

NWX - DISEASE CONTROL & PREVENTI (US)

**Moderator: Dale Babcock
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11:00 am CT**

Coordinator: Welcome and thank you for standing by. At this time all lines are in a listen only mode until the question and answer portion of today's call. Today's call is being recorded. If you have any objections you may disconnect at this time.

I would now like to turn today's call over to Dr. Candice Robinson. Ma'am, you may begin.

Dr. Candice Robinson: Thank you very much and welcome to Current Issues in Immunization Net Conferences: A CDC Net Conference. I am Candice Robinson, a medical officer in the Immunization Services Division of the National Center for Immunization and Respiratory Diseases -- or NCIRD -- at the CDC.

I will be your moderator for today's session.

To participate in today's program, you will need a telephone connection and a separate internet connection.

The learning objectives for this session are: 1 -- describe an emerging immunization issue; 2 -- list a recent immunization recommendation made by the Advisory Committee on Immunization Practices, or ACIP; 3 -- locate resources relevant to current immunization practice; and 4 -- obtain, assess, and apply patient information to determine the need for immunization.

Today is October 28, 2015 and we have two topics for today's net conference. First, Dr. Andrew Kroger, a medical officer within the Immunization Services Divisions at CDC, will discuss vaccination in adults with altered immunocompetence. Then, Dr. Miwako Kobayashi, an Epidemic Intelligence Service Officer with in the Division of Bacterial Diseases at CDC, will give an update on intervals between PCV13 and PPSV23 vaccines.

A question and answer session will follow.

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Presentations will not include any discussion of unlabeled use of products or a product under investigational use with the exception of Dr. Kroger's discussion of the use of PCV13, PPSV23, DTaP, Hib, Hep A, Hep B, MenACWY, IPV, IIV, and HPV vaccines in a manner recommended by the Advisory Committee on Immunization Practices, but not approved by the Food and Drug Administration. CDC does not accept any commercial support.

I will now turn the presentation over to Dr. Kroger. You may begin.

Dr. Andrew Kroger: Thank you very much Dr. Robinson. One of the challenges of adult immunization is that the providers often are presented with complex medical histories that make immunization decisions very difficult. And so now I'd like to discuss the adult patient who presents with altered immunocompetence.

As an overview, I'll define what I mean by altered immunocompetence and describe some general principles. Then I'm going to discuss effectiveness and safety, not from the perspective of the individual vaccines, but looking at the broad categories of inactivated and live vaccines.

Then I'm going to talk about three special categories which fall under the umbrella term "altered immunocompetence;" those being: hematopoietic cell transplants; asplenia; and renal disease.

The source material for this presentation comes from two publications primarily. The first is the General Recommendations on Immunization, which is a serial MMWR report and recommendations document that highlights cross-cutting recommendations that apply to all vaccines. The most recent edition of the General Recommendations on Immunization document was published in 2011. We anticipate posting revisions to this document in early

2016. There will be many revisions and some of the major revisions will be in the section entitled “Altered Immunocompetence.”

Most of the new data which informs these revisions comes from an Infectious Diseases Society of America publication from 2013 entitled “2013 IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host.” This document - Lorry Rubin is the first author and it was published as an e-journal article in “Clinical Infectious Diseases” in 2013.

The General Recommendations Work Group adopted the term “altered immunocompetence” back in 2006. The intent was to create a term that encompasses other terms like immunocompromised, immunosuppression, and immunodeficiency. Sometimes these synonyms are selectively used. Immunosuppression is a label often applying to medications, whereas immunodeficiency is often used to describe diseases. The workgroup attempted to generalize and use one term, altered immunocompetence, for all potential circumstances.

The truth is that it’s very complicated and altered immunocompetence is a matter of degree. And one of the most important general principles when making recommendations is the fact that the degree of altered immunocompetence in a patient should be determined by a physician. So that language is in the general recommendations and will remain there. And what that means is preferentially the provider who makes the original diagnosis of immunosuppression, altered immunocompetence, or prescribes the medication that causes the immunosuppression is a good source to go back to to determine if someone does have altered immunocompetence.

But over the course of three decades, the ACIP has also tried to describe specific conditions that could be categorized as altered immunocompetence.

These include primary immunodeficiency diseases, which involve quantitative or qualitative deficiencies in one or more components of the immune system. These conditions are typically congenital. They're often genetic and heritable; usually not common in the adult population. They could be quite severe and shorten the lifespan. Defects can be to B or T lymphocytes, complement, or phagocytes.

HIV AIDS is an example of an acquired or secondary immunodeficiency disease, as are certain types of cancers to the blood inclusive of leukemia, lymphoma, multiple myeloma.

Also, any cancer which has progressed to metastasis is described as generalized malignancy and a patient with this level of cancer severity should be considered immunosuppressed as well.

Patients with cancer or with other illnesses may not be immunosuppressed by virtue of their illness alone, but they can be considered immunosuppressed because of the medications they are taking. Some of the treatments for cancer used over the last half century include alkylating agents like cyclophosphamide or carmustine, antimetabolites like methotrexate and 6-mercaptopurine, mitotic spindle inhibitors -- vinblastine and vincristine are examples of those -- and radiation therapy. All of these are anticancer therapies that should be generally considered to cause a state of immunocompetence.

Other agents that are immunosuppressive used not only in anticancer therapy but many types of autoimmune diseases include isoantibodies. Some of the strongest of these are actually considered to be more immunosuppressive than the anticancer agents I just described. They're directed at specific sites on immune cells. Some of them affect so many sites that they basically weaken

or destroy the B lymphocyte. And so B cell inhibitors are an important class to consider. Rituximab is an example of such an inhibitor.

There are other isoantibodies focused on specific types of cytokines or lymphokines secreted by B or T cells. An example of these are the tumor necrosis factor alpha inhibitors. Weaker than the B cell inhibitors, these drugs are widely used for rheumatoid arthritis, psoriatic arthritis, psoriasis, and Crohn's disease. They include infliximab, adalimumab, and etanercept - are three examples of these medications.

And then there are other types of immune mediators and immune modulators. The difference between these labels is really insignificant in a general sense. They include things like colony stimulating factors like granulocyte colony stimulating factor and interferons. These are medications that are often used to treat severe forms of hepatitis and multiple sclerosis.

BCG is Baccilus Calmette-Guerin. That is a vaccine for prevention of tuberculosis that's not used in the US as a vaccine but is used for the treatment of bladder cancer in the United States. And then there are agents like levamisole, which is a drug used alongside other anticancer drugs to often enhance the immune response and perhaps ameliorate side effects of other anticancer agents.

As mentioned, these types of drugs - they sometimes can be thought of as counterbalancing the immunosuppressive effects of other drugs, but we do include them under this umbrella. The question of whether they serve as proxies for immunosuppression because the patients that are on them are immunosuppressed is a complicated issue.

This brings us to steroids and I'm going to talk a little bit later how we specifically define steroids, whether they're immunosuppressive or not. Not all steroid use is considered immunosuppressive. There's high and low immunosuppressive characteristics of steroid use.

Lastly, there are specific agents, therapies for solid organ transplant or hematopoietic cell transplant patients. They generally create a relative immunosuppression so patients will accept their transplant grafts.

So the challenge is knowing how to vaccinate patients that come into your office that could be considered to have altered immunocompetence. Some general principles - it might make sense to withhold vaccines in these patients because they have a comorbid condition; but actually, some persons with altered immunocompetence may be specifically recommended to receive certain vaccines because of their status. These vaccines tend to be inactivated vaccines but not always.

Some live vaccines are specifically recommended for HIV infected patients if they have a relative immunocompetence. And the reason for that is that the risk of severe complications from the vaccine-preventable disease is so high in HIV patients that it actually is safer to vaccinate them with a live vaccine than to withhold that vaccine.

A second important general principle is that household contacts of persons with altered immunocompetence should receive both inactivated and live vaccines generally. Of course, for the altered immunocompetence patient themselves, live vaccines should generally be withheld. This is an issue of safety and effectiveness.

It is safe, generally, to use inactivated vaccines in patients with altered immunocompetence, but sometimes the vaccines may not work as well because we need a working immune system to respond to vaccines. So there may be effectiveness issues.

So now to talk about some of these bullet points in more detail. First, vaccines specifically recommended in patients with altered immunocompetence - this includes pneumococcal vaccines, meningococcal vaccines, and Haemophilus influenza type B vaccine. These are bacterial vaccines that prevent disease caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* serogroup B. These vaccines are of course routinely recommended for children and adolescents in narrowly defined age ranges. But what we're talking about here is those patients that have certain risk factors that make them at high risk for invasive disease. So there are additional recommendations for their use outside of the universally recommended age ranges.

For pneumococcus, these risk factors include immunosuppression, broadly, and also include some other risk factors -- asplenia, renal disease. For meningococcus, the risk factors include more specific subsets of immunosuppression, which is really linked to the increased risk for invasive disease caused by *Neisseria meningitidis*. The risk factors include complement component deficiency, asplenia, use of a medication: eculizumab which is an isoantibody used to treat nocturnal paroxysmal hematuria.

For Hib, the risk factors include complement component deficiency, asplenia, some deficiencies of certain subclasses of IgG, chemotherapy, or radiation therapy.

So again, these risk factors are indications to give these vaccines. They don't necessarily apply to every age outside of the universal recommendations. So there's some additional details and these details can be found in the ACIP vaccine-specific statements or the harmonized ACIP schedules.

Next, vaccinating household contacts of someone with altered immunocompetence provides the benefit of preventing disease in the household contact and therefore reducing the risk of transmission to the person with altered immunocompetence. This benefit outweighs the risk of transmission of live vaccine microbe from the vaccinated person to the contact with altered immunocompetence.

There is one circumstance where some additional guidance is critical that we make. There is evidence that transmission of varicella vaccine virus from a vaccine to a household contact can occur if the vaccinated individual develops a vaccine-associated rash. However, because the development of the vaccine-associated rash is so rare and the likelihood of transmission from the rash is also rare, we still recommend vaccination of household contacts but advise that in the event of a rash to separate the vaccinee from contacts with altered immunocompetence.

We also make a recommendation for healthcare providers not to receive the live attenuated influenza vaccine if they're going to be rounding on patients that have severe immunocompetence requiring care in a protected environment.

So now I'd like to talk about use of vaccines in the patient who himself or herself has altered immunocompetence. So all live vaccines work by replicating and generating an immune response. So there is a theoretical risk

that in someone with altered immunocompetence the vaccine microbe will continue dividing and could eventually cause severe disease.

This has been observed with measles vaccine causing pneumonia in HIV infected patients, with oral polio vaccine causing polio myelitis in patients with congenital immunodeficiencies, and with smallpox vaccine causing generalized vaccinia and necrotic rashes in HIV patients.

So safety is our major concern with live vaccines and altered immunocompetence. Effectiveness of the vaccine, of course, is a secondary concern.

For patients that have permanent immunosuppressive conditions, we generally state this as a permanent contraindication for receipt of that live vaccine. However, there are temporary conditions, types of immunosuppression particularly with medication use or remission from certain types of cancers like leukemia at which point the patient may be assumed to have immunocompetence.

The point at which this is reached is best ascertained by the treating physician, but CDC does provide some interval guidelines. Traditionally we've talked about a three month period added to the point at which remission occurs from hematologic cancers. Keep in mind, though, that if a patient continues on immunosuppressive medications you should continue to prolong that interval. We're talking three months as a period once immunocompetence is restored.

We also have made some exceptions to that three month period for certain vaccines. An example of this is zoster vaccine. We've said that a one month interval might be appropriate for certain types of medications because if someone is on corticosteroids or immunomodulators, we would similarly talk

about a similar washout period of three months. With zoster vaccine we have shortened that to a one month period.

And the reason for that is that patients that have altered immunocompetence - they're relatively immunosuppressed. They may have an immune response still, though, to varicella zoster virus on the basis of their previous natural chicken pox infection -- hence the exception that really has been made for this zoster.

There are additional recommendations that are in the IDSA document. They talk about the circumstance where vaccines may be given first before medications are given. And that is the issue of live vaccines. IDSA has a published recommendation that if there's anticipation of medication beginning -- try to give the live vaccines four weeks before starting the medication. So that's the other direction.

Most primary immunodeficiency diseases are diagnosed in infancy. They're severe. They're not really seen very often in adults. So I don't want to spend too much time on these conditions, but we do have some recommendations in the ACIP general recs document regarding the specific types of live vaccines that should be withheld with certain conditions.

So it's dependent on the actual immune cell that is deficient. If a patient has a T cell deficiency, there is a general recommendation to withhold all live vaccines. In isolated B cell deficiencies, varicella and zoster vaccines can be administered. There's some reliance on vaccine response due to cell mediated factors or T cell responses which allow their use in certain isolated B cell deficiencies.

There are specific primary immunodeficiency diseases in which the deficiency is defined as such that live viral vaccines but not live bacterial vaccines can be given. For instance, in a patient who has a defect of interferon alpha or interferon gamma, there is a recommendation to withhold all live vaccines. But if the specific defect is of the interferon gamma interleukin-12 axis, the recommendation is to withhold live bacterial vaccines specifically. And these aren't commonly administered anyway.

With certain phagocytosis disorders, Leukocyte Adhesion Defects, Chediak-Higashi syndrome -- all live vaccines should be withheld. However, the syndrome of Chronic Granulomatous Disease, which involves immune deficiencies most relevant to the immune response to certain bacterial infections, only the live bacterial vaccines need to be withheld.

The IDSA document states that patients with minor antibody deficiencies can receive all live vaccines except OPV.

Now, probably more relevant to the adult immunization context is the issue of immunosuppressive medications and intervals. I mentioned the IDSA document described minor antibody deficiency as not being a concern. However, if patients have antibody deficiencies to such a degree that they're actually receiving immunoglobulin therapy, live vaccines should be withheld.

Likewise, live vaccine should be withheld during induction or consolidation chemotherapy. If patients are on B cell inhibitors, I talked about rituximab. It's recommended to withhold to live vaccines and the inactivated vaccines during the therapy and for six months after therapy is complete.

There are safety and efficacy issues with these specific medications. For traditional anticancer therapies or high dose corticosteroids or for other types

of isoantibodies the most conservative recommendation is to wait three months after the cessation of the immunosuppressive therapy and the administration of the live vaccines. I discussed already zoster vaccine as an exception to this rule.

For patients who have received solid organ transplant recipients IDSA recommends a two month interval. Lastly, there are certain medications for which there have been defined doses -- methotrexate, aziothiaprine, 6-mercaptopurine -- where IDSA - where we recommend a one month interval for the high dose amount but a low interval and actually no interval for zoster vaccine if these medications are used at a low enough dose. And the details are in the zoster vaccine-specific statements.

Which brings me to corticosteroids, and here CDC has some specific parameters for defining high dose versus low dose. We consider corticosteroids to be immunosuppressive if they are administered at a dose of twenty milligrams per day or a weight equivalent dosing of two milligrams per kilogram per day, prednisone equivalent dose every day for a two week period. The medications have to be systemic so we're not including injectable, not topical, and not replacement therapy for endocrine deficiency diseases.

The interval for high dose steroids - a three month period after cessation of the dose before administering a live vaccine. This is a more conservative IDSA recommendation than that published in the CDC recs. It currently is a one month recommendation.

IDSA also makes the flip recommendation that if the vaccine is given first, if feasible, wait one month after the administration of the live vaccine before beginning a high dose corticosteroid or other immunomodulator therapy.

So as far as HIV infection, obviously – not considered a temporary condition, per se. However, the immunosuppressive effects of HIV can be considered temporary in the context of withholding certain live vaccines. Because of the severe complications of measles and varicella infections specifically that can occur in patients who have HIV infection, once patients with HIV are considered immunocompetence they can and should receive MMR and can be considered to receive varicella vaccine.

The specific laboratory parameters are discussed in detail in the MMR and varicella ACIP specific statements. I'm not going to discuss them here because this really is more of a pediatric recommendation. They involve CD4 counts, CD4 percentages, and usually a fixed period of time after a specific immunocompetent cutoff is reached before the vaccine is administered.

Switching to inactivated vaccines - so with inactivated vaccines, our concern is more with effectiveness than with safety. It's often important to give a dose of vaccine and have a reduced response than to withhold the vaccine completely and have no response. On the other hand, we don't want to have wasted doses. So the trick is to tease out those circumstances where you still want to vaccinate for prevention of disease and maybe you'll need to give a repeat dose.

Safety is a secondary concern. Inactivated vaccines are safe in patients with altered immunocompetence. Withholding the vaccine, therefore, is usually not necessary. IDSA does make recommendations to withhold vaccines in patients with antibody deficiencies receiving immunoglobulins as well as patients on induction consolidation chemotherapy. These are efficacy concerns. The vaccines are just not going to work well with the levels of immunosuppression that we're talking about.

Influenza vaccine is a common exception to the exception in the IDSA document because of the importance of timing your dose of vaccine during the influenza vaccination season. We recommend that you give inactivated influenza vaccine to someone with altered immunocompetence.

As far as some intervals that are necessary with inactivated vaccines - since we're talking about effectiveness, it's usually not too much of a concern. However, patients on rituximab, again, because of the level of immunosuppression, there's a recommendation to wait six months following cessation of therapy before giving inactivated vaccines as well.

And again, influenza vaccine is another exception there. It can be given but you might have to repeat the dose.

Flipping the order for patients with chronic inflammatory conditions about to receive medications, IDSA makes an anticipatory recommendation that the inactivated vaccines can be given two weeks prior to the initiation of medication, but optimally four weeks prior to initiation of the medication.

I'm now going to discuss some special situations, beginning with hematopoietic cell transplants. This term encompasses bone marrow transplants that can either be autologous -- meaning the transplanted bone marrow is harvested in advance from the same patient that receives the transplant -- or allogeneic transplants, which is the transplant from a closely matched donor.

--The umbilical cord is another source of stem cells as well. And we often define these as "stem cell transplants" are not necessarily bone marrow derived.

These patients are immunosuppressed for several reasons. Either the underlying condition for which the transplant is being considered, the process of the transplant itself, immunoablates or eliminates the donors' preexisting blood cell lines. And then post-transplant therapy is often administered to prevent rejection of the graft, which also causes immunosuppression.

Why this is singled out as a special topic is that we do of course consider that these patients are immunosuppressed and apply the previous rules. What's significant here is that the patient also has been immunoablated and has had their lifetime of immune memory from their history of past vaccine doses completely wiped out. Even those doses that were administered during the period of immunocompetence.

These patients are currently at risk for some vaccine preventable diseases that are common in not only childhood but also in adult patients that are recipients of these transplants.

Because of the immunoablation, therefore, patients need to have their entire historical vaccination series repeated. Many of these patients are immunosuppressed for a considerable time after the transplant has occurred so there are important intervals. Inactivated vaccines are typically recommended six months after the transplant. These include pneumococcal vaccine, DTAP vaccine, Hib, Hep A, Hep B, meningococcal vaccines, inactivated influenza vaccine, inactivated polio vaccine, and HPV vaccines.

We also recommend certain live vaccine vaccination with MMR and varicella vaccine, but only after twenty-four months post-transplant, only if the patient is considered immunocompetent, and only if they do not have graft versus host disease. That's a condition typified by rash, jaundice, diarrhea, that can occur when immune cells from the graft react to host tissues as foreign.

None of this content is on the package inserts. There's really not a discussion, so therefore this type of recommendation has to be considered off-label.

Not recommended for post-hematopoietic cell transplant patients are the vaccines BCG, LAIV, typhoid vaccine, rotavirus vaccine, and zoster vaccine. The last one may seem a little surprising, but remember zoster vaccine is recommended for adults with a history of chicken pox or varicella disease. And the immune response to that has also been ablated by the bone marrow transplant. So often varicella vaccine is what is recommended.

I've already discussed asplenia as a condition for which some bacterial vaccines should be administered -- meningococcal conjugate vaccines. They include Men ACWY. Not listed but included is the MenHibrix (Hib Men CY) serogroup B vaccines, PCV13, PPSV23, and Hib vaccines.

I haven't talked about the intervals yet and circumstances where the removal of the spleen is elective. You should try to administer these vaccines in advance of the splenectomy, preferably two weeks before the surgery. Keep in mind there are a lot of vaccines on this list. There may be intervals between the vaccines that you need to keep in mind. And it may not be possible to administer all of them before the surgery.

Asplenia differs from other types of immunosuppression in that we do not recommend generally withholding live vaccines from patients with asplenia.

Renal disease is considered a type of immunosuppression in certain contexts. Renal disease does affect the persistence of antibodies like other proteins. These proteins and antibodies can be wasted in patients that have problem with their kidney functioning.

So for this reason, certain vaccines -- pneumococcal polysaccharide vaccine, for instance - is recommended to be repeated on a one-time basis after a five year period because of this renal wasting. However, like asplenia, renal disease does not carry with it a recommendation to withhold live vaccines except perhaps in circumstances where a patient has an autoimmune disease. They may be on immunosuppressive therapy. That of course needs to always be considered.

LAIV is also recommended to be withheld. Many chronic diseases including renal disease are considered precautions to LAIV, and in this circumstance the inactivated vaccine is an available alternative.

So we hope the general recommendations will be posted early next year and we'll try to incorporate as many of the general IDSA recommendations that have been discussed today. It's a very challenging topic. Most issues are too complicated to make concrete decisions about withholding vaccines and at what intervals except for the provider that is actually treating the altered immunocompetence. We're going to try to give providers the answers to the questions they ask and we receive a lot of complicated scenarios.

There are questions we continue to receive. The next frontier will be looking more closely at certain anatomic barrier defects like CSF leaks, the impact on immunocompetence and concerns about vaccines like LAIV which are administered sometimes locally at the point of the anatomic barrier defect. We receive questions about immunomodulatory use during pregnancy and the effect on the infant's immune system post-delivery, during which rotavirus vaccine is an example of a live vaccine that needs to be administered.

Finally, there are new immunomodulatory drugs being used all the time. It begs the question what intervals do we apply to these drugs? Do we treat them like B cell inhibitors or you treat them like the tumor necrosis factor alpha inhibitors? And there's just some examples on the slide.

IL-1 receptor antagonists like Anakinra, T cell co-stimulation modulators like abatacept, and IL-6 receptor antagonists like tocilizumab. These are prescribed for rheumatoid arthritis. These are - which is common condition in adulthood. So we are going to have to deal with these types of questions in the future.

So that's all I'm going to say right now and I will turn the mic back over to Dr. Robinson. Thank you very much.

Dr. Candice Robinson: Thank you Dr. Kroger. And now we will turn the presentation over to Dr. Kobayashi for her update on intervals between PCV13 and PPSV23.

Dr. Miwako Kobayashi: Okay. Thank you Dr. Robinson. Good afternoon or good morning depending on where you are and thank you for joining us today.

The title of my talk is "Update on Intervals Between 13-valent Pneumococcal Conjugate Vaccine -- or PCV13 -- and 23-valent Pneumococcal Polysaccharide Vaccine -- or PPSV23."

In this talk I will first go over the basics of sequential administration of PCV13 and PPSV23. Then I will go over the new recommendation on the intervals between these two vaccines. Afterwards, I will go over some of the frequently asked questions related to the intervals between PCV13 and PPSV23 in adults. And lastly, I will spend a few minutes on co-administration of inactivated influenza vaccine and pneumococcal vaccine in adults.

Currently in the United States there are two types of pneumococcal vaccines that are being used. The 13-valent pneumococcal conjugate vaccine, or PCV13, and the 23-valent pneumococcal polysaccharide vaccine, or PPSV23. For individuals with underlying conditions aged two years and older and for all adults aged sixty-five years and older, administration of both vaccines as a series is recommended to maximize protection against pneumococcal disease.

For these groups, PCV13 should be given first, followed by PPSV23 whenever possible, as studies have demonstrated that the immune response was greater when PCV was given first.

Under current ACIP recommendations, recommended intervals between PCV13 and PPSV23 are not consistent across age and risk groups, and also depends on the sequence the two vaccines are given in.

This table summarizes the intervals that were previously recommended for different groups. There are potentially two ways to harmonize these recommendations -- either by changing the interval recommended for children and adults with underlying medical conditions, or changing the interval recommended for routine administration for adults aged sixty-five years and older.

Since individuals with underlying condition listed here are at higher risk of getting invasive pneumococcal disease, the pneumococcal workgroup did not think that the recommended interval for these age groups should be for longer than the current eight weeks. Therefore, changing the recommended interval of six to twelve months between PCV13 and PPSV23 for adults aged sixty-five years and older was considered.

Having different recommended intervals has caused confusion among healthcare providers. It also creates challenges in programming vaccine reminders in computer-based programs or use as a quality measure.

And lastly, Medicare currently covers a different second pneumococcal vaccine one year after the first vaccine was administered. This suggests that Medicare beneficiaries who received PPSV23 within that year of receipt of PCV13 would not be covered.

Currently, there are no studies available that were designed to evaluate the optimal interval between PCV13 and PPSV23. What we really would like to know is the best interval between vaccines that would result in the best clinical outcome, such as number of invasive pneumococcal diseases prevented. But there are no clinical studies evaluating efficacy of sequential administration.

Therefore, the change in the recommendation was based on reviews of available evidence from existing immunogenicity studies.

The purpose of the review was to assess whether the available evidence would support changing the recommended interval for the PCV13 followed by PPSV23 sequence for immunocompetent adults aged sixty-five years or older. The intervals used in the studies reviewed ranged from two months to three to four years in immunocompetent adults aged fifty years or older.

Comparisons of immune responses observed across studies utilizing these intervals showed that longer intervals such as a year or longer may result in improved immune response compared to shorter intervals such as two months or six months.

Of note, one study that compared the two month versus six month intervals reported that shorter interval was associated with increased reactogenicity and was statistically significant.

Based on these findings, recently ACIP changed the recommended interval of six to twelve months between PCV 13 followed by PPSV23 to at least one year.

Although the recommended interval between PCV13 followed by PPSV23 among immunocompetent adults aged sixty-five years and older is still different from other age and risk groups, this change allows harmonizing the interval within the same age group; that is, with the interval recommended for the sequence of PPSV23 followed by PCV13.

This slide summarizes the current recommended intervals for a sequence of PPSV23 followed by PCV13 for different age and risk groups. No changes have been made for any of the intervals for this sequence. Please note that the recommended sequence is PCV13 followed by PPSV23 and the sequence shown here is only applicable to those who already received PPSV23 and are also recommended to receive PCV13.

As you can see, the recommended intervals for adults aged nineteen years and older for whom both PCV13 and PPSV23 are indicated is at least one year; whereas for children it is at least eight weeks.

Now I would like to discuss some scenarios to highlight the changes in the new recommendations regarding PCV13 and PPSV23 in adults. What is the recommended interval between a sequence of PCV13 followed by PPSV23 in a sixty-six year old man with an immunocompromising condition?

Although this person's age is older than sixty-five years, the new recommendation only applies to those who do not have the following conditions -- CSF leak, cochlear implants, functional or anatomic asplenia, or are immunocompromised. For persons with these conditions, the recommendation of at least eight weeks between PCV13 and PPSV23 still applies.

The next question is if an adult aged sixty-five years or older has previously received PCV13 before age sixty-five, is another dose of PCV13 indicated?

The answer is no. An additional dose of PCV13 is not indicated if a dose has already been given, even if that was before age sixty-five years. However, an additional dose of PPSV23 should be given if the indicated dose or doses was completed before age sixty-five years.

Which is our next question - is a dose of PPSV23 indicated for someone who has turned age sixty-five years and has previously received both PCV13 and PPSV23 before age sixty-five years?

And the answer is yes. PPSV23 should be given at least one year after the last PCV13 dose for immunocompetent adults aged sixty-five years and older, and that interval is at least eight weeks for immunocompromised persons. Also, this PPSV23 should be given at least five years after the last PPSV23 dose.

I would like to spend the next few slides on co-administration of PCV13 and trivalent inactivated influenza vaccine, or TIV, in adults. There's one randomized double-blind study that compares immune response to PCV13 and TIV between two groups.

One group received PCV13 and TIV concomitantly followed by placebo one month later. The other group received placebo and TIV concomitantly followed by PCV13 one month later.

The results showed that compared to the group that received TIV and PCV13 one month apart, the group that received PCV13 concomitantly with TIV had slightly lower pneumococcal serotype-specific geometric mean concentrations. However, the observed immune response in the concomitant group met the non-inferiority criteria for all except for one pneumococcal serotype. And even for the one serotype that did not meet the non-inferiority criteria, the value was very close to the cutoff and these differences are interpreted to be clinically indistinguishable.

Also, the concomitant group had lower proportion of responders achieving at least a fourfold rise in hemagglutinin inhibition assay titer for one of three influenza vaccine antigens. However, it was also noted that the mean pre-vaccine titers for H3N2 were higher than the two other influenza vaccine antigens, H1N1 and influenza B. therefore, the fourfold increase may not have been achievable.

So in conclusion - available evidence supports co-administration of PCV13 and TIV and therefore ACIP currently does not recommend giving TIV and PCV13 on separate days.

So in summary, the new ACIP recommended interval for PCV13 followed by PPSV23 is at least one year for immunocompetent adults aged sixty-five years and older. The recommended intervals remain the same for children who are indicated to receive both vaccines and adults aged nineteen years or older who are indicated to receive those vaccines, including immunocompromised adults

sixty-five years and older. For these groups the recommended interval is at least eight weeks.

The recommended interval for the sequence of PPSV23 followed by PCV13 also has not changed. And lastly, PCV13 and TIV can be administered during the same visit.

Thank you very much. That's the end of my presentation and I would like to be happy to take any questions.

Dr. Candice Robinson: Thank you very much, Dr. Kobayashi. We're going to move into a question and answer session. If you have a question, please dial star one to get into queue for the operator. Please be sure that your question is related to today's content.

A recast of this presentation will be available at www.cdc.gov/vaccines/ed/ciinc the week of November 2, 2015.

While we wait for for the queue to fill, I will give you some continuing education information. For continuing education credits, please go to www2a.cdc.gov/tceonline. For continuing education, the course number for this program is E as in Edward, C as in cat, 2064-102815.

Note that 102815 is today's date and that this course number is specific to today's course. You will need this course number when completing your CE requirements. You will also need the verification code, which is pnemo28 -- P as in Paul, N as in Nancy, E-U, M as in Mary, O, 28 with no space. This verification code also applies to today's program only.

CE credit for this program expires November 30 2015. I will repeat this information at the end of the question and answer period as well.

Now, I'll turn it over to the operator so that our participants may ask questions. Operator, are there any questions in queue?

Coordinator: Yes, there are. (), your line is now open.

(): Good morning. Thank you so much for this presentation. I have a question about Pneumovax. We have a - we're holding a lot of flu clinics and we're giving pneumovax and zoster at the clinics. And there was some questions, I guess, regarding the package insert saying pneumovax and zoster should be administered at least a month apart. Is there - I couldn't find anything in ACIP. I just wanted to know if you knew anything about that, or is there a different recommendation?

Dr. Andrew Kroger: This is Dr. Kroger. I can take that question. The package insert actually does have some information talking about reduced titers to the varicella zoster virus component of zostavax vaccine with simultaneous administration. However, studies have been done since the posting of that package insert looking at the effectiveness of the vaccine for prevention of zoster, which demonstrates that there is no effect on the efficacy around the effectiveness of the vaccine. So CDC recommends simultaneous vaccination of pneumovax and zoster vaccine if both are indicated.

So yes, that would be another example of a CDC off-label recommendation. I believe the paper was Tseng, Vaccine (sic 2006) 2011 that's the efficacy paper that discusses this. So yes, if both are indicated you should give simultaneously.

(): Okay, thank you very much.

Dr. Andrew Kroger: You're welcome.

Dr. Candice Robinson: Thank you very much. Operator we'll take the next question.

Coordinator: Our next question comes from (). Your line is open.

(): Yes, thank you. I was wondering if I have a patient who's sixty-five years or older and they're going to be starting radiation next week, is it a good idea to give the PCV13 today?

Dr. Miwako Kobayashi: Hi. This is Miwako Kobayashi. Thank you for your question. So yes. So if there is an opportunity to provide PCV13 prior to radiation therapy initiation, it is the best to give it prior to initiation of the therapy.

(): What would be the recommended - would you say, if possible, a minimum of two weeks? Or what would you say would be the best?

Dr. Miwako Kobayashi: You mean the interval between starting the radiation therapy and the vaccine administration?

(): Yes.

Dr. Miwako Kobayashi: Yes. For the - I believe that for radiation therapy we don't have any recommendation or any evidence supporting any interval. For surgery there are recommendations of two weeks. But for radiation therapy I believe that there are no recommended intervals.

(): Thank you.

Dr. Candice Robinson: Thank you very much. Operator, do we have the next question?

Coordinator: The last question I show in queue is (). Your line is open.

(): Thank you very much. My question is if we have an unknown pneumococcal vaccine history for the patient, recommendation currently is to go ahead and begin the series. Is that going to be the same even once the prevnar has been out for a long period of time and we don't really know if they've had one or both?

Dr. Miwako Kobayashi: Right, thank you for your question. So as of now, as you said, if the vaccine history is unknown, it is to consider that person as unvaccinated. And then give the series.

(): So is there any change in that because of the prevalence now of the PCV13 being more used and (unintelligible)? Or just go ahead and start the series anyway?

Dr. Miwako Kobayashi: Yes. So there's a plan to review the - all the recommendations by 2018 (note: this is regarding the recommendation of routine use of PCV13 among adults aged 65 years or older). And then at that time there may be changes in recommendation based on changes in coverage and serotype distribution, and we don't know how it will be. But as of now, the recommendation is to give the series.

(): Okay.

Dr. Miwako Kobayashi: Similar to those who haven't bene vaccinated.

(): Thank you.

Dr. Miwako Kobayashi: No problem.

Dr. Candice Robinson: Thank you very much.

Coordinator: There's no other questions in queue at this time.

Dr. Candice Robinson: Alright. Well, while we wait to see if anyone has any additional questions, we'll ask a question that we often receive. So what if someone is sixty-five years old or older and they have an immunocompetent high risk condition like liver disease. Is the interval between PCV13 and PPSV23 eight weeks or one year?

Dr. Miwako Kobayashi: Okay. So the answer to that question would be - the person with chronic liver disease will still follow the new recommendation, which is at least one year. And there is a summary table in the new MMWR that was published in September. So for those who are recommended to have an eight-week interval - at least eight week interval between PCV13 and PPSV23 are going to be those who have CSF leak, cochlear implants, persons with functional or anatomic asplenia such as sickle disease, or those who are considered to be immunocompromised.

And since chronic liver disease does not fall under the category of any of those, they will still follow the new recommended interval of at least one year.

Dr. Candice Robinson: Great. Thank you very much. Operator, we do have any questions in queue?

Coordinator: I do show two more questions have queued up. The first question comes from (). Your line is open.

(): Thank you. This question's for Dr. Kroger. When you were talking about the stem cell transplants, you said not to give zoster because the ablation of the immune system would have deleted their immune memory of having had varicella disease, but doesn't the herpes virus live in the nerve endings? Wouldn't you still have a risk of having a shingles outbreak?

Dr. Andrew Kroger: Thank you for that question. The point is well taken. I think that when patients receive these transplants, I honestly - I'm not an immunologist so I don't know exactly to what degree there might be residual virus in the dorsal nerve root ganglia. Because you're right, that's where the virus remains latent.

Zoster vaccine traditionally has not been recommended in these patients, and that goes back to publications in Tomblyn M, Blood and Marrow transplantation in 2009. They excluded zoster from the list of recommended vaccines. There was some discussion of this at the recent ACIP meeting and because there is a recommendation to use varicella vaccine in those that have received these transplants, that's the recommendation that dominates. So that's the vaccine that should be given.

And there probably will be more discussion on this based on the immunology that you described. But right now varicella vaccine is the vaccine that is recommended post HCT.

(): Thank you.

Dr. Andrew Kroger: You're welcome.

Dr. Candice Robinson: Alright, thank you very much. In the interest for your questions, everyone - in the interest of time we're going to move to some closing CE credit information.

So for CE credits, once again, please go to www2a.cdc.gov/tceonline. The course number is E as in Edward, C as in cat, 2064-102815. The verification code is pneumo28 with no space. Once again, it's P as in Paul, N as in Nancy, E-U, M as in Mary, O, 28. CE credit expires November 30, 2015.

Again, please note that the course number and verification code apply only to today's program.

For help with the online system, which is available from eight AM to four PM Eastern Time, please dial 1-800-41-TRAIN. T-R-A-I-N. This corresponds to the number 1-800-418-7246.

Or you can email ce@cdc.gov. You can email immunization questions to us if you did not get to ask them today at nipinfo@cdc.gov. We will try to respond to those as quickly as possible.

You can also call in immunization questions at 1-800-CDC-INFO. That corresponds to 1-800-232-4636. Available eight AM to eight PM Eastern Time Monday through Friday.

Additional resources that you can use include the Pink Book. The Web site for the Pink Book is there at www.cdc.gov/vaccines/pubs/pinkbook/index.html. It is available online or you can purchase a hard copy. If you go to that site, there is a link for the Public Health Foundation Learning Resource Center.

Our CDC vaccine home page is cdc.gov/vaccines/default.htm. Our resource guide for healthcare personnel, which is entitled “CDC Immunization Resources” for you and your patients is listed at www.cdc.gov/vaccines/ed/downloads/imz-resources.pdf.

Follow us on Twitter for immunization news, information, and resources for private and public healthcare professionals. And that’s @cdcizlearn on Twitter.

With that, I would like to thank everyone for joining us today and with very special thanks to our subject matter experts, Dr. Andrew Kroger and Dr. Miwako Kobayashi. Thank you very much from Atlanta and have a great day.

Coordinator: This does conclude today’s conference call. We thank you for your participation and you may disconnect at this time.

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