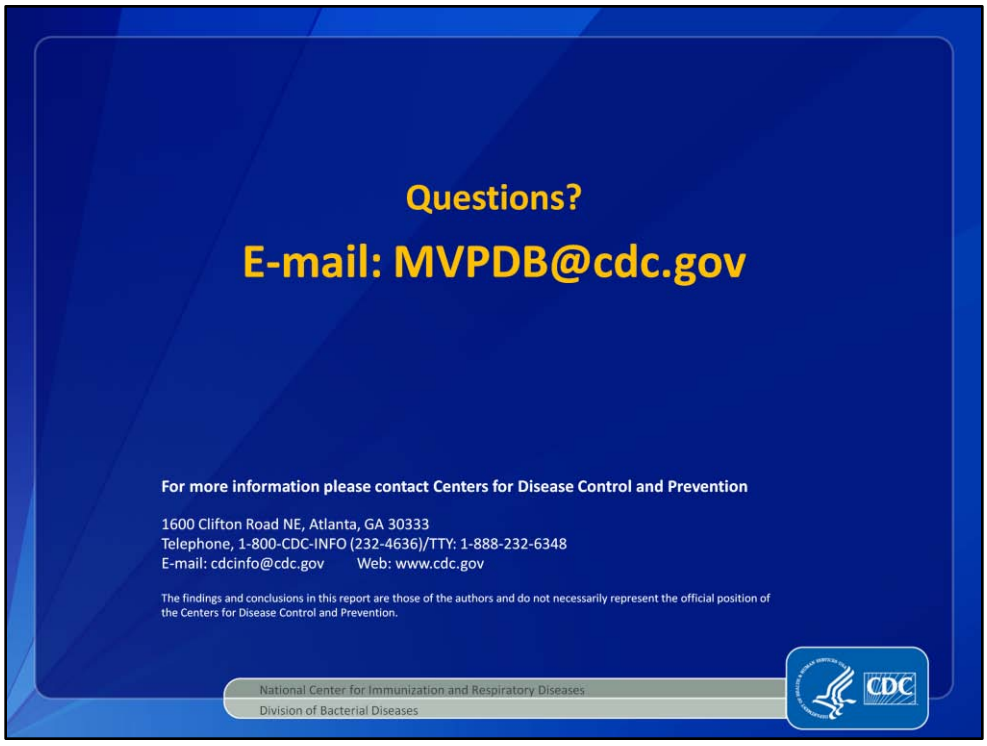
In addition to the pertussis site, you can find great provider resources for discussing vaccine issues with parents at the vaccines conversations site listed on the slide.

I wanted to make sure you were aware of the web features on pertussis. They provide a brief overview and then drive readers to the pertussis website and other helpful resources. Our features are syndicated so it's easy to have current CDC content on your website.

Now a few final thoughts. Pertussis continues to be a significant public health problem and vaccination remains our best prevention tool. No infant should die of pertussis and to meet this goal we need to improve Tdap coverage in adults, continue to remove barriers to vaccination of pregnant women, and implement cocooning where feasible. Maintaining high cover with DTaP during childhood is critical and we need to continue to evaluate and refine vaccination policy and prevention and control recommendations.



Thank you and I am happy to take questions, but if we run out of time you can send additional questions to the MVPDB email address listed on the screen.