Hello, my presentation will provide an overview of pertussis epidemiology in the United States.

I will start with a basic overview of pertussis including clinical characteristics. I will briefly touch on laboratory diagnosis for pertussis and some of its associated challenges. We will take a look at the current epidemiology including some of the epidemiological changes that have occurred over the last decade or so. I will review recent studies looking at the effectiveness of pertussis vaccines. I will provide an overview of recently detected molecular changes occurring within the population of Bordetella pertussis and data from the FDA's non human primate models. And most importantly will end on the importance of protecting infants from this serious disease.

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. 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. Pertussis is difficult to diagnose in this age group because it can be challenging to distinguish from other causes of cough illness and patients often present late in their course of illness when PCR 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 can 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 been the historic 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 same course is recommend for chemoprophylaxis to prevent disease in high risk contacts.

While there is limited evidence that antibiotics may provide moderate protection against pertussis disease if given prior to symptom onset, there are no data to indicate that widespread use of PEP among contacts effectively controls or limits the scope of pertussis outbreaks. Another important consideration is the overuse of antibiotics; CDC is engaged in actively promoting the judicious use of antibiotics among healthcare providers and parents. For these reasons, the primary objective of postexposure chemoprophylaxis is to prevent death and serious disease in those at highest risk.
Within families, secondary attack rates are very high, even when household contacts are current with immunizations. Accordingly, PEP should be provided to all household contacts of a pertussis case.
Given the substantial risk of pertussis to infants, 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. Furthermore, 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. These may include neonatal intensive care units, childcare settings, and maternity wards.
Please see the website on this slide for more details. The pertussis team at CDC is also available to discuss specific situations since we've learned there isn't a one size fits all approach to prevention and control.

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 reduce secondary transmission of pertussis. Respiratory etiquette and hand hygiene should be routinely encouraged.
How rigorously these recommendations are implemented, again, may depend on the setting and available resources. With waning immunity and undiagnosed asymptomatic infections, the effectiveness of some of these approaches at reducing the disease burden may be limited.

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

In this slide, nationally reported diagnostic test use for cases with a known lab result from 2006 to 2012 is shown. PCR has become the dominant test, the red line, used in approximately 45-80% of reported pertussis cases with associated lab results. Culture use has dwindled over time, with fewer than 5% of cases currently using this test. Nationwide, serology is used for about 15-20% of cases.

Laboratory confirmation of pertussis can be very challenging for several reasons. The stage of disease is an important factor impacting the clinical 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 may prevent isolation and inhibit PCR, and vaccination status may influence test results as well. Culture requires special media containing the antibiotic 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 is the lack of clinically validated and standardized tests.

A number of pseudo-pertussis outbreaks have been described as a result of falsely-positive PCR results, including ahospital outbreak in New Hampshire in 2006, and more recently community outbreaks in Jefferson County, NY and Durango, Colorado.

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 keyboards, 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.
A recent paper published in JCM further suggests that vaccine may become aerosolized during preparation and vaccine administration, possibly leading to further contamination of specimens or the anterior nares.

In response to these recent pseudo-outbreaks, CDC developed best practices 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.

Now we will look at the changing epidemiology of pertussis.

The CSTE case definition for pertussis changed in 2014. The current case definition includes a component for the clinical presentation, which requires at least 2 weeks of cough in addition to at least one symptom such as paroxysms, whoop, post-tussive vomiting, or apnea for those less than 1 year of age.
A probable case meets the clinical case definition but is not laboratory confirmed or epi-linked to a laboratory confirmed case. In addition, infants less than one year of age who have acute cough illness of any duration plus one clinical symptom and who are PCR positive or who had contact with a laboratory confirmed case of pertussis are considered probable cases.
Confirmed cases include those with culture positive results and cough of any duration, or those who meet the clinical case definition and who are PCR positive, or those who meet the clinical case definition and who are epi-linked to a laboratory confirmed case.

Starting in the late 1940s, the US began vaccinating with whole cell pertussis vaccines. In the 1990s, safer acellular vaccines became available in the US to replace the whole cell vaccine. In 1992 acellular vaccines were recommended for the 4th and 5th doses of the childhood series given at 15 through 18 months and 4 through 6 years of age, respectively. In 1997, DTaP was recommended for all 5 doses of the childhood series, including the priming doses given at 2, 4, and 6 months of age.
In 2005, two tetanus toxoid, reduced diphtheria toxoid and acellular pertussis, or Tdap vaccines, were licensed for use among adolescents and adults. The current recommendation is for a single dose of Tdap at 11 or 12 years of age. All adolescents and adults who did not receive Tdap should receive a dose as soon as feasible, including persons 65 years of age and older. Tdap can be administered regardless of the interval since the last dose of Td. Additionally, children 7 to 10 years of age that are not fully immunized should receive a single dose of Tdap.

Tdap is also now recommended for pregnant women and I'll talk more about these recommendations later in my presentation.

Licensure and widespread use of pertussis vaccines in the United States had a major impact on the reported number of cases. During the pre-vaccine era, the number of pertussis cases peaked with approximately 270,000 reported in the mid 1930s, and more than 10,000 deaths. Since the introduction of DTP vaccine in the late 1940s, the number of reported pertussis cases has fallen dramatically. However, despite this dramatic decrease, pertussis continues to be endemic in the United States and (looking at inset in upper right hand corner) the number of reported pertussis cases continues to peak every 3-4 years.
Increases in reported pertussis cases 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.

This uptick in the number of cases is occurring despite high levels of vaccination coverage among infants and adolescents. Vaccination coverage from the National Immunization Survey shows continued high DTaP coverage among 19-35 month olds, with little variability since 2004. Coverage for 3 or more doses is approximately 95%. Coverage with Tdap has been slowly increasing since vaccine introduction in 2005 and now is approximately 86% in adolescents, but Tdap uptake has been slow in adults with current estimates around 14% (all adults).

This map gives an overall picture of pertussis incidence across the US, with red representing the highest incidence states. This depicts 2012, when we had over 48,000 cases reported which was the largest number reported in the US in over 55 years. As you can see here, incidence varies considerably by state. While some of this is likely driven by differences in case recognition and reporting, we do know that there is variability in when states experience peaks in disease.

Overall incidence for 2013 was 9.1 per 100,000. When we look at 2013, the overall incidence and number of reported cases was about 40% lower. However, about a quarter of states reported increases in 2013 compared to 2012. While we saw less activity overall in 2013, we did see increased incidence in some areas that were active back in 2010.

In looking at pertussis deaths by age group we see that 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.

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 a remarkable increase in teens during 2012, which had not been seen since the introduction of Tdap. The next few slides will provide a closer look at some of these newer age-related trends.

Here is a breakdown of cases by age in 2004, the first large epidemic peak following vaccine introduction. On the bottom the bar shows the ages for the cohorts that received acellular versus whole cell vaccines for at least their first three priming doses. Based on this epidemiology, Tdap was recommended in 2005 for 11 or 12 year olds to address the apparent waning of immunity following the whole cell childhood schedule.

Moving to our next significant epidemic peak in 2010, we see a significant shift in the age related epidemiology. Disease in teens seems to be well controlled in the whole cell primed cohorts with the introduction of Tdap, but now we have a stair step increase starting at age 7 through age 10. This raised concern that we may be seeing early waning in children who received aP vaccines as children.

We move onto 2012, another peak year for pertussis. What is notable here is that there was a new peak in disease among 13-14 year olds. This was concerning for a couple of reasons: one, most of these kids had been vaccinated with Tdap, and two, the timing of disease also coincided with the aging of the acellular cohort.

In 2013, the trends have continued, and the increase in cases now includes 15 years olds. So as the acellular cohort ages, we are observing apparent issues with durability of protection from acellular pertussis vaccines –and we are seeing higher burden of disease among adolescents.

These cohort driven trends in disease prompted us to conduct some large-scale evaluations of vaccine effectiveness to quantify the waning problem.

Many of you have seen this data before. 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. 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.

There have been similar observations of waning of the Tdap vaccine. Separately, CDC and Wisconsin evaluated Tdap vaccine effectiveness and duration of protection among 2 separate populations during the 2012 pertussis epidemic. Despite the methodologies being different, both studies demonstrated substantial waning of the protection over time.
We collaborated with the Washington State Department of Health to conduct a study looking at Tdap vaccine effectiveness and duration of protection. The initial effectiveness within 12 months of Tdap vaccination was 73%. Following this, the effectiveness declined substantially. Between 2 and 4 years post-vaccination, the VE was only 34%. Again this waning in protection is consistent with the observed epidemiology.
Wisconsin published results that were very similar to our findings.

In summary, we found high initial DTaP vaccine effectiveness, but with modest and immediate waning of immunity. Tdap VE in adolescents vaccinated fully with acellular vaccines shows modest immediate effectiveness but with substantial and rapid waning, consistent with observed epidemiology. These results strongly suggest that the impact of additional doses of Tdap will be limited and unlikely to further reduce the burden of disease. These results with cost-effectiveness data led ACIP to not recommend additional doses of Tdap for adolescents and adults.

Considerable attention has been placed on genetic changes in the population of circulating
B. pertussis and many have questioned whether these changes have led to increased virulence or a pathogen that is evading vaccine immunity. An example of this is the loss of pertactin. Pertactin is a key immunogen in all currently licensed pertussis vaccines in the US.

The pertussis bacterium is composed of numerous antigenic and biologically active components and some important virulence factors are listed here. The role and the importance of each for infection and invasion of host defenses are not well understood. The first four listed here are the ones included in the vaccines. In the United States pertussis toxin, FHA and pertactin are in all current vaccine formulations, fimbriae is not always included. There is some evidence to suggest that the pertactin protein may play a role in adherence to the respiratory track and possibly, resisting neutrophil-mediated clearance.

Prompted by recent publications from other countries noting the emergence of pertactin-deficient B. pertussis, the CDC pertussis laboratory set out to look at our isolate collection to see if they could possibly identify the timing

of the emergence of this pertactin-deficiency in the US, as well as determine what the prevalence of this change is at a national level.
The earliest pertactin-deficient mutant was seen in 1994; the next mutants were seen in 2010. In 2012, 85% of isolates were pertactin-deficient and in 2014, 100% have lacked the protein.

Interestingly, it wasn't a single mutation that led to pertactin deficiency. At least 10 different mutations were identified in the population of B. Pertussis that resulted in the loss of pertactin production. These included insertions, deletions, stop codons, and point insertions.

To determine the clinical and epidemiological significance of pertactin-deficient B. pertussis. We used isolates and routinely collected case investigational data collected from our 6 U.S. Enhanced Pertussis Surveillance sites, Oregon, Minnesota, New York, Connecticut, Colorado and New Mexico along with a large number of isolates from Washington and Vermont. Both of which experienced epidemic levels of disease in 2012.
Pertactin variants were fully characterized using PCR amplification, sequencing, Western blots and/or ELISA.
85% of isolates were pertactin-deficient and all states had a high proportion of pertactin-deficient isolates. The proportion of case patients reporting pertussis symptoms was similar by pertactin status, except more patients without pertactin-deficiency reported apnea.
Vaccinated patients had higher odds of having PRN deficient B. pertussis as compared to unvaccinated patients. The odds ratio was 3.2 and when vaccinated patients were restricted to those up-to-date with vaccination the odds ratio increased to 3.7.

Our findings of an approximate 4-fold greater odds of having pertactin-deficient B. pertussis when up-to-date with vaccinations compared to unvaccinated is the first evidence for a possible selective advantage of pertactin-deficient strains.
The large number of mutations identified by the pertussis laboratory suggests that vaccine pressure may have played a significant role in the emergence of pertactin-deficient strains.
The absence of substantial clinical differences by pertactin status was also recently reported in France in infants, however our finding for apnea warrants further study using clinical data with greater sensitivity and specificity.
Finally, I'd like to mention our next steps. While the studies I've mentioned here provide evidence for a likely selective advantage of pertactin-deficient strains, we are unable to determine the impact of pertactin-deficiency on vaccine effectiveness. To do this, this we would need to conduct a formal study looking at differences in vaccine effectiveness by pertactin status. We are currently collaborating with Vermont Department of Health on a case-control evaluation to assess for any potential impact on vaccine effectiveness.

Before we conclude I would like to highlight some novel work from the FDA.

The FDA has recently developed a non human primate model of pertussis using baboons.
This represents an important step forward as baboons offer the most human-like model for pertussis. In a recent paper published in 2013 they reported that acellular vaccine effectively prevented baboons from developing symptomatic pertussis in the short-term.
However, acellular vaccinated animals were infected, meaning colonized with the bacteria, and transmitted the bacteria to other baboons that they were cohoused with and did not clear infection faster than naïve primates.
FDA reported significant differences in T-cell immunity, with a mismatch between acellular derived immunity as compared to whole cell and infection.

Before concluding I want to emphasize the importance of vaccination strategies aimed at 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.

More recently, studies have identified siblings as the most common source of transmission. Using CDC's enhanced pertussis surveillance data collected between 2006 and 2013, 44% had an identified source of infection. Of those 65-84% were classified as a family member. During this period we've seen an emergence of siblings as the major reservoir of infection.

Given the resurgence in pertussis with widespread community transmission, we know we can't prevent every case of disease. But we can focus on protecting high risk infants, especially those that are too young to be directly protected by childhood pertussis vaccines.
To protect infants, the ACIP currently recommends two strategies: cocooning and vaccination during pregnancy. Cocooning is the strategy of vaccinating all close contacts of infants to reduce disease transmission. Ideally, infant close contacts should be vaccinated at least 2 weeks before infant contact. Although cocooning has been recommended since the introduction of Tdap in the U.S., a number of challenges and barriers continue to impact the implementation of cocooning programs and the uptake of Tdap. Additionally, conflicting evidence exists on the effectiveness of this strategy.
Vaccination of pregnant women was recommended by ACIP in 2011, and was expanded to include a dose during EVERY pregnancy in Oct of 2012 . Pregnant women should be vaccinated with Tdap preferably between 27 and 36 weeks gestation in order to provide the highest concentration of maternal antibodies for passive transfer to the infant before birth.

Moving forward, the emphasis will be on vaccination during pregnancy as this is believed to be the most effective means of protecting infants during those first few critical months of life. The benefits of vaccinating during pregnancy are really two-fold. First of all, 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 during the first few critical months of life.

So how are we doing in terms of Tdap coverage during pregnancy? Well, the recommendation is still relatively new but estimates from an internet panel survey that looked at Tdap and influenza vaccinations administered to pregnant women during flu season shows that approximately 6.2% of women received Tdap during pregnancy during the 2012-2013 flu season.
2012 coverage data are also available from the Vaccine Safety Datalink network, a collaborative effort between CDC and 9 managed care organizations. Data from VSD showed Tdap pregnancy coverage at 17.1% in 2011 and 13.7% in 2012. Because coverage is likely to be higher within managed care organizations, true coverage is probably somewhere between these estimates.

In summary, the resurgence of pertussis in the U.S. is real and probably here to stay. Waning immunity from acellular vaccines is likely a large contributor to this resurgence, but the contribution of pertactin-deficient strains to this increasing burden is not currently understood. Kids primed with acellular vaccines have a higher risk of pertussis. Acellular vaccines may not prevent infection and the significance of silent transmission is unclear. Much remains to be done on the microbiologic and immunologic basis for vaccine effectiveness and failure.

Although pertussis vaccines aren't perfect, vaccination remains our best prevention tool and we should continue to maintain high levels of DTaP coverage among children, sustain Tdap coverage in adolescents and increase Tdap coverage in adults and pregnant women.

Our biggest goal is to protect infants. No infant should die of pertussis and to accomplish this, we need to continue to work to remove barriers to vaccination of pregnant women and to focus chemoprophylaxis efforts on high risk individuals, especially infants.
And finally, you can really consider a baby's first dose of pertussis vaccine as the dose its mother gets during pregnancy.

I invite you to visit the CDC website for more information about pertussis and resources developed for public health workers, healthcare workers and laboratorians.

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