NWX-DISEASE CONTROL & PREVENTI (US)

Moderator: Dale Babcock
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Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen-only mode.

During our Q&A session, you may press star 1 on your touchtone phone if you would like to ask a question.

Today's conference is being recorded. If you have any objections, you may disconnect at this time.

Now I'd like to turn the meeting over to Dr. (Raymond Strikas). Sir, you may begin.

(Raymond Strikas): Thank you very much and welcome to Current Issues and Immunization Net Conferences, a program presented by the Immunization Services Division of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention, or the CDC, in Atlanta, Georgia.

To participate in today's program, you need both a telephone connection and a separate Internet connection, as designated on our website for this net conference.

The learning objectives for today's program are: that you'll be able at the end of the program to describe an emerging immunization issue, in this case about pneumococcal disease and vaccines; to list the recent immunization recommendation made by the Advisory Committee on Immunization Practices, also called the ACIP; to be able to locate resources relevant to current immunization practice; and to obtain, assess and apply patient information to determine the need for immunization.

Today's agenda has one topic: pneumococcal disease and vaccines, which is part of the Epidemiology of Prevention of Vaccine-Preventable Diseases webinar series from our book of the same name, also called the pink book. The presenter will be Dr. (Andrew Kroger), who's a medical officer in our program at the Immunization Services Division, NCIRD, CDC.

Please make a note, if you have technical difficulty, you may dial star 0 to reach the operator, and when we reach the question-and-answer session, during that period, you can dial star 1 to get in a queue to ask questions.

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CDC, our planners, and our presenters wish to disclose we have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. The presentations we give, including today's presentation, will not include any discussion of the unlabeled use of a product or a product under investigational use, with the exception of Dr. (Kroger)'s discussion of the use of pneumococcal vaccine in a manner recommended by the Advisory Committee on Immunization Practices but not approved by the Food and Drug Administration. CDC does accept any commercial support.

Let me turn it now over to Dr. (Kroger).

(Andrew Kroger): Thank you, Dr. (Strikas). It gives me pleasure to present to you today from Atlanta. Today I will discuss pneumococcal disease and pneumococcal vaccines.

The flow of my presentation will correspond to the chapter entitled Pneumococcal Disease on Page 279 of the pink book. The slides that I'm using are similar to the sidebars you see in the margins of the pink book, and I will be posting these slides in the near future.

Streptococcus pneumoniae, or pneumococcus, causes an acute bacterial infection. This bacterium was first isolated by Pasteur in 1881 from the saliva of a patient with rabies. The association between the pneumococcus bacterium and lobar pneumonia was first described by Friedlander and Talamone in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the discovery of the Gram stain in 1884.

From 1915 to 1945 the chemical structure and antigenicity of the pneumococcal capsular polysaccharide, its association with virulence, and the

role of bacterial polysaccharides in human disease were explained. More than 80 serotypes of pneumococci had been described by 1940.

Efforts to develop effective pneumococcal vaccines began as early as 1911. However, with the advent of penicillin in the 1940s, interest in the vaccine declined until it was observed that many patients still died despite antibiotic treatment.

By the late 1960s, efforts were again being made to develop a polyvalent pneumococcal vaccine. The first pneumococcal vaccine was licensed in the United States in 1977. The first conjugate pneumococcal vaccine was licensed in 2000.

Streptococcus pneumoniae bacteria are lancet-shaped Gram positive facultative anaerobic organisms. They are typically observed in pairs, known as diplococci, but may also occur singularly or in short chains. There are 92 known serotypes. Some pneumococci are encapsulated, their surfaces composed of complex polysaccharides. Encapsulated organisms are pathogenic for humans and experimental animals, whereas organisms without capsular polysaccharides are not.

Capsular polysaccharides are the primary basis for the pathogenicity of the organism. They are antigenic and form the basis for classifying pneumococci by serotypes. Type-specific antibody to capsular polysaccharide is protective. These antibodies and complement interacts to opsonize pneumococci, which facilitates phagocytosis and clearance of the organism.

Antibodies to some pneumococcal encapsular polysaccharides may cross-react with related types as well with other bacteria, providing protection against additional serotypes.

Most *Streptococcus pneumoniae* serotypes have been shown to cause serious disease, but only a few serotypes produce the majority of pneumococcal infections. The ten most common serotypes are estimated to account for about 62% of invasive disease worldwide. The ranking in serotype prevalence differ by patient age group and geographic area.

In the United States, prior to widespread use of the seven-valent pneumococcal conjugate vaccine, the seven most common serotypes isolated from blood or cerebral spinal fluid, or CSF, of children younger than six year of age, accounted for 80% of infections. These seven serotypes account for only about 50% of isolates from older children and adults.

Pneumococcal disease is the second most common cause of vaccine-preventable death in the US, causing over 5,000 preventable deaths every year. Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease among adults, although pneumonia alone is not considered to be invasive disease.

The incubation period of pneumococcal pneumonia is short, about one to three days. Symptoms generally include an abrupt onset of fever and chills or rigors. Typically there's a single rigor, and repeated shaking chills are uncommon. Other common symptoms include pleuritic chest pain, cough productive of mucopurulent rusty sputum, dyspnea, which is shortness of breath, tachypnea, which is rapid breathing, hypoxia, which is poor oxygenation, tachycardia, which is a rapid heart rate, malaise and weakness. Nausea, vomiting and headache occur less frequently.

Other clinical symptoms include the two most common forms of invasive disease: bacteremia and meningitis. Bacteremia is bloodstream infection, and

meningitis is infection of the meninges, the lining covering the brain. The clinical symptoms, CSF profile, and neurologic complications of pneumococcal meningitis are similar to other forms of purulent bacterial meningitis. Symptoms may include headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures, and coma.

Approximately 400,000 hospitalizations from pneumonia occur every year in the US. The case fatality rate is 5 to 7% and may be much higher in elderly persons. Current use of the PCV13 vaccine is thought to prevent 12,000 cases of pneumonia.

More than 30,000 cases of invasive pneumococcal disease occur each year, of which most are bacteremia. It occurs in as many 25 to 30% of patients that have pneumococcal pneumonia. The overall case fatality rate for bacteremia is about 15% but may be as high as 60% among elderly patients. Patients with asplenia, who develop bacteremia, may experience a fulminant clinical course. Most of the deaths prevented with current use of the vaccine occur in children.

Pneumococci cause 50% of all cases of bacterial meningitis in the United States. An estimated 3,000 to 6,000 cases of pneumococcal meningitis occur each year. One-fourth of the patients with pneumococcal meningitis also have pneumonia. The case rate fatality of pneumococcal meningitis is about 8% in children and 22% in adults. Neurologic sequelae are common among survivors. Persons with a cochlear implant appear to be at increased risk of pneumococcal meningitis.

Risk factors for invasive pneumococcal disease include age. Among children, 70% of invasive pneumococcal disease occur in children two years old or younger. Invasive disease is also common in older individuals, especially

persons 65 years of age and older, as well as younger adults. Only 15% of invasive disease occurs in children younger than six years of age.

Underlying medical conditions that increase the risk of invasive pneumococcal disease include chronic heart disease, pulmonary disease, including asthma in persons 19 years old and older, liver disease, CSF leaks, or renal disease. Other risks include smoking cigarettes in persons 19 years old or older, and cochlear implants.

Other conditions that increase the risk for invasive pneumococcal disease include decreased immune function, especially HIV infection. Children with HIV infection have rates of invasive pneumococcal disease 50 times higher than rates among children without HIV infection. Children with asplenia are also at higher risk of invasive pneumococcal disease.

We do use this term functional or anatomic asplenia with intent. Functional asplenia includes persons with sickle-cell disease because their disease destroys the spleen and prevents it from functioning. The spleen is an important organ for preventing infection with encapsulated bacteria like pneumococcus.

Anatomic asplenia, by the way, means the complete absence of a spleen, which can occur through elective surgery for various conditions, such as non-Hodkgin's lymphoma, or it can occur through emergent removal of the spleen, for instance, following trauma.

Here's a breakdown of the burden of pneumococcal disease in children. Bacteremia without a known site of infection is the most common invasive clinical presentation of pneumococcal infection among children two years of age and younger, accounting for 13,000 cases. Bacteremia that occurs with

pneumonia accounts for about 3,300 of these cases, or 12 to 16% of invasive pneumococcal disease among children two years of age and younger.

If you look at children five years of age and younger, there are actually a total of 17,000 cases of invasive pneumococcal disease, which include 700 cases of meningitis. With the decline of invasive Hib disease, *Strep pneumoniae* has become the leading cause of bacterial meningitis among children younger than five years of age in the United States.

Before routine use of pneumococcal conjugate vaccine, children younger than one year had the highest rates of pneumococcal meningitis, approximately 10 cases per 100,000 population. An estimated 200 children died every year as a result of invasive pneumococcal disease. Although not considered invasive disease, an estimated five million cases of acute otitis media occurred each year among children younger than five years of age. And pneumococci are a common cause of acute otitis media detected in 28 to 55% of middle ear aspirates.

By age 12 months, more than 60% of children have had at least one episode of acute otitis media. Middle ear infections are the most frequent reason for pediatric office visits in the United States, resulting in more than 20 million visits annually. And complications of pneumococcal otitis media may include mastoiditis and meningitis.

Risk factors for invasive pneumococcal disease among children are similar to risk factors generally, including functional or anatomic asplenia, especially sickle-cell disease, and immune compromise and I've already mentioned the impact of HIV in children in invasive pneumococcal disease.

Attendance at a child care center has also been shown to increase the risk of invasive pneumococcal disease and acute otitis media. Rates are also increased among children of certain racial and ethnic groups, including Alaska natives, certain American Indians, specifically Navajo and White Mountain Apache tribes, and African Americans.

The reason for this increased risk by race and ethnicity is not known with certainty, but was also noted for invasive *Haemophilus influenzae* infection, which is also an encapsulated bacterium. Children with a cochlear implant are at increased risk for pneumococcal meningitis, as well as patients with CSF leaks.

The reservoir for pneumococcal disease are human carriers. Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasal pharynx of 5 to 90% of healthy adults. Rates of asymptomatic carriage vary with age, environment, and the presence of upper respiratory infections. Only 5 to 10% of adults without children are carriers.

On military installations, as many as 50 to 60% of service personnel may be carriers. The duration of carriage varies and is generally longer in children than adults. In addition, the relationship of carriage to the development of natural immunity is poorly understood.

Transmission of *Streptococcus pneumoniae* occurs as a result of direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract. Pneumococcal infections are more common during the winter and in early spring when respiratory diseases are more prevalent.

The period of communicability for pneumococcal disease is unknown but presumably transmission can occur as long as the organism appears in respiratory secretions.

This graph of invasive pneumococcal disease rates by age group demonstrate that the highest rates of invasive disease occur in those younger than two years of age and those 65 years of age and older. These data are generated by CDC's active bacterial core surveillance system, or ABC's data.

ABC's data also suggests that the use of pneumococcal conjugate vaccine has had a major impact on the incidents of invasive disease among young children. The overall incidents of invasive disease among children younger than five years of age decreased from approximately 99 cases per 100,000 population during 1998 to 1999 to 21 cases per 100,000 population in 2008.

The incidents of invasive disease caused by PCV7 serotypes decreased from 82 cases per 100,000 population to 0.2 cases per 100,000 population. The incidents of invasive disease caused by PCV7 serotypes plus serotype 6A, a serotype against which PCV7 provides some cross protection, has been reduced by 99%. The decreases have been offset partially by increases in invasive disease caused by serotypes not included in PCV7, in particular 19A.

So I'm now going to talk about the pneumococcal vaccines. These vaccines are composed of pneumococcal polysaccharide, and the first vaccines licensed were considered pure polysaccharide vaccines. The first contained polysaccharide from 14 different types of pneumococcus and was licensed in 1977.

In 1983 a 23-valent polysaccharide vaccine was licensed and replaced the 14-valent form. In 2000, the first pneumococcal conjugate vaccine was licensed,

consisting of polysaccharide from seven types of pneumococcus conjugated to a protein. And in 2010, an expanded 13-valent conjugate vaccine replaced the seven serotype conjugate vaccine.

PPSV23 vaccine contains polysaccharide antigens from 23 types. These types cause 60 to 76% of invasive disease generally. However, this vaccine is not effective in children younger than two years of age because it does not generate lasting immune memory. It also has not been demonstrated to provide protection against pneumococcal pneumonia. For this reason, providers should avoid referring to PPSV23 as a pneumonia vaccine.

The pneumococcal conjugate vaccine, or PCV13, contains the original serotypes from PCV7, and those were 4, 9V, 14, 19F, 23F, 18C, and 6B, as well as the six additional serotypes: 1, 3, 5, 6A, 7F, and 19A conjugated to a nontoxic diphtheria cross-reactive material 197 carrier protein. It does contain one additional serotype that is not in PPSV23, and that's type 6A.

More importantly because it is a conjugate vaccine, it generates a long-lasting immune response that is useful in children as well as adults. It was approved by the FDA based on a demonstration of immunologic non-inferiority to PCV7 rather than clinical efficacy.

Between 1998 and 2009, PCV7 reduced rates of PCV7 type invasive disease along with serotype A by 99%, and reduced rates of invasive disease caused by all serotypes by 76%.

In 2008, 61% of invasive pneumococcal disease cases among children younger than five years of age were attributable to the serotype in PCV13. But those types contained in PCV7 only accounted for 2% of the cases. The

remainder were accounted for by the additional six serotypes in PCV13, and serotype 19A accounted for 43% of those cases.

In 2013, 20 to 25% of invasive pneumococcal disease cases among adults 65 years age and older were attributable to PCV13 serotypes. PCV13 serotypes accounted for 10% of community-acquired pneumonia cases in adults. This does include pneumonias with no bacteremia. The manufacturer of PCV13, Pfizer, was able to determine type-specific non-bacteremic pneumonia cases as well with the use of a urinary antigen test based on an immunochromatographic membrane technique.

So by knowing the frequency of serotype for various types of diseases, we can estimate the number of cases potentially preventable by using the vaccine in adults 65 years of age or older. This is going to decrease over time because PCV13 vaccine is preventing adult cases as it's used in children as well because it prevents the acquisition of carriage.

In the year 2015 the community immunity will account for 20% of the effect, but by 2019 it will account for 86% of the effect, the “effects” being the number cases preventable in adults so the direct effect of the vaccine will be less because of these effects of herd immunity and community immunity.

But still if you look at the right-hand column, vaccination with PCV13 in adults by the year 2019 will prevent 80 cases of invasive pneumococcal disease, 1,070 cases of inpatient community-acquired pneumonia, or CAP, and 1,560 cases of outpatient community-acquired pneumonia in adults 65 years of age or older.

So understanding this reduction in disease, it makes more sense if you know how immunogenic and effective each vaccine is. So now I'll discuss immunogenicity and effectiveness beginning with PPSV23 vaccine.

So while 80% of healthy adults who receive PPSV23 vaccine do develop the antibodies against serotypes contained in the vaccine, most estimates of effectiveness range between 60 to 70% against invasive disease. And this is among immunocompetent persons, older person and adults with underlying illnesses.

Effectiveness among the immunocompromised, or very old persons, is not demonstrated, and some effectiveness estimates are as low as 10%. And as I've mentioned previously, this vaccine is not thought to prevent pneumococcal pneumonia at all.

Pneumococcal conjugate vaccine is highly immunogenic in infants and young children, including those with high risk medical conditions. The efficacy of PCV7 was 97% effective for prevention of invasive disease caused by vaccine serotypes. Furthermore, children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanectomy tube placements than did unvaccinated children.

PCV13 was licensed in the United States based upon studies that compared the serologic response of children who received PCV13 to those who received PCV7. These studies showed that PCV13 induced levels of antibodies that were comparable to those induced PCV7 and shown to be protective against invasive disease.

In another study of PCV13, children 7 through 11 months, 12 through 23 months, and 24 through 71 months of age who had not received

pneumococcal conjugate vaccine doses previously were administered one, two, or three doses of PCV13 according to age-appropriate immunization schedules. These schedules resulted in antibody responses to each of the 13 serotypes that were comparable to those achieved after the three-dose infant PCV13 series in the US immunogenicity trial, except for serotype 1, for which IgG GMC was lower among children age 24 to 71 months.

A randomized placebo-controlled trial, known as the CAPiTA trial, was conducted in the Netherlands among approximately 85,000 adults 65 years old or older during 2008 through 2013 to evaluate the clinical benefit of PCV13 in the prevention of pneumococcal pneumonia. PCV13 demonstrated 75% efficacy against vaccine-type invasive pneumococcal disease, and 45% efficacy against PCV13 serotype non-bacteremic pneumonia.

So I will now discuss recommendations for the use of these two pneumococcal vaccines. The PCV13 recommendations as well as the PPSV23 recommendations for infants and children were published in MMWR on December 10, 2010.

A note on the complexity of recommendations for PCV13. PCV13 is approved by the Food and Drug Administration for children six weeks through 17 years of age, and for adults 50 years of age and older. But ACIP's recommendations and CDC's guidance do not match the package insert.

Beyond routine infant toddler recommendations, which I'm going to discuss shortly, ACIP recommended use of PCV13 for immunocompromised persons six years of age and older in 2012 and 2013, and ACIP recommended use of PCV13 for adults 65 years of age and older.

But the routine universal recommendation for PCV13 use in children go back to 2010 and match to some degree the original recommendations for PCV7 with a few important differences.

The routine recommendations for PCV13, as mentioned, are the same as PCV7 for children two months through 59 months of age. The vaccine should be administered as a four-dose series at two months, four months, six months, and 12 to 15 months of age. Fewer doses are needed to complete the series if the series is started at seven months of age or older.

The number of doses depends on the child's current age and the age at which the first dose was given. Children who have received one or more doses of PCV7 can have those doses count but they should complete the immunization series with PCV13.

Here is the routine catch up schedule for unvaccinated older children. These are children who begin the series with PCV13 but they begin the series late. If the age of the first dose is between 7 and 11 months of age, a primary series of two doses should be administered, with four weeks in between, followed by a booster dose after 12 months of age, and it has to be eight weeks later minimum.

If the PCV13 series is begun at 12 to 23 months of age, then two doses are recommended, separated by eight weeks. If the series is begun between 24 and 59 months of age and the child is considered healthy, then only one dose of vaccine is necessary. However, if the child has an underlying medical condition and begins the series between 24 and 71 months of age, then two doses are recommended, with eight weeks between the doses.

There are also recommendations for catch up in children who have received the complete series of PCV7. A single supplemental dose of PCV13 is recommended for all children 14 through 59 months of age who have received four doses of PCV7 or another age-appropriate complete PCV7 schedule. For children who have an underlying medical condition, a single supplemental PCV13 dose is recommended through 71 months. This includes children who have received PPSV23 previously.

PCV13 should be administered at least eight weeks after the most recent dose of PCV7 or PPSV23. This will constitute the final dose of PCV for these children. Now by December of 2015, this recommendation will be obsolete for healthy children, because on this date it will not be possible to have received a complete four-dose series consisting of PCV7. By December of 2016, this recommendation also will be obsolete for the high risk children who have it pushed out a little bit later.

There are also recommendations for children who have received less than a three-dose series of PCV13 and it is - using PCV7 for instance, and it is slightly different from the catch up schedule in lapsed children who began the series with PCV13. So children age 24 to 71 months with underlying medical conditions who receive fewer than three doses of PCV7 should receive two doses of PCV13 eight weeks apart.

Children age 24 to 71 months with underlying conditions who receive any incomplete schedule of three doses of PCV7 before age 24 months should receive one dose of PCV13.

A single dose of PCV13 should be administered for children six through 18 years of age who have not received PCV13 previously and are at increased risk for invasive pneumococcal disease because of anatomic or functional

asplenia, which includes sickle-cell disease, immunocompromising conditions, such as HIV infection, cochlear implant, or CSF leak. And this is regardless of their previous history of PCV7 or PPSV23.

Now this is the list of high risk conditions for children from the 2010 ACIP pneumococcal vaccine recommendations for children. Note this list includes both immunocompetent and immunocompromising conditions. The conditions listed on this slide are those that should be considered when you're playing catch up with PCV13 vaccine in the older infants and toddlers to determine whether catch up doses are needed out to 71 months as opposed to 59 months of age.

So notice this list includes the immunocompromising conditions like asplenia and other immunocompromising conditions, renal failure, which is a list that's important for that dose between six and 18 years. But when you're playing catch up in the infants and toddlers, you also want to include the chronic diseases like chronic heart disease, chronic lung disease, and diabetes mellitus. So that's why I show you this chart now.

So now I'd like to discuss PCV13 use in adults. PCV13 was licensed for use among adults 50 years old or older on December 30, 2011. FDA approved this use under an accelerated approval pathway, and it was based on serologic studies that compared the response of PCV13 recipients to a response of PPSV23 recipients.

One of the post-approval conditions of licensure was the performance of a randomized control trial of PCV13 against pneumococcal pneumonia among adults 65 years old and older in the Netherlands, which was the CAPiTA trial.

Now I want to show you some data. This is the incidents of invasive pneumococcal disease, or IPD, in adults ages 18 through 64 years, who are healthy compared to those with selected underlying conditions. Cases of IPD per 100,000 persons are shown on the vertical axis, and various conditions are listed on the horizontal axis.

The two columns on the right demonstrate that individuals with hematologic cancer and HIV/AIDS, have a more than twenty-fold increased rate of IPS compared to persons without these conditions. Adults with the other conditions on the graph have a three to sevenfold increased risk for IPD compared to persons without these conditions.

So adults with immunocompromising conditions are at much greater risk of invasive pneumococcal disease than adults without these conditions. At the June 2012 ACIP meeting, the committee concluded that the benefits of vaccination likely outweigh any risk for use of PCV13 in immunocompromised adults for the entire age range of adults 19 years of age and older.

ACIP believes the indirect effect of PCV13 use in children are not likely to eliminate invasive pneumococcal disease due to PCV13 serotypes in adults. And so PCV13 use alone may not provide adequate coverage of the serotypes causing disease among the adults. Combined use of PCV13 and PPSV23 vaccine in adults would likely be more effective than either vaccine alone.

So all of these factors kind of came into play when we were discussing whether to lower that age range for the immunocompromised adults from 50 years as per licensure down to 19 years of age. And in fact, that's what we did. In 2012, CDC published guidance based on these ACIP recommendations that definitely differ from FDA's package insert. So instead, CDC recommends

PCV13 for the adults older than 19 years but with the certain high risk conditions.

And this chart lists with checkmarks the various conditions for which PCV13 is recommended for adults. Only pay attention to the middle column with the header PCV13. So out of all the conditions that we've discussed in the first block, immunocompetent persons, only CSF leaks and cochlear implants are risk factors for PCV13 use in this 19 and older group of adults. But we also recommend PCV13 for adults with functional and anatomic asplenia.

And all of the other immunocompromising conditions are listed in the bottom half of the table, and I will repeat myself a little bit but repetition is good. Note that chronic renal failure is listed under the categorical group immunocompromised persons.

So adults 19 years of age and older with one of these risk factors should receive a dose of PCV13. Note that if that both PCV13 and PPSV23 are recommended, a dose of PCV13 should be administered first, followed by a dose of PPSV23 at least eight weeks later. I'm going to get to this a bit later in some more detail, but adults with one of these conditions will then be recommended for a second dose of PPSV23 five years later.

ACIP now as of 2014 also recommends a dose of PCV13 for all adults 65 years of age and older. And the recommendation is for those adults that are PCV13 naïve, and note that some adults may have already received PCV13 already which will lead to complexity, which I will address later.

But first let me talk about the individual recommendations for PPSV23 use in children and adults. So we recommend pneumococcal polysaccharide vaccine for persons two years old and older that have normal immune systems but

with the following chronic illnesses: cardiovascular or pulmonary disease, and for pulmonary it's asthma if it's someone 19 years of age or older, diabetes, liver disease, alcoholism, cigarette smokers 19 years of age and older, and patients with CSF leak or cochlear implants.

Pneumococcal polysaccharide vaccine should also be considered for persons in environments or settings with increased risk for pneumococcal disease or its complications, such as current Alaska native or American Indian populations. And of course pneumococcal polysaccharide vaccine is also recommended for persons two years old and older who are immunocompromised either due to disease or treatment.

Immunocompromising conditions, including functional or anatomic asplenia, chronic renal failure, nephrotic syndrome, Hodgkin's disease, lymphoma and leukemia, multiple myeloma, organ transplant, and HIV infection, or really any condition that is considered immunocompromising, and this can be a complicated set of conditions, especially when you consider the medications.

Routine revaccination with PPSV23 vaccine is not recommended for patients with those - that first set of high risk conditions grouped under immunocompetent persons nor is it recommended for persons with CSF leak and cochlear implant.

However, revaccination is recommended for persons two through 64 years of age who are at the highest risk of serious pneumococcal infection. And so by revaccination, we mean at a five-year interval, no shorter than that, between your two doses of PPSV23. So this is recommended for patients with functional or anatomic asplenia, including sickle cell disease, immunosuppression, including HIV infection, transplant, chronic renal failure, and nephrotic syndrome.

Once someone turns 65 years of age, another dose of PPSV23 is recommended regardless of the number of previous doses of PPSV23 that had been given previously, but only one dose is recommended after the 65th birthday.

Note that because we always recommend the dose after the 65th birthday, patients with chronic conditions who are immunocompetent, who may receive a dose of vaccine in childhood or young adulthood, actually will receive a revaccination dose. It's just going to wait until the 65th birthday. And so I've listed those conditions again.

And to repeat: chronic heart disease, chronic lung disease, which includes asthma in persons 19 through 64 years of age, diabetes mellitus, chronic liver disease, CSF leak, cochlear implant, alcoholism, and cigarette smoking in persons 19 through 64 years of age. Again, remember a dose is recommended after the 65th birthday, but only one dose is recommended after the 65th birthday.

So now that I have discussed vaccine recommendations for PCV13 and PPSV23, I'd like to discuss how to use the two vaccines together. And remember these recommendations call on our CDC guidance, not FDA licensure. First, some general rules. PCV13 and PPSV23 should not be administered during the same clinic visit.

Either vaccine may be administered simultaneously with influenza vaccine and most other routinely recommended vaccines, but do not give PCV13 and PPSV23 together. And administer PCV13 before PPSV23. In children, this will generally mean finishing the series of PCV13 and then waiting eight

weeks, and then administering PPSV23, either one or two doses, depending on the risk condition.

So it's more straightforward in children, but vaccination of adults is more complicated. And I would now like to explain the adult recommendations as they've evolved over the time period 2010 to 2014.

So in 2010, all adult vaccine recommendations really involved only PPSV23 vaccine. If an adult was immunocompetent with one of the underlying conditions, they would be recommended for PPSV23. And then the next dose would not be recommended until the 65th birthday. You would have to keep in mind a minimum interval that's important here.

It's a five-year interval between the two doses of PPSV23, and that's because this vaccine frequently causes mild local reactions upon revaccination that are best avoided by maintaining a five-year interval between the doses. If an adult had asplenia, renal disease or an immunocompromising condition, two doses with a minimum five-year interval should be administered prior to the 65th birthday, and then an additional dose after the 65th birthday.

And of course with that five-year minimum interval as well. If an adult began at 65 years of age and older, only one dose of PPSV23 is recommended. And that's everybody, immunocompetent and immunocompromised.

In 2012 came the first set of recommendations for PCV13 and adults 19 years old or older with immunocompromising conditions. And the risk groups include asplenia, renal disease, other immunocompromising conditions, and CSF leak and cochlear implants. So a dose of PCV13 is recommended first, followed by a dose of PPSV23 with a minimum interval of eight weeks. And we have an eight-week minimum interval. This exists to reduce the risk of

mild local reactions when doses of two different pneumococcal vaccines are administered close together in time.

After the dose of PPSV23, remember for this group a second dose of PPSV23 is recommended five years later but only for asplenia, renal disease and immunocompromising conditions, not CSF leak or cochlear implants. And then of course a dose of PPSV23 is recommended for all after the 65th birthday.

Looking at the same group of individuals, what happens is PPSV23 had already been administered. Data show that the optimal response from PCV13 vaccine occurs when it is separated from a dose of PPSV23 by at least a year. What's going on is a dose of PPSV23 given first generates an immune response, it generates a set point for that response, beyond which it's not possible to boost the antibody levels any higher.

The effect is thought to last for at least a year, so ACIP made the recommendation that when PPSV23 is administered first in adults, regardless of the risk factor present, the dose of PCV13 given second must wait an entire year. That’s the first interval you see on this slide then, one year.

In this group of individuals, a second dose of PPSV23 will follow the dose of PCV13. This dose must be spaced eight weeks from the dose of PCV13. It also has to be spaced five years from that first dose of PPSV23. Also remember that the second dose of the PPSV23 is not recommended for CSF leak or cochlear implant.

Finally like in every scenario, the last dose of PPSV23 is recommended after the 65th birthday, and this will be the only dose of any pneumococcal vaccine recommended after the 65th birthday.

Now we come to 2014 and our new recommendations, which highlight routine use of PCV13 for all adults 65 years of age and over, how does this overlay for the previous intervals described. First of all, note that this recommendation is for PCV13 vaccine-naïve adults 65 years of age and older. So you wouldn't give a dose of PCV13 after the 65th birthday if a dose of PCV13 had been administered prior to the 65th birthday.

Also remember that a dose of PPSV23 still is recommended after the 65th birthday for all. Keep in mind that a substantial portion of invasive disease in adults 65 years of age and older is caused by non-PCV13 types that are in PPSV23. So PCV13 is the vaccine that has demonstrated efficacy against pneumonia without invasive disease. So we recommend this vaccine first.

In a healthy adult, the recommended interval between the first dose of PCV13 and PPSV23 is 12 months. This is not a biologic rationale for this interval. Really it's - note PCV13 is being given first but it's more of a programmatically-derived interval. In fact, if PPSV23 cannot be given 12 months later, it should be given during the next visit after that.

We do state a minimum interval of eight weeks, however, between these two different vaccines, and I've already talked about that eight-week interval because of risk of mild local reactions that can occur with the two vaccines.

So if you have an adult 65 years and older, that is high risk. So note that this is the interval that should be interval that should be observed if PCV13 if given first. You would then give PPSV23 and it could be at an eight-week interval for this high risk adult that is at risk for all serotypes.

So remember, if a healthy adult has already received a dose of PPSV23, these intervals and recommendations will change. So now we're looking at an adult 65 years of age and older and they have a history of a dose of PPSV23 given first. If the dose of PPSV23 was given first and given after the 65th birthday -- remember this is a healthy adult -- PPSV13 has to wait a year prior to receipt of PCV13. If a dose of PPSV23 was given before the 65th birthday, the one-year rule remains. So you have to give a dose of PCV13 now.

And because that dose of PPSV23 historically was given prior to the 65th birthday, they're going to be recommended for another dose of PPSV23 after the 65th birthday, which should follow the programmatic interval. This is a healthy adult of 12 months, as well as making sure you have five-year interval from the prior dose of PPSV23.

If the adult 65 years old or older previously received a dose of PPSV23 after the 65th birthday and this is a high risk adult, you still - we still recommend a one-year interval between that dose of PPSV23 and PCV13. So if you have control and no vaccine has been given yet, give PCV13 first. When PPSV23 is given first, this is bad for expeditious vaccination but sometimes it happens. So you wait one year, given PCV13.

And then in the bottom row, this is the case where PPSV23 was given first but before the 65th birthday. Same one-year rule applies for PCV13, and then of course now that we're older than 65, you give the second dose of PPSV23. Because this adult is high risk, it can follow the dose of PCV13 by eight weeks.

Moving onto to contraindications and precautions. And thankfully, these recommendations are somewhat straightforward. The only contraindication for both of these vaccines is a severe allergic reaction to a vaccine component

or following a prior dose of vaccine. And the only precaution is a moderate or severe acute illness.

I'll take some time to talk about adverse reactions that occur with these vaccines. Local reactions occur in 30 to 50% of doses of PPSV23. With PPSV23 the rate of fever and myalgia is less than 1%, and severe adverse reactions are rare.

For PCV, local reactions are similar to PPSV23. As you can see, 5 to 49%. The rate of fever is higher. And febrile seizures have been observed to occur with PCV vaccines. While they're rare, they occur in 1 to 14 out of 100,000 doses, with a slightly higher rate when other vaccines are administered concomitant, particularly influenza vaccine. If both vaccines are administered simultaneously, the rate of febrile seizures rises to 4 to 45 out of 100,000 does.

Severe local adverse local reactions occur in 8% of doses of PCV vaccine. The grading of “severe” included tenderness that affects limb movement. That's an interesting categorization of that, but that's what they used when they came up with this 8% number.

The rate of febrile seizures with PCV13 and in concomitant influenza vaccine was first identified in 2010, 2011 when the vaccine safety data link program and Immunization Safety Office looked at 200,000 children six months through four years of age and determined various rates of febrile seizures above baseline for these vaccines, individually and in combination.

The rate of febrile seizures with simultaneous PCV13 and inactivated influenza vaccine was 2.5 times higher than PCV13 alone, and 2.4 times higher than IIV alone. What does this mean? It means that if, you know, we

lived in a world where only one of these two vaccines were recommended, it would be preferable to choose one and only one; however, we don't live in that world. The risk of the disease exists for both influenza and pneumococcal - invasive pneumococcal vaccines.

Furthermore, febrile seizures are benign and the risk is especially high of diseases high for infants for both of these diseases. So in spite of the increased risk for febrile seizures, ACIP made no change to the general recommendation that these two vaccines can and should be administered simultaneously if both vaccines are recommended.

Severe pneumococcal disease occurs in adults as well as children, as I've mentioned repeatedly and are - we have healthy people, 2020 goals, to achieve coverage of this vaccine in adults. And we're talking the polysaccharide vaccine. We have a recommendation for 90% coverage for persons 65 years of age and older. We have a ways to go.

The 2005 behavioral risk factor surveillance system, a population-based random digit dial telephone survey of the non-institutionalized US population, estimates that 64% of persons 65 years of age and older were ever vaccinated. We have some follow-up data as well from 2012. The National Health Interview Survey, which is a household visit survey, estimated 60% coverage in this age group, so, you know, those low numbers, 64, 60. We want to get up to 90%. And it's even - coverage is much lower, around 20%, among persons 18 through 64 years of age with a chronic illness.

And this is because of missed opportunities. We think one of the most important missed opportunities to be aware of with this vaccine is mild illness. Sixty-five percent of patients with severe pneumococcal disease had been hospitalized within the preceding three to five years, yet few had received the

vaccine. They should have been vaccinated when no longer moderately or severely acutely ill, whether during the hospitalization or at discharge, or shortly thereafter.

There are a number of web pages listed on this slide, job aid to assist in the complicated, if you haven't already figured out, risk factor-based decision making involved with these two vaccines.

I would now like to conclude and turn the mic back over to Dr. (Strikas).

(Raymond Strikas): Thank you very much, Dr. (Kroger). To get in queue to ask your questions about today's program, please dial star 1 now and we'll have our operator line up the questions for queue. While the operator is doing that, let me give you some information that the recast of this program and the slides that'll be available at www.cdc.gov/vaccines/ed/ciinc for current issues and immunization net conference. And they'll be available next week. That is the week of August 31 of this year.

Continuing education to get CE credit, as I said earlier, I'll repeat the website. Http://www.2a.cdc.gov/tceonline. The course number for today's program is E as in Edward, C as in cat, 2064-082615. Please note the date-specific extension when completing the CE requirements for today's program. The verification code, which you need to access the CE information, is pneumo26, P-N-E-U-M-O 26. I'll repeat that code later. CE credit expires in about one month, September 28, 2015.

And so, operator, do we have any questions in the queue?

Coordinator: We do. Our first question comes from (). Ma'am, your line is open.

XXXX: Oh hello. Thanks so much for this great presentation. I just wondered about the febrile seizure. You said with pneumo13 and inactivated influenza vaccine, there was a 2.4 times increase in febrile seizures than in - than receiving it alone. I wondered if that was the same type of - is it observed with the live attenuated influenza vaccine also?

(Andrew Kroger): Great question. They didn't - I don't think it's been looked at as closely. I mean, this first came out of observations from a vaccine not even used in the United States, a vaccine used in Australia, that febrile seizures could occur with administration of influenza vaccines given to young children, and that prompted our vaccine safety data link to look at the vaccines used in this country.

They focused mainly on the inactivated product, because that is the one administered to persons younger than two years of age. So I don't think a lot has been looked at with respect to the live vaccine and febrile seizures given concomitantly with pneumococcal conjugate vaccine. So I don't - I certainly don't have any detailed data on that combination of the two vaccines.

This is an ongoing topic of interest, and, you know, these vaccines, you know, do cause fever and there's a lot that's being learned about kind of the risk of febrile seizures in persons that have - whether they have fevers or not, whether it's an intrinsic characteristic of a patient to have a tendency for febrile seizures or whether there isn't some kind of additive effect of these vaccines.

But I can't answer specifically for the live vaccine. All I can say is that there is a lot of interest about fever alone in general with a lot of different vaccines. I can tell you that live vaccines do tend to cause fevers more often than inactivated vaccines. So it's a very good question, but I don't have specific data on that.

XXXX: And I just wondered do you recommend that the parents be advised of the possibility of that increased risk of febrile seizure and give them the opportunity to have the vaccine separated?

(Andrew Kroger): We - it's an excellent question, and we actually have information on our VIS to discuss this situation with the provider. And it's on the influenza VIS. And a bit about the history of that. We know that febrile seizures occur more commonly in persons that have already had a febrile seizure. So that for a child that has a first febrile seizure, whatever the cause of that first febrile seizure, we wanted to make sure this discussion occurred with the provider because there are things that can be done.

We don't want the vaccines separated. That could cause, two fevers a month apart, which could be just has high risk of febrile seizure, we don't know. We haven't looked at that kind of control data at all for people that actually had the two doses separated. But we did want the discussion with the provider to occur because of this risk of a repeat febrile seizure occurring, and there are other things such as use of antipyretics.

You know, antipyretics, Tylenol, ibuprofen, are medications to reduce fever once fever starts. We don't really like -- they're available for pain as well -- but we don't really like them to be used before a fever occurs, although, you know, in the circumstance where someone has a history of febrile seizures they are faced with having both these vaccines simultaneously. We know that the risk of febrile seizures is higher if they're given simultaneously. It makes sense to have that discussion with the doctor because of the existence of these medicines. So - to reduce fever.

So that's kind of the reason. That's the discussion that we want to have happen, but I'll just - the ACIP does not recommend the separation of the two vaccines.

XXXX: I really don't understand that because for pneumococcal13, there - that increased risk of febrile seizure is not associated with that just given by itself, is it?

(Andrew Kroger): You know, we're still looking at this. It doesn't look like it based on - although, you know, we're still doing studies on this. There has been some follow-up work that's been done on combinations of other vaccines such as DTaP vaccine. And there was - it did kind of reveal that there's not much going on with PCV13 given by itself.

But just to repeat, these vaccines do have no windows of administration when they have to be given. Someone may be of an age where they're recommended for pneumococcal conjugate vaccine during flu season. We know that these diseases themselves can cause fevers which can lead to febrile seizures, and the vaccine would prevent the disease presumably. And for influenza it's a very common disease that's, you know, that very possibly could occur if someone's not vaccinated.

And so no, it does make sense to make sure we prevent the diseases, which can cause, you know, the fever just as well as the vaccines can. And we're talking about, again, a condition that it extremely scary for parents. Providers have a different outlook on febrile seizures. They're benign, they're self-limited, they're very different from afebrile seizures, and they're quite common. So that's the reason why ACIP made a decision not to separate the two vaccines.

XXXX: Thank you.

(Ramond Strikas): Thank you very much. Operator, do we have another question?

Coordinator: We do. Our next question comes from (). Ma'am, your line is open.

(XXXXX): Yes. In the 2014 MMWR there was a recommendation of giving PCV13 to 65 and above. The initial interval between the 13 and the 23 was six to 12 months, with a minimum of 18 - I'm sorry, minimum of eight weeks between the 13 and the 23. But with this last ACIP meeting, it was just 12 months for 13 to 23. And then Medicare of course will not pay - they'll pay for both vaccines but only if they're separated by 12 months.

And you had stressed that high risk people would benefit from having the 13 followed in eight weeks by the 23 valent. We are working on algorithms to try to educate our - the people in our state. And so which in the printed MMWR that's going to come out through working with (unintelligible) what is the balance between the two recommendations?

(Andrew Kroger): I think you're right that the balance is leaning towards - I mean I think, you know, ACIP has discussed this at the last meeting. There's been a lot of back and forth on this. The pink book has actually undergone some changes on this basis on what that interval should be for high risk. You know, the high risk interval between 19 and 64 I believe has been published as eight weeks.

And so it was a question of why would we rule out the 65 years olds for that same interval. And I think we are moving that way, and yes the recommendations are coming out in early September. So that's my prediction.

XXXX: Wonderful. We won't finish our algorithms before then. Thank you.

(Andrew Kroger): Thank you. Please wait. Thank you.

(Raymond Strikas): Thank you. Do we have an additional question?

Coordinator: We do have final question from Dr. (). Ma'am your line is open. Your line is open.

(Raymond Strikas): Operator, is there a question?

Coordinator: I'm not sure. Dr. () did star 1. She recorded her name, but she's not speaking now.

(Raymond Strikas): Do we have another question?

Coordinator: No, there are no additional questions.

(Raymond Strikas): Well let me ask Dr. (Kroger) one or two questions. We've got a few minutes left in our period here. Dr. (Kroger), a question we receive not infrequently is if someone reports having received a dose of pneumococcal vaccine but there's no documentation of that vaccination or which vaccine they received, can it count?

(Andrew Kroger): Yes, for the pneumococcal polysaccharide vaccine. We've had a published recommendation on self-report for that vaccine, but not the pneumococcal conjugate vaccine. We do also -- as an aside -- we have a self-report allowance also for influenza vaccine.

For the pneumococcal polysaccharide vaccine, the reason why we allow self-report, it has its origins in concerns that frequent doses of PPSV23 can cause

mild local reactions and, you know, that frequent is a concern when it's, you know, within a five-year interval because of the risk of local reactions, and five years is quite a long time.

So hence the reason why, you know, we want to make sure that we limit repeat doses of this vaccine, which really caused us to have a low threshold for allowing self-report for pneumococcal polysaccharide vaccine. It might cause a low threshold for withholding the vaccine on a too-frequent basis. We want to make sure that no more than five years between doses of pneumococcal polysaccharide vaccine.

(Raymond Strikas): Okay thank you very much. Operator, do we have any questions?

Coordinator: No, currently we do not have any questions.

(Raymond Strikas): Okay. Well I have more here that we've gotten fairly often. Dr. (Kroger), can you tell us why you demonstrated that pneumococcal disease risk increases substantially for older person, particularly past the 65th birthday, why then is only one dose of both the conjugate and particularly the polysaccharide vaccine recommended on or after the 65th birthday?

(Andrew Kroger): Well so data suggests that the immune response or the boosting effect for subsequent doses is very low, especially after the 65th birthday. There's no really any immune yield from additional doses. ACIP also doesn't recommend routine revaccination because of insufficient data regarding the clinical benefit, particularly the degree and duration of protection and safety. So that follows. But nevertheless, ACIP is going to reevaluate this recommendation in the near future.

(Raymond Strikas): Okay thank you. Operator, any questions?

Coordinator: Currently there are still no more questions in queue.

(Raymond Strikas): All right. Well we've got another couple that we might be able to fit in. Dr. (Kroger), if an adult has already received the conjugate, pneumococcal conjugate vaccine and the pneumococcal polysaccharide vaccine simultaneously, and I guess this could happen to a child as well, but if they're administered simultaneously, that's not recommended, so which should be repeated?

(Andrew Kroger): So yes if an adult received PCV13 and PPSV23 simultaneously, neither vaccine should be repeated. You know, in this circumstance of course, as you mentioned, it should not have been done, and because it was done the PCV13, the immune response to that one is no longer as optimal as we would have liked it.

But there's not really any added value in repeating doses of vaccine, especially immediately. And likewise, repeating doses of PPSV23 we've talked about how there's no boosting effect. It's really not effective at all. So no value there either. So it's an interesting situation and very new and very contrary to much of what we've recommended in the past with respect to vaccination that, you know, we're going - well you can use the term invalid to describe those doses but we're not recommending repeating either of them.

(Raymond Strikas): Okay. Thank you. Operator, any questions waiting for us?

Coordinator: No sir, there's still no questions.

(Raymond Strikas): Okay well we'll do one more and I think then we'll wrap up. Dr. (Kroger), could you state why the risk factor of invasive pneumococcal disease is so

specifically stated as cigarette smoking? Does that apply to other tobacco products?

(Andrew Kroger): So we've been asked this a lot about cigars, pipes, and we are - we tailored our response to the data that we had, which was limited to cigarettes, and so that's how we answer that question is that it's a risk factor limited to cigarette smoking. It's interesting but we live in a data-driven world. That's the data that we had.

I want to - as a follow up upon that, the more important point with this situation is it's a risk that was identified in persons 19 years old and older. So we actually used the data that we have and we limit the recommendation to 19 year old and older. And we go back and forth on this from time to time, and it's a complicated issue how we're going to use, you know, the evidence base to make our recommendations when there's not really much of a rationale for excluding persons younger than 19 years of age. But that's kind of the recommendations as they are written.

You know, the cigarette smoking, it's - interestingly it's linked to the outcome-invasive pneumococcal disease. So it is really a nuanced data-driven finding. It's not a simple issue of, you know, what you might think - destruction of the respiratory system and any effect that would have on the risk of pneumonia. We're talking about invasive pneumococcal disease. Perhaps it's linked to the outcome of invasive disease, and so that's why we have that recommendation that's specific to cigarette smoking in persons 19 years of age and older.

(Raymond Strikas): Okay well thank you very much. Then I'll thank you for the presentation and addressing the questions. So can we go to the last slide set please?

So I'll remind you again about the continuing education information to make sure you have it. You've seen the website several times for CE credit. I won't read it again. It's there on your slide set. It's also on our website for these Internet conferences.

The course number again is E as in Edward, C as in cat, 2064-082615. Please note again the data-specific extension to the course number when completing the CE requirements. The verification code again is pneumo26, P-N-E-U-M-O 26, and CE credit expires on September 28, 2015 in about one month.

For help with the online CE system, you may call us between 8 and 4 Eastern Time at 1-800-41-TRAIN, or you can e-mail us at ce@cdc.gov. If you have questions that you didn't get a chance to answer or prefer to ask it by e-mail, please e-mail us at nipinfo@cdc.gov and please refer to today's program so we know how to direct your questions.

You may call us about your immunization questions at 1-800-CDC-INFO 8 am to 8 pm Eastern Time, and one of our staff will answer the question or refer it to a specialist as necessary. And that phone line is available 8 am to 8 pm Eastern Time Monday through Friday.

Additional resources for this program are available in the pink book, The Epidemiology and Prevention of Vaccine-Preventable Diseases, the 13th edition, published this year at cdc.govvaccines/pubs/pinkbook. The CDC vaccines homepage is cdc.gov/vaccines. And CDC immunization resources for you and your patients are listed there on the vaccines website, and you can also tweet us using Twitter at cdcizlearn, L-E-A-R-N, if you wish to.

Thank you very much for joining today's program. We'll repeat - not repeat the program, but the recast will be available next week and we'll have a new

program for you a week from today at noon Eastern Time. Thank you very much and goodbye from Atlanta.

Coordinator: This concludes your conference call and you may disconnect. Once again, your conference call has ended and you may disconnect. Thank you for joining.

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