Vaccine-Preventable Diseases, Session 1
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SLIDE 1 TITLE

SLIDE 2

Hello. Welcome to Unit 10, Vaccine-Preventable Diseases. My name is Kristin Sullivan and I am the vaccine preventable disease epidemiologist in the Communicable Disease Branch with the North Carolina Division of Public Health.

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The vaccine-preventable disease unit will be divided into two sessions.

Session 1 will provide an introduction to vaccine-preventable disease, or VPDs as they are commonly referred to, followed by an overview of the clinical and epidemiological features of pertussis, pertussis vaccine benefits and limitations, and an introduction to pertussis case investigations.

Session 2 will cover the other VPDs listed here and tips for reporting VPDs in NC EDSS.

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After viewing this VPD session, you should be able to:

•recognize the public health significance of vaccines and their associated diseases,

•describe the epidemiology of pertussis and its changing trends, and

•describe the basic steps in a pertussis case investigation.

SLIDE 5 So now let's begin the first session of the unit.

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Traditionally, vaccine-preventable diseases are thought of as those that are prevented by routine childhood immunizations, such as measles, pertussis and polio. However, the number of these diseases for which we now have available vaccines is quite large. Listed here are 26 diseases for which a licensed vaccine exists.

Vaccines are generally divided into two categories – those that are routinely recommended and those that are recommended only for certain groups or situations. [CLICK] The diseases highlighted here all have vaccines that are routinely recommended as part of the current immunization schedule for children and adolescents. Shingles vaccine is not highlighted, but it is routinely recommended for all adults age 60 and over.

Vaccines to prevent the other diseases listed here are considered non-routine. They are only recommended for persons who have been exposed to the disease or for groups who might expect to have a higher risk of exposure to the disease including travelers, individuals with certain occupational exposures or military personnel, to name a few.

[CLICK] In this unit, we are going to cover these 8 diseases with vaccines that are routinely recommended as part of the US childhood vaccination program. For each of these diseases, we will discuss the disease, the vaccine and the public health impact of the illness.

Influenza, hepatitis A and B and the invasive bacterial diseases, including *Haemophilus influenza* type b, meningococcal and pneumococcal disease, are covered elsewhere in this course.

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As you probably know, vaccines have been one of the greatest public health achievements of the 20th century and as a result, vaccine-preventable disease levels are at or near record lows. As you can see from this table, comparing 20th century annual morbidity with reported cases in the United States in 2011, we have had over a 90% decrease in annual morbidity for all diseases listed. Smallpox has been eradicated world-wide and polio, measles and rubella have been eliminated from the United States, however cases of measles continue to be imported. Although pertussis has increased in recent years, the vaccine has still led to a 91% decrease in morbidity compared to the pre-vaccine era. It is evident from this success that vaccines are one of the most effective tools in preventing these diseases.

However, to sustain these record low numbers, we need to remain vigilant about maintaining high immunization rates. Some vaccine-preventable diseases, such as pertussis, are still endemic here in the United States, and are only controlled because of high immunization rates.

Other diseases which are uncommon or even eliminated here in the United States remain poorly controlled around the world and still remain a risk. With the relative ease of global travel, maintaining high immunization rates is essential. Outbreaks can and do occur when unvaccinated travelers return to or visit the United States and introduce these pathogens into communities with low vaccination rates.

As you may know, this very scenario occurred in the spring of 2013 here in North Carolina when an unvaccinated traveler returned from India and transmitted measles to his unvaccinated community contacts, resulting in the first outbreak of measles in almost 25 years in our state.

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Measles outbreaks like the one here in North Carolina are not uncommon in the United States. Although measles was declared eliminated in 2000, cases are regularly imported. That is because measles is highly infectious and remains one of the most poorly controlled VPDs around the world. In the map shown here, the dark shading indicates areas where measles is still prevalent, including Asia, Africa and Western Europe.

Measles still remains a leading cause of death in children around the world. In 2011, there were an estimated 350,000 cases of measles and 140,000 associated deaths globally.

Cases of measles occurring here in the United States are almost exclusively a result of import or import-associated cases in unvaccinated individuals. Over 200 measles cases were reported during 2011, the highest number since elimination. Ninety percent of the cases were associated with importations and 86% of cases were either unvaccinated or had unknown vaccination status. This same pattern has been seen in US measles cases reported since that time.

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Measles is not the only disease where the threat of importation remains. Other VPDs are also still being transmitted world-wide, take polio for example.

A global initiative is underway to eradicate polio; however the disease remains endemic in three countries – Afghanistan, Nigeria and Pakistan. As shown in the recent CDC travel alert pictured here, cases of polio have also now spread from these countries to other areas, including recent outbreaks in Syria.

Rubella, another disease eliminated from the United States, has caused outbreaks in North Carolina as recently as 1996 and is currently causing outbreaks in Japan and Poland with over 50,000 cases in these two countries alone.

So, although many VPDs are uncommon in the United States, a threat of introduction still exists. Maintaining high immunization rates, early detection and rapid public health response are all necessary to prevent outbreaks of these diseases in our communities.

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Fortunately, our vaccination rates remain relatively high.

According to data shown here from the 2012 National Immunization Survey, MMR coverage among children aged 19-35 months in North Carolina was just under 90%. DTaP coverage was approximately 86% and ¾ of children had completed the combined series of DTaP, polio, MMR, *Haemophilus influenzae* type B, hepatitis B, varicella and pneumococcal vaccine. Among adolescents, 93% were fully-immunized against measles, 87% had received a Tdap and almost 80% reported immunity to varicella either through disease or vaccination.

Although these rates are high, there is still room for improvement. With some diseases, even a small proportion of susceptible individuals can sustain continued transmission and lead to outbreaks. In addition, persons with religious or philosophical objections to vaccination tend to congregate both geographically and socially, resulting in “pockets” of unvaccinated individuals; a disease can be easily transmitted in such a setting, much like we saw in the 2013 measles outbreak here in North Carolina.

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You have already learned about the importance of public health surveillance in a previous unit.

Surveillance data for VPDs is used for the same reasons as all other diseases, such as detecting outbreaks, measuring the burden of a disease, monitoring trends and guiding public health policy.

For VPDs, surveillance data are also used to document and monitor impact of vaccination program on disease incidence, morbidity and mortality. This is especially important after the introduction of new vaccines or changes to vaccine recommendations.

VPD surveillance will also evaluate the effectiveness of prevention strategies, including monitoring disease elimination.

It is also important to evaluate vaccine effectiveness under conditions of routine use. Vaccine efficacy, a measure of effectiveness under optimal conditions, can differ from real-world use. Data can be used to determine if outbreaks are a result of 'vaccine failure' or 'failure to vaccinate.'

From all of this information, immunization policies can be developed and adapted.

And surveillance data can also be used to inform the need for future vaccines and their development.

Because of this, it is very important to collect information about vaccination status for all cases that are suspected of having a VPD.

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Vaccination status is essential to collect for surveillance purposes, but it also is necessary to inform decisions about case investigations.

When investigating a suspected case, it is important to consider how the vaccination status of a patient might affect the likelihood that he or she has the disease in question, how lab results can be interpreted and whether being vaccinated might alter the clinical picture of the disease.

Consider measles for example. Vaccine effectiveness for 2 doses of MMR vaccine is 99% and immunity is not believed to decrease over time. Based on this information, a patient who has received 2 doses of vaccine is much less likely to have the disease. Now consider lab results. The preferred method of diagnosis for measles is serological testing of IgM levels. This test is straightforward in unvaccinated individuals, however in vaccinated persons, this test is difficult to interpret and results need to be carefully reviewed. And in many cases cannot be used to rule out the diagnosis of measles. Lastly, the clinical picture. Measles is a fairly well-defined illness with a typical presentation in unvaccinated individuals. However, as I mentioned, measles in fully vaccinated individuals is uncommon, but it does occur. In these persons, presentation of the disease may

be modified – for example, the fever may not be as high and some of the classic symptoms (such as runny nose or cough) may not be present.

Now take for example, pertussis. Unlike measles, vaccine effectiveness is not quite as high and vaccine immunity to pertussis does decrease over time. So, when assessing the likelihood of illness in a vaccinated person, vaccination status does not factor in as strongly as it would with a disease like measles. Lab results for pertussis are also less likely to be affected by vaccination status, since PCR and culture are most often used.

So, when investigating a case, knowing vaccination status is critical when assessing and interpreting the clinical and epidemiological features and the diagnostic results of a suspected case.

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Here are some questions you might consider asking when investigating a suspected case of a vaccine preventable disease. Most are questions you would routinely ask when investigating any suspected diseases.

Collecting enough clinical and laboratory testing information to determine if the case meets the case definition is essential. [CLICK] Inquiring about other explanations for the illness that the health care provider may be considering is also important.

Aside from clinical information, epidemiological information is important, especially when the suspected disease is not one that is common. As I mentioned, knowing the vaccination status of a patient is important for many reasons. However, knowing the immune status of the patient is not limited to receipt of vaccine. [CLICK] Depending on the disease you are investigating, birth year, serological testing and a history of disease may also be evidence of immunity. So, be sure to include this information when determining immune status. Asking about recent travel and contact with travelers may identify a potential source of exposure and give additional evidence to support the likelihood of disease, as will identifying contacts with similar symptoms.

Lastly, more likely epidemiological explanations for illness must be considered. For example, you may learn in the course of investigating a suspected measles case with a positive IgM that the child attends a day care in which parvovirus is circulating. This may give some indication that the results of the IgM testing may be falsely positive and are more likely attributed to a parvovirus infection.

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In summary, even though VPDs are at record lows here in the United States, they are still a threat to public health both nationally and globally. Maintaining high immunization rates will be crucial in ensuring these diseases remain at low levels.

When investigating cases of suspected vaccine preventable diseases, knowing the vaccination status is important for providing surveillance data to monitor the impact and effectiveness of vaccines, and also for accurately interpreting epidemiological, clinical and laboratory findings of suspected cases.

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So I would like to shift gears now and begin the discussions of the specific VPDs I have already mentioned more generally. The remainder of this session will cover pertussis and the second session will cover the remaining 7 diseases.

Pertussis generally commands an extended discussion because of its relatively high incidence and its somewhat complex epidemiology and public health response. In this session, I will discuss the clinical and epidemiological features of the disease, the benefits and limitations of its vaccine and key steps in case investigations.

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You may have noticed when I talked about this table earlier that although we have made impressive strides in controlling pertussis in the United States, it remains at much higher incidence than the other VPDs. [CLICK] Unfortunately, the 18,719 reported cases in 2011 do not accurately reflect our current burden of disease in the United States. Provisional data from 2012 indicate that we had close to 50,000 cases of pertussis, the highest number of cases in over 50 years.

So, unlike some of the VPDs that will be discussed in the next session that are quite rare, pertussis is a common disease that you are likely to encounter as a communicable disease nurse.

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Part of the reason that pertussis is difficult to control is that it is a highly contagious respiratory infection. It is spread from person to person through droplets from a cough or sneeze or by direct contact with respiratory secretions.

It is so infectious, that in households with susceptible individuals, over 80% will become infected. Compare that to influenza, which is only around 30%.

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Bordetella pertussis is the bacterium that causes pertussis. It is a fastidious organism and requires a complex set of nutritional requirements for growth. This has implications for the diagnosis that I will discuss later.

Pertussis is primarily a toxin-mediated disease. The bacteria cause disease by attaching to the cilia in the upper respiratory tract. It is here that they release toxins that paralyze the cilia, and cause inflammation of the respiratory tract making the clearing of secretions difficult for infected individuals.

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As I mentioned, pertussis is spread from person to person through droplets, either from coughing or sneezing or through direct contact with secretions.

Once exposed to pertussis, a person will generally develop symptoms within a week to 10 days, but it can be as short as 4 days to as many as 21 days. And, in rare circumstances, up to 42 days.

Persons with pertussis are infectious from the start of symptoms through 3 weeks of cough, or if treated, through 5 days of appropriate antibiotic treatment.

Immunity following infection with *Bordetella pertussis* is not permanent. Some observational studies suggest that pertussis infection will provide immunity for 4-20 years (http://www.cdc.gov/pertussis/about/prevention.html).

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Before discussing the clinical features of pertussis, I wanted to review a few terms that are often associated with the disease.

First, a paroxysmal cough is sudden, uncontrollable 'fit' of coughing. One cough will follow another in rapid succession without a break.

Following one of these fits of coughing, the patient may gasp for air, which can sometimes result in a high-pitched noise or 'whooping' sound.

Apnea is the transient cessation of respiration or a prolonged period of breathlessness. Apnea is most commonly associated with infant pertussis.

And, lastly, posttussive vomiting is vomiting that occurs after a paroxysmal coughing episode.

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The clinical course of pertussis is divided into 3 stages.

The first is the catarrhal stage. This phase generally begins with the gradual onset of runny nose, sneezing and low-grade fever with a mild, occasional cough, similar to the common cold. Unfortunately, unless a patient has had a known exposure to pertussis, there are few clues to distinguish pertussis from other illnesses at this point. This stage can last from 1-2 weeks and is the period during which infected persons are most contagious.

The cough gradually becomes more severe and the second, or paroxysmal stage, begins.

The paroxysmal stage is characterized, as you might guess, by the onset of paroxysmal coughing. The paroxysmal stage can be quite long with paroxysms increasing in frequency during the first 1-2 weeks and then remaining stable for 2-3 weeks. During this time, a patient is likely to average 15 attacks in a 24 hour period, with many occurring at night. It is during this stage that pertussis is usually suspected. Other

symptoms commonly associated with pertussis, such as whoop, apnea, cyanosis and posttussive vomiting may also be present at this time.

A gradual recovery begins during the convalescent stage and the coughing fits become less frequent. Secondary infections are most likely to occur during this stage. The convalescent stage can last weeks to months. However, paroxysms can recur with later respiratory infections for many months after the onset of pertussis.

These stages are considered the classic presentation of pertussis; however, it is important to note that presentation will vary with age and immune status.

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Pertussis can cause serious and potentially life-threatening complications - most often in infants and young children who are not fully vaccinated.

Infants are at highest risk of complications and death from pertussis. From 2004 – 2008, 111 infant deaths were reported, with 83% being in infants less than 3 months old. In infants who get the disease, more than half are hospitalized. Hospitalization is most common in infants younger than 6 months of age who have not received 3 doses of vaccine and who are not yet fully protected. Hospitalized infants are reported to have apnea, pneumonia, seizures and 1% of them will die.

Secondary bacterial pneumonia is the most common complication in both infants and other age groups.

Adolescents and adults can also develop complications from pertussis, but they are usually less severe, especially in those who have been vaccinated. Hospitalizations and pneumonia occur, but are less frequent. More commonly, weight loss, urinary incontinence, syncope and rib fractures are reported.

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Let's take a moment to watch this short video of an infant with pertussis.

[CLICK]

You can see the difficulty the infant is having breathing and you can hear her whooping after each coughing episode.

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Unlike the older infant in the video, many infants often do not have some of these classic pertussis symptoms.

Infants who present with pertussis frequently have atypical symptoms. The catarrhal stage is often absent and cough can be minimal or absent all together.

Whoop is infrequently seen in infants because they lack the strength to make this noise.

Apnea is a commonly reported symptom, and sometimes the only symptom. Seizures can accompany apnea.

And infants will often sneeze, gag and vomit.

Because of these atypical symptoms, capturing infants through our current surveillance system can be challenging and their true burden of disease is likely much higher.

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Like infants, pertussis in vaccinated individuals can also be atypical.

Vaccinated children, adolescents and adults often have milder disease than infants and young children; however there is a wide spectrum of presentation. As I mentioned, asymptomatic infections can occur, although they are thought to be rare. Disease can be limited to a mild cough or, cases can have prolonged cough with classic presentation.

Like infants, whoop is uncommon in vaccinated individuals.

However, all cases on the spectrum can still transmit disease and are often the source to infants. Household members account for about 80% of infections in infants.

Cases of pertussis, especially those with non-classic presentation, may go undiagnosed even after multiple medical visits and evaluations.

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Let's now look at pertussis trends over the last century in the United States. This graph shows the number of reported pertussis cases in the United States from 1922-2012.

First, you might notice that pertussis is cyclical in nature with peaks occurring every 3-5 years. The reasons for this are not fully understood, but could possibly be associated with an increase in the number of susceptible persons accumulating following peak years.

What is most apparent in this slide is that following the introduction of the whole cell pertussis vaccine, DTP, in the 1940s you can see that there was a dramatic decrease in the number of cases. However, in the 1980s pertussis began to increase gradually and then, over the last 10 years, began to increase rather dramatically. By 2012, we saw the highest number of cases nationally in more than 50 years with over 48,000 cases.

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North Carolina has also seen this rise in the number of cases over the last 20 years. In 2012, we had a record number of 626 cases – roughly twice as much as any year in the previous 20.

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This graph shows the reported incidence of pertussis by age group in the United States from 1990-2012.

The pink line, representing infants less than 1 year old, is clearly and dramatically different from other age groups. Infants, our age group at highest risk of severe outcomes from the disease, also have the highest incidence of disease of any age group by far.

What is interesting to note on this graph is the shift in burden of disease after the mid-2000s. In the years surrounding 2005, you can see that the 11-19 year age group (the yellow line) had the 2nd highest incidence of disease. As you increase in year, you can see that around 2007 the incidence in the 7-10 year age group (the orange line) begins to rise and takes over rather distinctively as the 2nd highest incidence group. This "cohort effect" is likely a result of conversion to a full acellular vaccine schedule around 1998. I will discuss this "effect" in more detail later, but take away from this slide that, first, infants remain at highest risk of disease and, second, a shift in disease trends is occurring in other age groups. We are seeing similar trends here in North Carolina.

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Before I talk about why we are seeing this rather substantial increase in disease and shift in age group incidence, I wanted to discuss the case definition for pertussis as it relates to infants. As you know, case definitions are uniform criteria used to determine, for public health surveillance, which patients are considered to have had disease.

The pertussis case definition prior to 2014, established the criteria for a case of pertussis to have both a [CLICK] prolonged cough of over 2 weeks plus one associated symptom of pertussis listed here [CLICK], unless the case is culture positive. Whether or not the case has lab confirmation by PCR or epidemiological linkage would then distinguish between confirmed and probable cases.

As I discussed earlier, infants, the group most affected by the disease, often do not present with symptoms allowing them to meet this case definition, or, tragically, they may die before meeting the criteria. So, although the incidence in infants is considerably higher than other age groups, it is likely that the true burden is actually much higher.

Because of this, in 2014 the case definition was changed to more accurately reflect the disease in infants.

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The revised 2014 case definition allows for additional pathways for infants to become cases. The changes in this definition apply to infants only. First, [CLICK] apnea is now permitted as a defining accessory symptom, allowing infants with prolonged cough and apnea alone to meet the case definition.

The new case definition now allows for infants who do not have two weeks of cough to become probable cases if they have [CLICK] any cough, one accessory symptom (including apnea) and a positive PCR or epi-linkage to another lab-confirmed case.

By increasing the sensitivity of the case definition, the true burden of disease in infants will hopefully be more accurately captured.

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So, going back to this dramatic increase in cases over the last decade, "Why are we seeing this?" Several factors have likely contributed to the increase in reported cases.

[CLICK] First, we have better diagnostic testing available. PCR testing has become the predominant means of diagnosing pertussis infections and has been included in the case definition since 1996.

[CLICK] Increased awareness and improved recognition of pertussis among clinicians is also likely a factor. And the new 2014 infant case definition will result in increased reporting of infant cases.

[CLICK] Also, the natural 3-5 year cycles I discussed earlier may contribute to an increase, but alone are unlikely to explain the lengthier increase over the past few decades.

[CLICK] There have also been recent reports of a pertussis strains that don't produce one of the proteins targeted by pertussis vaccines. However, pertussis vaccines remain effective against these strains since other components of the vaccines provide protection. These strains are not thought to be the cause of the increase, but this will continue to be monitored.

[CLICK] And lastly, the theory that predominates and may best explain the increase is waning immunity from acellular pertussis vaccines.

So let's look more closely at the types of vaccines used in the United States to prevent pertussis and how these vaccines may be affecting the epidemiology of the disease.

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As I mentioned earlier, the whole cell DTP vaccine was first used in the 1940s. This vaccine contained inactivated Bordetella pertussis cells. It was an effective vaccine and its success is demonstrated by the dramatic decrease in the number of cases after its introduction, but it did cause local and systemic reactions.

Concerns about the safety of the whole cell vaccine led to the introduction of a more purified acellular vaccine in the 1990s. Theses acellular vaccines contain inactivated components of the *Bordetella pertussis* cells. The use of the acellular vaccine for children (called DTaP) was phased in throughout the 1990s and by 1997 was recommended for all doses. Infants born in 1998 or afterwards have only received acellular vaccines.

Tdap is the most recently available acellular pertussis vaccine. It is licensed for ages 10 and up. Tdap was introduced in 2005 and is recommended for children ages 7 to 10 who are not fully immunized against

pertussis, adolescents 11-18 and adults 19 and over, especially those in close contact with infants. Tdap is now recommend for pregnant women during *each* pregnancy so that maternal antibodies can be passed to the newborn and provide some protection against pertussis until the infant can be protected by vaccine.

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So let's look at these acellular vaccines.

DTaP, the vaccine given to children, offers excellent initial effectiveness, with efficacy estimated in the 80-85% range. It is highly effective, but you should not rule out infection based on receipt of the vaccine.

Like its predecessor, DTP, vaccine protection fades over time. Original estimates suggested a range of 4 – 12 years, but more recent studies suggest it may be in the shorter range. A California study published in 2012 in the Journal of the American Medical Association found that vaccine effectiveness declined to approximately 70% if greater than 5 years had passed since receipt of the 5th dose of DTaP (Misengades, JAMA 11/28/12).

Studies have also found that receipt of an all acellular series put patients at increased risk of disease compared to those who have received at least one dose of whole cell vaccine (Witt, CID 5/1/13), even after receiving a 6th dose of vaccine.

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Now let's look at the Tdap vaccine. Field observational studies have indicated that Tdap effectiveness is estimated to be around 70%. Data suggest that the effectiveness of the vaccine wanes within 3-4 years in those receiving the all acellular series. However, even given the limitations of waning immunity, Tdap has been shown to have reduced the burden of pertussis in adolescents.

Unfortunately, Tdap coverage rates in adults have been low. A 2010 MMWR indicated that only an estimated 6% of adults aged 18-64 had been vaccinated. Healthcare worker coverage was approximately 6% and, of adults who had infant contact, only 5% reported being vaccinated (MMWR, October 15, 2010 / 59(40);1302-1306). This is concerning because adults are often the source of infection to infants in their households, and healthcare workers will likely have contact with patients at risk for severe outcomes of pertussis.

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The important message surrounding concerns about waning immunity is to remember that acellular pertussis-containing vaccines are highly effective initially, but immunity likely wanes within 5 years.

The 'cohort effect' of children receiving only acellular vaccine for their primary series is likely a primary contributor to the shifting burdens in age groups, especially 7-10 year olds.

And lastly, vaccine still remains the best way to prevent pertussis. The same California study mentioned earlier found that unvaccinated children had almost 9 times the odds of developing disease as those who had received 5 doses of the acellular vaccine. And those vaccinated individuals that do develop disease typically have less severe illness.

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I'd like to move now to pertussis case investigations. There are many resources available to assist you with this process, including the CDC VPD Surveillance Manual, guidance provided in the online North Carolina CD Manual, and of course, the epidemiologist on call in the Communicable Disease Branch. Please familiarize yourself with the written resources before beginning an investigation, as they will cover in more detail many of the topics discussed in this presentation.

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I'd like to begin by reviewing the laboratory criteria for the diagnosis of pertussis.

Two testing methods are currently acceptable for reporting purposes here in North Carolina, positive *Bordetella pertussis* cultures and positive PCR tests for pertussis. For PCR positive cases, remember that they must also meet the clinical case definition of a cough of 2 or more weeks plus one associated symptom to be confirmed. PCR positive infants may meet the new 2014 case definition as I discussed earlier.

Serological testing is available at commercial labs, but commercial serological tests cannot be used for diagnosis due to unproven or unknown clinical accuracy. Serological testing performed with a CDC-validated test is acceptable, but unlikely to be utilized much, as the availability is limited. We now have the capacity to offer this test here in North Carolina through the use of a VPD Reference Lab. This test can be requested in consultation with the Communicable Disease Branch for cases that may have public health implications.

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One of the difficulties with pertussis testing is that there is no perfect test available and there is often a divergence in the needs of clinicians versus the needs of a public health department.

Healthcare providers want a test that is high sensitivity to ensure that cases will not be missed. And, to determine patient management in a timely manner, results need to be available quickly.

These things are also important to public health, but, on the other hand, because of the public health implications of a case of pertussis, health departments will often prefer a test with high specificity resulting in fewer false positives and fewer unnecessary public health interventions. Confirming the true cause of an outbreak is important, as is avoiding "pseudo outbreaks" of pertussis, which I'll talk about in just a minute.

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Given the limitations of pertussis testing, the diagnosis of pertussis should be based on epidemiological and clinical findings, as well as supporting lab work.

PCR has become the predominant method for testing for pertussis. It is both sensitive and fast, and something healthcare providers are using almost exclusively now to test for pertussis. However, PCR is not standardized

across labs and can vary in specificity, result reporting and has falsely associated outbreaks with pertussis that were not in fact due to *Bordetella pertussis*.

Culture, of course, is the gold standard for diagnosis. It is 100% specific. However, results are slow and because of this, not often clinically useful. Fastidious growth requirements, difficult collection technique, transportation and isolation make its sensitivity quite low. However, positive cultures are very important to obtain in outbreak situations to provide unquestionable evidence identifying the causative agent.

Unlike PCR and culture, which are most useful early in the onset of disease, serology can be used for patients coughing greater than 2 weeks. The assay developed by CDC and the FDA has been extremely useful for confirming diagnosis, especially during suspected outbreaks. As I mentioned earlier, commercial assays are not FDA approved and should not be used for public health purposes at this time.

DFA is listed because it is sometimes performed by clinicians, but it has low sensitivity and also should not be used for public health purposes.

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The preferred time for specimen collection is shown in this illustration.

Culture is most useful during the catarrhal stage of the illness. Since patients are not often suspected to have pertussis early in the illness, the window of opportunity to collect a specimen for culture has often passed before pertussis testing is considered.

PCR has a somewhat longer window for specimen collection. Ideally, a nasopharyngeal swab should be collected within 3 weeks of onset, but up to 4 weeks may yield positive results since live bacteria do not need to be present for this test.

You can see why serological testing could be quite useful in diagnosis of pertussis. The window for serology is much longer and can be useful up to 12 weeks after cough onset.

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Since PCR is primarily used to diagnosis pertussis, I wanted to spend a minute discussing some of the limitations of the test.

Although PCR is typically used independently, ideally it should be used in addition to culture, not as a replacement. Positive PCR should be evaluated together with clinical and epidemiological information available because both false positives and false negatives can occur.

Falsely negative results can occur if, as shown on the previous slide, the patient is tested too late in the illness or if the specimen collection is not done appropriately.

False positives can also occur for a variety of reasons. Some of these are related to the assay and lab performing the test, as no PCR product has been approved and standardized. False positives can be minimized

at the collection-level by testing only patients with signs and symptoms of pertussis. Do not test asymptomatic patients or contacts of cases.

PCR has also been known to be falsely positive due to contamination at the site of collection by vaccine DNA. Vaccines shown to contain PCR-detectable DNA include Pentacel, Daptacel, and Adacel. Techniques to avoid contamination have been outlined by CDC in the "Best Practices for Health Care Professionals on the use of PCR for Diagnosing Pertussis" document.

I would recommend reading this document and working to ensure the providers in your community are familiar with it.

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A key point to remember about pertussis testing is that there is no perfect test. Clinical history and lab results should always be evaluated together.

PCR, although a useful tool for diagnosing pertussis, does have limitations. When collecting specimens for PCR testing, cultures should also be performed to ensure that appropriate public health measures are being taken.

Lastly, the role for serological testing in pertussis is expanding but still limited. However, we do now have the ability to use CDC-validated serological testing if the need should arise.

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Treatment for pertussis is primarily intended to prevent transmission. Antibiotics can lessen the duration and severity of symptoms, but only if they are started very early in the illness, during the catarrhal phase.

Antibiotics will eliminate the organism from the nasopharynx of infected persons and will also prevent further transmission of the organism. After three weeks of cough, treatment is not recommended, as ~80-90% of untreated cases will clear the organism within 3-4 weeks. However, because of the prolonged colonization seen in infants and the severe outcomes in infants, treatment should be considered for infants and pregnant women (especially those near term) if within 6 weeks of cough onset.

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When a case of pertussis is suspected by a healthcare provider, he or she should report it to the local health department within 24 hours, as required by North Carolina Statutes.

The communicable disease nurse should collect from the provider the necessary information to determine if the suspected case has met the case definition and also ensure that proper testing and, if indicated, proper treatment was given.

If the case has been coughing for less than 3 weeks, he or she should refrain from public activities and avoid contact with high-risk individuals until he or she is no longer infectious.

Cases of pertussis are infectious for the first 5 days of antibiotic treatment or until 21 days after cough onset, whichever comes first.

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Contact investigations are necessary for cases of pertussis to both identify symptomatic individuals and to identify individuals who may need post-exposure prophylaxis. A contact investigation worksheet, or line listing, might be useful in organizing these contacts.

After identifying the time period that the case was infectious, consider for this time frame, anyone who may have had either direct face-to-face contact with the case, shared the same confined space in close proximity for over 1 hour or had direct contact with respiratory, oral or nasal sections. Because of the high attack rate in households, ALL household members are considered contacts.

In high-risk settings, such as neonatal intensive care units, infant rooms in childcare facilities or other settings, determination of contacts should be more inclusive. If a high-risk setting is involved, consultation with the Communicable Disease Branch is recommended.

SLIDE 46

With the increasing incidence of pertussis in school-age children, identifying contacts in the school setting is often necessary. School contacts might include core groups of friends, students sitting next to the case in class or other school-related activities, students who work closely together, sharing rides to and from school or students attending the same after school programs. School settings can vary greatly and contacts should be identified on a case-by-case basis.

Also, remember to consider staff, aides, and volunteers that may have had close contact with the case.

SLIDE 47

Symptomatic contacts should be referred to their provider for evaluation and to have appropriate testing performed and, if indicated, receive antibiotics.

Symptomatic contacts of a pertussis case should also be excluded from public activities, such as school or work, until pertussis has been ruled out or until he or she is no longer infectious.

SLIDE 48

Asymptomatic contacts should be considered for post-exposure prophylaxis, or PEP.

PEP is the mainstay of the public health response to cases of pertussis and is used for the prevention of secondary cases in high-risk contacts. The antibiotics used for the treatment of pertussis are the same as those recommended for use in exposed contacts.

Prior to 2013, post-exposure prophylaxis was recommended for all persons identified as close contacts of a pertussis case. However, because evidence was lacking to support the effectiveness of this broad-scale use and to promote the judicious use of antibiotics, the focus of post exposure prophylaxis shifted to support a more limited use to prevent death and serious complications in individuals at increased risk of severe disease.

The following groups are considered 'high-risk' for pertussis. [CLICK] Infants, [CLICK] women in their 3rd trimester of pregnancy, not because they themselves are at increased risk of complications, but because they are at increased risk of transmitting pertussis to their newborn. [CLICK] And lastly, any individual with a pre-existing health condition that may be exacerbated by a pertussis infection. These may include immuncompromised persons or patients with moderate or severe asthma, as well as other conditions.

SLIDE 49

With the narrowed focus of PEP, their use is now recommended for the following groups:

[CLICK] First, all household contacts of a case because of the increased likelihood they will develop, and then transmit, the disease.

[CLICK] Second, to protect vulnerable groups, PEP is recommended for all contacts at high-risk for disease complications or contacts who will have close contact with someone at high-risk. These groups include the high risk groups I described on the last slide, which were infants, pregnant women in their 3rd trimester and any individual with a pre-existing health condition that may be exacerbated by a pertussis infection.

[CLICK] Third, anyone who has contact with someone in one of these high-risk groups should receive PEP.

And, lastly, *all* contacts in high-risk settings that include infants or women in the third trimester of pregnancy. PEP should be used to both protect the high-risk contacts themselves and to provide a circle of protection around them.

The time since last exposure and time since cough onset in the index case also play a role in the recommendations for PEP and this information should be evaluated with each recommendation for PEP.

It is important to remember that vaccination status is important information to collect, but neither it, nor age should be used to evaluate the need for PEP.

SLIDE 50

I wanted to mention that, although the focus of PEP has shifted away from a broad-scale use, it can still be considered in some situations where there is reasonable expectation that providing more expanded PEP will limit the spread and prevent an outbreak from occurring. This may be used if there are a small number of cases within a closed setting and where no community-wide outbreak is happening.

Please consult with the Communicable Disease Branch if this approach is being considered.

SLIDE 51

And of course, it is important to ensure that contacts are up-to-date with their pertussis containing vaccine. A vaccine is available for all ages and is especially important for persons who may have contact with high-risk groups, such as healthcare workers and adults in close contact with infants.

Asymptomatic contacts, especially those who did not receive PEP, should be given information about the signs and symptoms of pertussis and asked to seek care should they develop symptoms.

In some settings, such as schools or healthcare settings, active surveillance should be initiated and maintained for at least 42 days after cough onset in the last case.

SLIDE 52

It can be challenging to determine how to proceed with an investigation when lab results are either unavailable or pending.

A reasonable guideline is that when pertussis is strongly suspected, based on clinical and epidemiological findings, attempts to identify and provide prophylaxis to close contacts should proceed without waiting for laboratory confirmation.

When suspicion of pertussis is low, the investigation can be delayed until there is laboratory confirmation of the diagnosis. However, prophylaxis of infants and their household contacts should not be delayed.

SLIDE 53

In summary, the incidence of pertussis is increasing both here in the United States and in North Carolina. Although the reasons for this increase are multifactorial, the shorter duration of immunity in children receiving the acellular vaccine since the late 1990s is a likely factor.

However, even with the limitation of the vaccine, vaccination still remains THE best tool for prevention. Unvaccinated individuals have a higher risk of developing disease and are more likely to have more severe disease than vaccinated individuals. And because they are more likely to develop disease, they are also more likely to transmit the disease to infants – who are the group at highest risk for complications and death.

And lastly, when investigating cases of pertussis, remember that the objective of the investigation is not only to minimize transmission in the community through early detection and treatment, but, above all to prevent death and serious complications in our vulnerable populations – most often our infants.

SLIDE 54

The resources listed here, as well as the online North Carolina Communicable Disease Manual, will be helpful to you in your investigations. I recommend reading through these resources prior to your first investigation, as they can be quite detailed.

This concludes the first session of the vaccine-preventable diseases unit. I hope you found this lecture useful and I thank you for your time.