

NWX - DISEASE CONTROL & PREVENTI (US)

Moderator: Dale Babcock
July 15, 2015
11:00 am CT

Coordinator: Welcome, and thank you for standing by. At this time, all participants are in a listen-only mode. During the question-and-answer session, you may press Star 1 on your touch tone 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.

I'd now like to turn the meeting over to Dr. (Raymond Strikas). You may begin.

(Dr. Raymond Strikas): Thank you very much. Welcome to the Current Issues in Immunizations: A CDC Net Conference.

I'm (Raymond Strikas). I'm a medical officer in the Immunization Services Division of the National Center for Immunization and Respiratory Diseases - or NCIRD at the CDC - and I'll be the moderator for today's session. To participate in today's program, you need a telephone connection and a separate Internet connection.

The learning objectives for this session are:

To describe an emerging immunization issue;

To list a recent immunization recommendation made by the advising committee on immunization practices;

To locate resources relevant to current immunization practice;

And to obtain, assess and apply patient information to determine the need for immunization.

Today is July 15, 2015.

We have one topic for today's Net conference. Dr. (Andrew Kroger), physician and educator in the communications and education branch immunization service division at NCIRD at CDC will discuss Basic General Recommendations on Immunization: Part 1, as presented in the CDC textbook, Epidemiology and Prevention of Vaccine-Preventable Diseases - also known as the Pink Book - whose 13th edition was published this year.

A question-and-answer session will follow today's presentation, and we will offer another question-and-answer session on Thursday, July 23 at 10 am, Eastern Daylight Time for those who cannot attend today's session or did not have time to ask a question.

Please make a note of the following information. If you have technical trouble, please dial Star 0 on your telephone. If you'd like to ask a question when we get to that segment of the program, please press Star 1 on the phone.

Continuing Education - or CE credit - is available only through the CDC ATSDR Training and Continuing Education online system at

[HTTP//www.2a.CDC.gov/tceonline](http://www.2a.CDC.gov/tceonline). CE credit for today's program expires on August 17th, 2015.

CDC, our planners and our presenters wish to disclose they have no financial interests or other relationship with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. Planners have reviewed the contents of the program to assure there is no bias.

The presentation does not include any discussion of the unlabeled use of a product - or product under investigational use - with the exception of Dr. Kroger's discussion of pneumococcal and zoster vaccines, yellow fever vaccine, and the interchangeability of various types and brands of vaccines. CDC does not accept any commercial support.

Let me now turn the microphone over to Dr. Kroger. You may begin.

(Dr. Andrew Kroger): Thank you, Dr. Strikas. It gives me pleasure to present to you today from Atlanta. Today's topic is General Recommendations on Immunization: Part 1. The flow of my presentation will correspond to the second chapter of the 13th edition of Epidemiology and Prevention of Vaccine-Preventable Diseases - or "Pink Book."

The slides that I am using are similar to the graphics you see in the margins of the Pink Book, and I will be posting these slides in the near future.

The term or concept, "general recommendations on immunization" refers to those recommendations that apply to all vaccines. CDC guidance often comes in the form of a single vaccine-specific recommendation, but in practice, you have to deal with at least 15 vaccines given routinely to patients, depending on the age of your patient.

So there is tentative guidance to address situations commonly encountered in vaccine practice and, essentially, applicable to all of these vaccines.

CDC publishes this guidance in a Morbidity and Mortality Weekly Report in the Recommendations and Reports series. Since the original publication of the General Recommendations in 1976, there have been eight revisions - the last in 2011, pictured here.

So this document is 62 pages long with 239 footnotes, and we do anticipate posting another revision to this guidance in about a year - perhaps sooner. CDC generates this guidance based on the deliberations of the Advisory Committee on Immunization Practices -or ACIP - a non-governmental advisory group of 50 members that meets three times a year in Atlanta and makes recommendations to CDC.

So this MMWR is considered not only CDC guidance, but also ACIP recommendations. This is essentially a table of contents list for the ACIP MMWR document.

It includes chapters on the timing and spacing of doses, contraindications and precautions, preventing and managing adverse reactions to immunization, vaccine administration, storage and handling, altered immunocompetence. There's a section called "Special Situations." What that is is a section designed to incorporate new general topics as they arise. This is a continually changing document.

And then the last three chapters on this slide are entitled "Vaccination Records," "Vaccination Programs," and "Vaccine Information Sources." The General Recommendations on Immunization also is the name of the second

chapter of the Pink Book. And the Pink Book structure is such that there are individual chapters for many of the topics mentioned on the previous slide.

For example, "Vaccine Administration: Storage and Handling of the Immunobiologics." So this allows us to focus today's presentation in two general topic areas. Timing and Spacing of Immunobiologics, and Contraindications and Precautions. Now we'll begin with Timing and Spacing.

The issues that come up most frequently with respect to the timing and spacing of vaccines are:

- 1) The interval between receipt of an antibody-containing blood product and live vaccines;
- 2) The interval between doses of vaccine that are not administered simultaneously; and
- 3) The interval between subsequent doses of the same vaccine.

I'll now begin with the first issue: antibody-containing blood products and live vaccines. So antibody-containing blood products include those products that are used to restore a needed component of blood - whole blood is an example, or packed red blood cells. Or products that are used to provide a passive immune response following disease exposure to provide protection against disease - like immune globulin.

Some of these products have multiple uses, and therefore contain multiple components of the immune system. And as you can tell by the header of this slide, antibody is always one of these components.

So this discussion is going to assist providers faced with the dilemma of circumstances of having one of these products to give at the same time that a vaccine is due. Can the vaccine be given? Can the blood product be given?

To understand why this is an issue, remember that vaccines work differently, depending on whether they are inactivated or live vaccines. So we've crafted a general rule that inactivated vaccines are generally not affected by circulating antibody to the antigen.

However, live attenuated vaccines might be affected by circulating antibody to the antigen. For the most part, antibody in these blood products are not specific to one antigen, so the idea is if a passive antibody is given to someone who receives a live vaccine at the same time - or in close proximity - temporally, the antibody in the blood product might reduce the effectiveness of the vaccine by preventing replication.

Based on what we know about these products, we can be even more specific and say that this is a concern with live vaccines and namely measles and varicella-containing vaccines. We do generalize the replication time of the live vaccine microbe to two weeks. So, if a measles or varicella-containing vaccine is given first, we recommend that providers wait two weeks, if feasible, before giving an antibody product.

After two weeks, the vaccine microbe has stopped replicating, and so inhibition is no longer a concern. Often it might not be feasible to wait two weeks, and so what happens if the antibody-containing blood product was given less than two weeks later? Well, the vaccine recipient can be tested for immunity, or the vaccine can be repeated.

Now if the antibody-containing blood product is given first, providers must wait an interval before giving the measles or varicella-containing vaccine. The duration of the interval does vary by the specific product. I can tell you the

product that has the least amount of antibody of concern still requires a three-month interval before giving the vaccine.

And this interval has been determined based on looking at the half-life of IG - its 30 days - and the effect of the immune response to measles vaccine and extrapolated for all other products and to varicella vaccine.

And so this next slide is an image from Appendix A-24 in your Pink Book, which lists intervals between specific products and measles and varicella-containing vaccines. So, the product type is listed in the left-hand column. The specific dose of IG contained in the product - which can vary not only by the product but by the indication for which the product is used - is listed in the middle column.

And then the interval that has to be waited before administering measles and varicella vaccine is listed in the right-hand column. It's difficult to see that last slide, so I've condensed some of the information on this slide.

So now you're seeing only the left and the right column. The product name and the interval. Remember, the variation in the interval is based on the particular dose of IG.

I won't go through every row on this table in the interests of time, but note that there are some products that don't contain any antibody - such as washed red blood cells - so because there's no antibody, there's no interference with a live vaccine. So therefore, no interval is necessary. Hence, the "zero months" written in the right-hand column.

Jump down two rows. You can see the dosage of immune globulin for measles prophylaxis. It requires a six-month interval. And notice, as well, that there is

a specification - whether the recipient of IG is healthy or - as this says, “normal contact” - or immunosuppressed.

This is because the dose of IG varies. In fact, IGIV is recommended for immunocompromised contacts, so the interval to MMR vaccine or varicella vaccine after one of these products could be six months - or if the recipient is immunocompromised, you can see in the footnote below, eight months.

It's true that a recipient of IGIV might even remain immunosuppressed after eight months, and so the vaccine - the live vaccine - would be contraindicated anyway, and perhaps not given at all. But if immune competence happens to be restored, the recipient must still wait eight months following the dose of IGIV. It's an effectiveness issue.

Notice in the last row on this slide, there are other uses as well for IGIV that have nothing to do with measles prophylaxis, and there are actually different recommended dosages for all of them. So on this slide I've just listed the range of 7-to-11 months.

There are products that have type-specific antibody or negligible antibody. So for type-specific, these products are basically engineered for the prevention of only one disease, and palivizumab - or trade name, Synagis - is an example.

This product only contains antibody against respiratory syncytial virus - or RSV. It doesn't contain antibodies against measles, mumps, rubella or varicella. So this product would not interfere with live virus vaccinations, so requires no interval. And I've already talked about washed red blood cells on a previous slide. They don't have any antibody at all, so also, no interval.

Why do these spacing rules only apply to MMR and varicella vaccine? Here on this slide we talk about other live vaccines. This rule does not apply to zoster vaccine because the large amount of live varicella zoster virus in zoster vaccine is thought to be high enough such that it is not affected by any antibody that's in a blood product given at the same time.

Yellow fever vaccine and oral typhoid vaccine are also exceptions. The reason here is because it's not thought that antibody-containing blood products - even those pooled from thousands of donors - contain antibody to yellow fever virus or *Salmonella typhi*, so it's not thought that replication of these vaccine microbes, when you give the vaccine, would be affected by the blood product.

For LAIV vaccine - live attenuated influenza virus - the vaccine itself is constantly undergoing change through regulation. There's a choice made season by season to change the vaccine, so the risk of interference is thought to be lower in this case.

For a rotavirus vaccine, because the vaccine is administered orally, the site of replication of the vaccine virus is in the GI tract. So it's an anatomical barrier from the circulation, and it's thought that there would be less interference from an antibody-containing blood product in the circulation, in that circumstance.

So now I'm going to talk about the second general timing and spacing issue. And that is the interval between two different types of vaccine. And note that I'm going to discuss the administration of two different vaccines using the word "simultaneous." That means the same clinic day. Rarely will it be at exactly the same time, but it's the same clinic day. Or "non-simultaneous," meaning different clinic day.

The next general rule is that all vaccines can be administered simultaneously - the same day at the same visit. It's true that not every possible combination of vaccines has been studied and measured. Many of the combinations have been measured, and for most, there is no observable effect on the effectiveness of these vaccines when given simultaneously.

There are two exceptions to this general rule. One of them is discussed in the Pink Book General Recs chapter, and one is discussed in the pneumococcal Pink Book chapter. And so I'll discuss them both here now. And I'll start with the exception that's discussed in the pneumococcal chapter.

If there is a need for both the pneumococcal polysaccharide vaccine and the pneumococcal conjugate vaccine - PPSV 23 and PCV13, respectively - if both are indicated, then we recommend PCV13 should be administered first, so you can't give them simultaneously.

This is because in studies that measured antibodies in adults receiving these vaccines, the antibody response to PCB 13 was higher in adults 50 years of age and older if they did not receive PPSV23 first. So, to optimize the immune response from PCB 13, we recommend that it be given first, and we recommend that PPSV23 follows one year later.

So it's an effectiveness issue - the efficacy issue, actually - because it was determined in a controlled research setting.

There also have recently been determined higher risk of local reactions with these two vaccines given simultaneously. They're mild. So we also have another eight-week interval rule for a minimum interval between the two doses. This is less of a concern than the efficacy issue that I just spoke about.

The other exception to simultaneous administration is co-administration of Menactra - meningococcal conjugate vaccine or MCV4D - and PCV13 in asplenic children.

Studies that looked at the co-administration of - it was actually the PCV7, another pneumococcal conjugate vaccine - and MCV4D demonstrated a reduced antibody response to three of the seven strains of pneumococcal bacteria if Menactra was co-administered with PCV7.

Children with no spleen - or asplenic children - are at risk for severe disease from both pneumococcal and meningococcal bacteria. The risk is higher because the disease is more common with pneumococcal bacteria.

So we prioritize usage of PCV13 first. So don't give them simultaneously. Give PCV13 first, and then we recommend Menactra when the PCV13 series is complete, and four weeks after the last dose of PCV13. So that's simultaneous administration.

Now let's talk about non-simultaneous administration. So, when a provider has decided to use a vaccine, they must be aware of other vaccines that may have been given recently. And this is relevant when two different live vaccines are in play.

So similar to the discussion we had about simultaneous administration, this is a concern with effectiveness. It's not a safety issue. And this rule doesn't apply to all live vaccines either. Only the injected or intranasal live vaccines.

So if an injected or intranasal live vaccine has been administered recently, there must be a four-week minimum interval between another injected or

intranasal live vaccine. So you just need to be aware of that - vaccines given recently.

This comes from reduction in the effectiveness of the vaccine that has been observed with cases of breakthrough varicella that occurred when varicella vaccine was given too soon after MMR vaccine. It did not occur if MMR vaccine and varicella vaccine were given on the same day. Hence, our general rule that we allow simultaneous vaccination but not non-simultaneous vaccination, for live injectable and intranasal vaccines.

And the vaccine that should be considered invalid is the vaccine given second with non-simultaneous administration. Last row on this slide is if one of the two vaccines is an inactivated vaccine, so other combinations - this effectiveness issue is not a concern.

So, a bit more on this now. If the second dose is administered non-simultaneously, and it is within a 28-day or four-week - those are equivalent - and conventionally how we define one month - then the dose given second is invalid, and should be repeated.

Now, the reason behind this recommendation - I've mentioned breakthrough varicella. We also know that the first vaccine interferes with the replication of the second vaccine. Back in the 1960s, this effect was observed with a reduced immune response to smallpox vaccine when it followed measles vaccine by less than a month.

It was believed to be due to an immune component called interferon, causing the negative effect of the vaccine given second. And so it's the second vaccine that's invalid. This is relevant also because whether it's caused by antibody or

interferon, whatever the cause - this is often invoked as something that can affect the immune response to live vaccines.

And as part of this rule, we've made the recommendation that you should wait to give the repeat dose 28 days after the invalid dose –i.e. the one given second. So you have to wait a full 28 days after the invalid dose.

There are exceptions to this general rule. Single antigen measles and yellow fever vaccine do not need to be spaced by 28 days. Presumably they could be given simultaneously as well.

This exception is a little outdated, because single antigen measles vaccine is not available in the U.S., and there's some information in the Pink Book that discusses this further, but I will let you know that you should be very careful with yellow fever vaccine, because our yellow fever vaccine experts do, in fact, recommend repeating yellow fever vaccine if it is given less than 30 days after a dose of MMR vaccine.

Our measles/mumps/rubella experts are not as concerned about this issue, but the yellow fever vaccine experts - if you're giving it in combination with any other live vaccine - we typically consult with them when yellow fever vaccine is given with another live vaccine, just to be sure that you do need to repeat the yellow fever dose.

So now I'd like to discuss the final timing and spacing issue. The interval between doses of the same vaccine. This is probably the most common issue you will face as a provider, because it's a relevant issue whether you're using one vaccine or many vaccines.

And so we have another general rule. And that is increasing the interval between doses of a multi-dose vaccine does not diminish the effectiveness of the vaccine. This is relevant and helpful because if doses are late and you fall behind in a series, you don't have to restart the series. The dose is not invalidated.

Now, not all permutations of all schedules for the vaccines have been studied. But we do know some things about certain vaccines - notably hepatitis B vaccine, human papillomavirus vaccine - that shows either no significant difference in the antibody titer or even an improved antibody titer when the intervals are extended.

So obviously you don't want to extend your recommended interval on purpose - because that delays protection with the vaccine, but it is very comforting to know that if the series is delayed, it is not necessary to restart the series. So increasing the interval is not a problem between doses of the same vaccine.

However, decreasing the interval between doses of a multi-dose vaccine might interfere with the antibody response and protection. The ideal is to use intervals recommended by the manufacturer, because studies of duration of protection and efficacy and effectiveness - when the series is complete - are based on the use of those intervals.

On the other hand, if a dose is administered early, does that mean you can't count the dose? The answer is no. Sometimes you can count the dose, and we have defined what are known as minimum intervals. These are intervals that can be used to validate doses that may have been received too early - shorter than the recommended interval.

And a list of all these intervals is included in Appendix A-13 of your Pink Book. Too much information on this slide to read, so I'll just give you a closer look.

As you can see, for every dose of every routine vaccine, we define the recommended age for the dose in the second column, the minimum age for the dose in the third column, the recommended intervals for the next dose in the fourth column, and in the right-hand column, the minimum interval for the next dose. So recommended and minimum ages and intervals on this table.

Now a couple of important points. Generally you should not administer vaccines at intervals less than the minimum intervals or earlier than the minimum ages. First of all, you should try to use the recommended ages and intervals, of course. But really, when we talk about the minimum, this is as far as we want to go, generally. And we'll count the dose if it's given.

When can the minimum interval be used? If you have a child in your office that's behind or lapsed in a series, then ACIP specifically recommends that you use these minimum intervals as part of your catch-up. And this information is described in the ACIP harmonized schedule for children and adolescents - the catch-up table.

Another circumstance in which you might choose to use minimum intervals is with international travel. For instance, someone who is travelling and concerned about measles exposure - they might choose to have their child receive the second dose of MMR vaccine four weeks after the first dose of MMR vaccine, even though our routine schedule states that the first dose should be given at 12-to-15 months, and the second dose at four years. That three-year plus/minus interval can actually be shortened to four weeks. And the doses will count and be valid.

But again, to repeat, in the absence of any increased risk - to maximize protection at the times for which we know that the risk for disease is highest among the particular age cohorts - try to use the recommended intervals and ages.

Now, there are circumstances where we still will validate a dose when the minimum interval is violated. This is called the grace period. So ACIP recommends that vaccine doses given up to four days before the minimum interval or age can be counted as valid.

You should not use this for scheduling future vaccination visits. We think of the grace period in the context of validating past doses. It is useful for reviewing vaccination records. From basic principles, though, even though you should not use the minimum intervals prospectively, you should use recommended intervals or ages.

I've talked about the fact that you can use minimum intervals for catch-up, and oftentimes we hear from providers that they want to use the grace period prospectively.

And actually, the whole genesis for the grace period comes from the need of providers to give a dose prospectively, so there are limited circumstances where we say, prospectively, you can use four days short of the minimum. Not to schedule a future appointment, okay? We're talking about really point-of-care interaction with a patient in your office.

Of course, I've mentioned this repeatedly - when evaluating the vaccination record, yes of course, retrospectively, you can count the grace period.

There may be times when a patient or client is in your office and you can consider giving a dose, even though it is earlier than their supposed visit time - like if they're going to be coming in a few days for a vaccination visit, and they happen to be in the office early - you potentially can use this grace period and give the dose of vaccine.

The issue is if you have a great relationship with your client, and you know they're going to return at a later date, don't use the grace period. Reschedule the patient. Remember, you should be using recommended ages anyway, so you wouldn't want to use the grace period in this circumstance. However, if you don't know whether a patient will return and you fear a missed opportunity, and the patient is behind schedule, lapsed and actually much older than the recommended age - then in that circumstance, yes. Maybe you can use the grace period, cut the minimum short by four days and vaccinate.

Note that sometimes the grace period may conflict with state school entry requirements. And so based on state law, immunization programs may not accept doses given earlier than the minimum age or interval. This happens often with varicella and MMR vaccines.

So we do want you to be cognizant of the law and don't use grace period in most circumstances. Most states have the grace period. But they might not have them for every single circumstance and every vaccine. So try to comply with state law.

Now I'd like to talk about violating minimum intervals and minimum ages. What happens if this occurs? What does the provider do? Well that dose is invalid. And we recommend repeating the dose. In this circumstance we recommend repeating the dose a minimum interval from the invalid dose.

So that sounds similar to what we talked about with the 28-day live vaccine rule with different live vaccines. But don't get them confused. This is a different rule. One, it applies to both inactivated and live vaccines. And two, the interval that you need to wait is sometimes 28 days, but not always.

It's really whatever minimum interval was recommended prior to the dose that's invalid. You then forecast an additional interval beyond that invalid dose to give the repeat dose, and so we've got this programmed into registries and other assessment programs. So you should try to follow these spacing rules.

Although the nuance has led to challenges with certain combination vaccines and sometimes we are forced to back off strictly from the recommendations, the "Pediarix-challenge" is the classic example. Because Pediarix is a three-dose combination vaccine that has hepatitis B vaccine as a component, yet it's not licensed to be given during the recommended age for the first dose of hepatitis B vaccine, which is birth, this often leads to multiple interval violations.

When Pediarix was being studied, there was not a full recommendation for the birth dose. So this situation is nobody's fault, but it has created complications. What can happen is if you dutifully give your hepatitis B vaccine at birth and then you start using Pediarix; let's say you give the first dose of Pediarix at two months of age. That would be the second hep B component, right?

And then you give your second dose of Pediarix, and let's say that one is administered even as late as five months of age which is late for the second dose of Pediarix. But that's actually early for the third dose of the hep B component. It's younger than 24 weeks of age by our strict minimum age rules for hepatitis B. So you would then invalidate that dose.

Then if you apply the rule that I just talked about about forecasting a minimum interval beyond the invalid dose, you would have to wait a while for that third dose of Pediarix. But if a provider doesn't and they gave Pediarix at six months of age, then that dose would also be considered invalid.

So what we have done in this circumstance is we backed off. And where it looks like two doses are invalid, we have programmed registries and other systems to drop one of the doses out so that we can count this type of series as a three dose hepatitis B series. And CDC does not recommend giving yet another dose which would be a fifth dose of hepatitis B vaccine in this situation. So that's timing and spacing.

I'm now going to move on to contraindications and precautions. This discussion will be a little less mathematical. I'll start with some important definitions - vaccine adverse reaction. An adverse reaction is an extraneous effect caused by a vaccine. It's any effect that occurs which is different from the purpose of the vaccine - that is to generate a protective immune response.

A synonym for adverse reaction is side effect.

That sounds like an intuitive definition. But there's more to this concept, so let's define another term - adverse event. This is any medical event which follows a dose of vaccine.

Is this really different from an adverse reaction? Yes because we're talking about clinical outcomes. And we want to make sure that we apply the right meaning to that outcome at the right time. The meaning might change over time, but we've got to use the right words. So an adverse event is really anything - any medical event of concern following a dose of vaccine.

It very well might be a true adverse reaction. Or it might just be a coincidence. So basically these outcomes need to be studied before we would redefine them as an adverse reaction. So in the meantime we all them adverse events.

And throughout the pink book you are going to notice this distinction in almost every vaccine-specific chapter. If the language which described the clinical outcome was backed up by significant data, you will see it fall under a header of adverse reaction. If it has been identified but there's not a lot of information and data, you will see it fall under the header of an adverse event.

Just note that this conceptually can change at any time. An outcome can be redefined as an adverse reaction. But I wanted to let you know about this change in the way the pink book was organized. It's basically a huge change from the way it was organized previously.

When do outcomes get redefined as adverse reactions? Well first they need to be reported. I have a slide here on the Vaccine Adverse Event Reporting System or VAERS. We want you to report any concern - any clinical significant adverse event. And we take reports from the public and private sectors - any event that occurs after a dose of vaccine even if the provider is unsure whether the vaccine caused the outcome.

We also allow for the reporting of vaccine administration errors, even if no clinical outcome occurs. We do want to collect information about errors. So while this is less of a vaccine safety surveillance issue. But we are collecting information about errors as well.

So to report to VAERS - to obtain a reporting form you can call 1-800-822-7967. Or we encourage online reporting of these adverse events at www.vaers.hhs.gov. I'll note also that you can report outcomes that are

already defined as adverse reactions. In fact the law requires you to report those adverse reactions that already exist.

So I'm going to focus now on adverse reactions. And they can be subcategorized as either local reactions, systemic reactions or allergic reactions, the last of these being the most severe and least frequent. Local reactions include pain, swelling, redness at the site of injection.

They're most common with inactivated vaccines, since inactivated vaccines contain in addition to antigen, preservatives, stabilizers, adjuvants, antibiotics - all required components of the vaccine. But they can generate the pain, swelling and redness. These local reactions are usually mild and self-limited, meaning they resolve without treatment.

Systemic reactions include symptoms and signs like fever, malaise, headache. They're not specific, so it can be very challenging to determine whether they're related or unrelated to the vaccine. I've got a slide here titled Live Attenuated Vaccines.

One clue as to whether as a systemic reaction might be due to the vaccine is to consider whether it is a live vaccine or not that was administered, because live-attenuated vaccines have to replicate in order to provide immunity. Reactions following live vaccines can mimic the symptoms that occur following the vaccine preventable disease which makes sense when you realize that the vaccine is an attenuated version of the live microbe.

But these symptoms are milder than natural disease, but characterized by the same types of symptoms. So we see things like fever and rash occurring after MMR and varicella vaccine. And the timing can be a clue as well.

If the reaction - if the vaccine reaction occurs one incubation period after administration of the live vaccine, that clues you in that it might be due to that vaccine because that's when symptoms occur after the incubation period. So that very well might be a systemic reaction to the vaccine.

Lastly, allergic reactions. Vaccines contain not only vaccine antigen but also adjuvants, preservatives, stabilizers and antibiotics. And allergic reactions can be due to any of these components.

Fortunately these types of reactions are rare. Their risk is made even rarer by screening for common anaphylactic allergies prior to vaccine administration. The pink book has a table of excipients and components of every vaccine. I'll also direct you to the FDA's web site as well though because, you know, the pink book is going to be a snapshot. And sometimes these components do change.

So if you really need to know what's in a vaccine, you can go on the FDA web site. But really the common sense thing to do is to screen for anaphylactic reactions in the patient history. Talk to the patient so you know what the possibilities are. An allergic reaction occurs so rarely that you can minimize the risk effectively just by doing the screening.

Let's define some new terms now - first a contraindication. This is a condition in a recipient which greatly increases the chance of a serious adverse event. When a contraindication is identified with a potential vaccine recipient, you should not give a dose of that vaccine to that patient.

A precaution on the other hand is a condition in a potential vaccine recipient which may increase the chance or severity of an adverse event. Or it may compromise the ability of the vaccine to produce immunity. Where a

precaution exists, clinicians need to weigh the risk and benefit – rather the risk of giving the vaccine versus the risk of withholding a dose of vaccine, and leaving the patient vulnerable to the disease.

So note that the definitions of contraindication and precaution - they're similar in that they apply to the patient and not to the vaccine, unlike the “adverse event - adverse reaction” definitions. These are conditions that apply to the patient. And they can be identified in your patients via screening.

I'm going to talk about screening next week. But I do want to flesh out contraindications and precautions a little bit more. Some contraindications and precautions are actually temporary conditions. And it's possible for providers to just delay giving a dose of vaccine. That's simple.

However some contraindications and precautions are permanent conditions. And this slide lists one permanent contraindication that applies to every vaccine that's out there. If a patient has a severe allergic reaction, for example anaphylaxis, to a prior dose of vaccine or to a vaccine component, this is a contraindication.

There are rare circumstances where complicated desensitization protocols can be used. These are performed by allergists only. But in general a vaccine should not be given to a patient that has a severe allergic reaction to a prior dose of vaccine or to a component.

The next slide lists some other permanent contraindications, two of them for specific to rotavirus vaccine - a history of severe combined immunodeficiency disease or SCID. This is because vaccine – derived rotavirus disease has been observed in patients with the severe immunodeficiency that were vaccinated.

A history of intussusception is also a contraindication to rotavirus vaccine. Intussusception is a gastrointestinal complication that is multi-factorial - it has many different causes. It was associated with a rotavirus vaccine that was used in the 1990s that's no longer used.

It is currently being investigated with the current vaccines, although the extent of the risk is extremely rare but not completely known. What we do know is that if someone has had a history of intussusception already, the risk of repeat intussusception is higher. And so that is why this exists as a contraindication for rotavirus vaccine.

And then another permanent contraindication linked to pertussis vaccine - encephalopathy not due to another identifiable cause occurring within seven days of a previous dose of pertussis vaccine. This contraindication drives from our use of the whole cell pertussis vaccine which was associated with encephalopathy. We no longer use the whole cell pertussis vaccine. And this outcome is extremely rare.

So in addition to these permanent contraindications, I've listed some other common conditions which serve as contraindications and precautions. This is a table in which the conditions are listed down the left hand side. And then those that are contraindications are abbreviated C. Those that are precautions are abbreviated P. And those for which a provider can vaccinate if indicated are abbreviated V for different classes of vaccines - live and inactivated vaccines.

So I talked about allergy and encephalopathy. The next condition listed is pregnancy. This is a contraindication to live vaccines. Pregnancy is generally not a contraindication to inactivated vaccines, although HPV vaccine is an exception to this rule.

Immunosuppression is a contraindication for live vaccines but not to inactivated vaccines. Acute, moderate or severe illness is considered a precaution for essentially all vaccines, live and inactivated. If someone has acute, moderate or severe illness, it is best to wait until a patient has recovered before vaccinating.

And I've already talked about recent blood products in the first half of today's presentation. This is considered a precaution for the live vaccine, specifically MMR and varicella containing. But this is not considered a contraindication for inactivated vaccines.

The specific contraindications and precautions for every vaccine are listed in your pink book in Appendix A28 through 30. It's an insert from the Immunization Action Coalition's table. I can't talk about all of them. But I'm going to focus on the two that I've just described - pregnancy and immunosuppression. So I'll go into these two in a little more depth.

So the risk to a developing fetus from vaccination of the mother is primarily theoretical. Only one vaccine has ever been demonstrated to injure a fetus, and that is the smallpox vaccine. Smallpox vaccine is a live vaccine, and we have made the generalization to say that pregnancy is a contraindication to all live vaccines.

In general inactivated vaccines may be administered to pregnant women for whom they're indicated. An important exception is HPV vaccine. We recommend deferring a dose of HPV vaccine during pregnancy. This is because of a lack of safety and efficacy data for this vaccine in pregnant woman. FDA however does not label pregnancy specifically as a contraindication. And there are no interventions required if this vaccine is

given in error to someone who is pregnant. Remember this is an inactivated vaccine.

Talking about some other inactivated vaccines, influenza and TDAP vaccine are actually both specifically recommended to be given during pregnancy because of the additional protection afforded by the vaccine to both the mother and the fetus in the case of influenza, and to the fetus in the case of Tdap. And for Tdap and influenza - that protection is felt to last after birth.

In other circumstances in which a vaccine - a vaccinee might be pregnant, the decision to vaccinate is based on other risk factors for disease. For hepatitis A and hepatitis B vaccine, note that these other risk factors are what make the vaccine indicated in the first place. And so they typically drive the decision to vaccinate a pregnant woman with these vaccines

It is less clear for some of the other vaccines. We specifically say not to get HPV vaccine if pregnant. For vaccines like PCV13 and HibB, these vaccines are not very commonly indicated for a pregnant woman anyway. It can be a challenging decision if there is a woman who is pregnant and has another indication for these vaccines.

And here's an interesting example of the live vaccines. So yellow fever vaccine is live. And the general recommendation would be not to give this vaccine during pregnancy. But it's not always a clear cut decision.

Again the risk of yellow fever vaccine virus to a fetus is theoretical only, we state that travel to areas of high risk for yellow fever disease should be avoided in pregnancy. Where that travel is unavoidable, the clinician has to make the difficult decision.

If someone is going to pass through a high risk area but remain on an airplane, there may be, you know, regulations requiring the vaccine where the risk is actually quite low for disease. And in most cases a medical waiver can sometimes be granted. However if there is travel to a high risk area, the vaccine should be administered because the risk of disease outweighs the risk from the vaccine.

Moving on to vaccination of immunosuppressed persons - this is a complicated topic. There are many different degrees of immunosuppression. But in general live vaccines should not be administered to a severely immunosuppressed persons because of the concern that the immunosuppressed host's own immune response will not be able to stop the live vaccine microbe from replicating.

And there have actually been instances where severe disease like pneumonia has been caused by a vaccine virus, for instance in HIV infected vaccine recipients. So we have that general recommendation. But there are exceptions as with everything.

Persons with isolated B cell deficiency can receive the varicella vaccine. An effective immune response to the vaccine is dependent on other components of the immune system. So we do allow its use if there's an isolated B cell deficiency. But if there's both B and T cell deficiency varicella would fall under the general recommendation of a contraindication. Inactivated vaccines are safe to use in immunosuppressed persons. But the response to the vaccine may be decreased. And this issue has led to some new complications.

Just to classify immunosuppression a bit further, beyond the degree or the cell type, there are specific interventions that we define in the general reqs - certain diseases or conditions like congenital immunodeficiency syndromes,

blood cancers like leukemia and lymphoma or any generalized malignancy or cancer really can be considered immunosuppressive in its own right on the absence of immunosuppressive medications.

But note that immunosuppressive medications are given to many other types of patients with other kinds of cancers or other diseases. Some of these types of therapies include alkylating agents, antimetabolites and radiation therapy. But there are other new classes of medications which make this complicated as well. Immune mediators and modulators and iso antibodies are some of the names that we use for some of these treatments.

They're used in cancer therapy but also for rheumatic diseases and other autoimmune diseases. And I've got listed here a big class used - anti tumor necrosis factor agents. These are agents like Etanercept or Enbrel as a trade name - infliximab is Remicade. And adalimumab is Humira.

And the point I would like to emphasize is that the best person to determine the level of immunosuppression in a patient on one of these medications is the clinician who originally prescribed the medication. So as a provider, if you're not the one that put the patient on this medication, one of our general recommendations is to defer to a physician to determine the level of immunosuppression in a patient. And so I mean it's acceptable to defer vaccination in the context of uncertainty. But it's really, really important to try to truly determine through consultation whether the patient is immunosuppressed or not.

And there's another class of immunosuppressing medications called corticosteroids. And these are so common that we developed some guiding metrics for these medications. So while the amount or duration of

corticosteroid therapy probably could benefit from some further precision, we have defined some parameters.

First of all, a cut off dose of 20 milligrams or more per day of Prednisone or the weight based equivalent for pediatric weights of two milligrams per kilogram per day, both for a duration of two weeks or longer as a definition for calling corticosteroid use immunosuppressive. And it's not only dose or duration.

We're focusing on what we call systemic steroid use and not aerosols, not topical treatment, not variations in the courses - those less than two weeks or alternate day courses NOT considered immunosuppressive. Physiological replacement schedules - corticosteroids used in adrenal insufficiency syndromes - NOT considered immunosuppressive.

If your corticosteroid regime is considered immunosuppressive, we recommend delaying live vaccines for at least one to three months after discontinuation of this high dose therapy. So that's - one month is what's printed in the general reqs - ACIP statement.

In your pink book you will see further discussion. The Infectious Disease Society of America classifies corticosteroids with other anti-cancer therapies, suggesting a three month washout period as opposed to one month - not an official ACIP CDC recommendation yet. It's not completely clear-cut in any case, since both ACIP and IDSA, you know, focus on one month for specific vaccines such as zoster vaccine. So this can get quite complicated.

But to summarize some important principles here, immunocompromised persons are at risk of adverse events following live vaccines. With many categories of immunosuppression, we do have a three month interval after the

therapy has - is concluded before you can give the live vaccine. We use three months for most of the forms of chemotherapy I mentioned. And the CDC ACIP recs currently in print say one month for steroid use of two weeks or more.

Another very important principle is that the household contacts of immunosuppressed persons - they should be vaccinated with all vaccines, inactivated and live, generally the benefit of preventing disease in the household contact outweighs the theoretical risk of transmission of live vaccine virus.

So the concern with immunocompromised patients and vaccinations is not only safety but also with effectiveness. So we have expanded a bit, and some of this language is in the pink book. And you can expect changes to the ACIP recs as well of a potential need to withhold both live and inactivated vaccines in someone who is immunosuppressed.

But inactivated vaccines - it's an effectiveness issue. And you'll see this language commonly with the tumor necrosisfactor inhibitors that I mentioned. While we say you can generally treat them like steroids, we emphasize that some experts do recommend waiting longer than one month after use of these medications before vaccinating with live or inactivated vaccines.

And I will confidently state that there's one new class of isoantibody I haven't spoken about - the lymphocyte depleting agents. Rituximab is an example here where the experts recommend a six month period after completion of the therapy before giving live vaccines and even inactivated vaccines. The inactivated vaccine will not be considered to work and will need to be repeated. This could be an issue with inactivated influenza vaccine which you want to give during the season, but you might need to repeat it.

Focusing on a particular type of immunosuppression, HIV infection - because HIV infection is very - is relatively common compared to other types of immunodeficiencies like the congenital syndromes, it's been extensively studied in the context of vaccine. And it is difficult to generalize withholding live vaccines which we still know are protective.

We know that the diseases like measles, varicella, influenza, and pneumococcal disease cause severe complications in patients with HIV infection. And so we have a higher threshold for withholding the vaccine in this circumstance.

And you can see on this slide a table - and I'm not going to go into detail on every row here in the interest of time. But the disease specific pink book chapters go into the detail. And so do the disease specific ACIP recommendations.

One point I'll make - note that some live vaccines - MMR, varicella vaccine are still recommended to be given to patients with HIV/AIDS. But the column header says asymptomatic. It's not really the issue of symptoms. It's really specific laboratory parameters that are beyond the scope of the pink book chapter in today's presentation.

Other considerations for using vaccines in patients with HIV/AIDS, we note that we mention LAIV vaccine not recommended for HIV infected persons. And really that's because we have an inactivated influenza vaccine which theoretically is safer.

I'm going to conclude my point today with a couple slides on hematopoietic cell transplant recipients, or HCT patients. These are patients that received

bone marrow or stem cell transplants -- either self-harvest or someone else's cells. The reason for these transplants is the need to restore an immune system that has been wiped out either by disease or chemotherapy.

And so these patients are immunosuppressed because of the disease that they had, because the process of the transplant wipes out their immune system, or because of the therapy they're on after the transplant designed to prevent a resection of the transplant. So these patients are immunosuppressed.

But not only are they immunosuppressed, but because of their HCT their entire immune memory, their entire vaccine history has been wiped out. So they must be revaccinated. And the timing and the vaccination schedule is driven in part by the risk of disease -- the encapsulated bacteria are the most problematic -- and we've vaccination is generally recommended six to 24 months post-transplant.

Essentially the inactivated vaccines are recommended four to six months after the transplant -- and this includes - inactivated influenza, DTAP vaccine, Tdap, PCV13, PPSV23, Hepatitis B HIB, and HPV and MCV4 vaccines are other examples that should be administered again even if you have a history of the vaccine already been given after the transplant. And it's a six month interval. For live vaccines, it's 24 months. And additionally patient must be considered immunocompetent at that point.

At the bottom of the slide I draw your attention to a citation – Rubin L, Clinical Infectious Diseases, 2014 – which really highlights specifics on not only HCT recipients, but the immune-suppressed. And so this is an accompaniment the general (Rx) pink book, and what's coming in the ACIP statement for many details regarding HCT transplant recipients.

So I'm going to stop now with my comments and move onto a poll question. I've given you a lot of information so I have just one poll question. "If the hepatitis B vaccine series is interrupted, and the interval between dose one and dose two is extended to two year, what action needs to be taken?" Your choices are, invalidate dose to repeat as soon as possible, invalidate dose two and repeat one month after the invalid dose, both doses count and continue the series, neither dose counts so restart the series. So why don't you take 10 seconds and will let you answer the - choose the best option?

So great. It looks like 96 percent of you elected the third option, both doses count and continue the series. And that is correct. Extending the interval between doses is not a problem. You don't want to do that on purpose, but if it happens to count the doses and just continue series. And 96 percent of you chose that response. So good job.

I will - that concludes my comments, so I'm not going to turn the microphone back over to (Dr. Strikas).

(Dr. Strikas): Thank you very much, (Dr. Kroger). I'd like to notify our listeners to call in and asked some questions. To do that please dial star 1 on your telephone.

Please restrict your question to the contents of the program discussed today. Please tell us your first and last name and where you're from. Now I'll turn the microphone over to our operator.

Coordinator: Thank you. There are two questions in queue. The first one comes from (Kelsey Holder).

(Dr. Strikas): Please go ahead.

(Operator): Miss (Holder), you have an open line. Please check to see if your phone is on mute. All right. Let me just get the name of the second question and I'll push that one. One moment. Our next question comes from (Lillian Yao).

(Dr. Strekis): Hello?

(Lillian Yao): Yes, hi. Just a clarification for the permanent contraindication for an allergic reaction. If I'm allergic to a dose of MMR and I get a different vaccine, or is it just because we don't know what I'm allergic to that all vaccines are now a contraindication?

(Dr. Andrew Kroger): So correct. –The permanent contraindication as defined, and contraindications in general, are linked by the content that's described with the particular vaccine, so that linkage is a one-to-one linkage. So yes. So if you have a history of that event, other vaccines - it would not serve as contraindication for other vaccines.

But know a couple of caveats there, if an anaphylactic allergy -- and we're really talking about anaphylaxis as the most common severe allergic reaction that we expect to occur, e.g. swelling of the lips or throat, itching, gastrointestinal, respiratory, cardiovascular symptoms -- really a severe anaphylactic response, occurs, you want to try to ascertain whether that really occurred. Anything short of that really doesn't qualify as a contraindication. So that's the first step is to make sure you screen your patients effectively to ascertain whether that really was what was experienced.

But then, if that was what occurred, that vaccine would be contraindicated. But you would need to consider the fact that there may be components in that vaccine that are in other vaccines. And the pink book does have a table of those components -- which for each vaccine has not only a long list a

complicated excipient names, but also a date indicating the last time that information was checked.

And you can get an instantaneous look at what components are specifically in that vaccine by going to www.fda.gov and clicking on the package insert for that vaccine to know precisely what is in there. And so the contraindication is “severe allergic reaction”. For example, anaphylaxis vaccine component or to a prior dose of that vaccine.

(Lillian Yao): Okay, so it's vaccine specific unless you can determine what the components are?

(Dr. Andrew Kroger): Right. I mean, if you're certain it's anaphylaxis you want to determine what the components are. It's rare, and it's something that requires medical and clinical evaluation to identify.

(Lillian Yao): Okay. Thank you.

(Dr. Andrew Kroger): You're welcome.

Coordinator: Our next question comes from (Patty).

(Patty): Hi. Good morning. When you were talking about the precautions of immunizing with live virus, I mean vaccines for those on immunosuppressive drugs, and you talked about immune mediators and modulators, where does therapy with, like, Xolair or (Phrasmatix), where does that fall in? How do they determine that? Would that be one that they would be contraindicated to receive live vaccines, like for shingles, say?

(Dr. Andrew Kroger): Yes. A lot of the asthmatic medicines involve interleukins or isoantibodies. What I do with most of the asthmatic medications is I end up going to the package insert and just seeing whether it's immunosuppressive or not. I may need some help from my colleagues. I'm not 100 percent certain whether that one is or not. But that's what I would do is go and look at the package insert, see if it's listed as something that's immunosuppressive, and then, you know, if you prescribed medication yourself you would then apply precautions for the use of that vaccine.

I've never considered a three month interval, I don't think, with any asthmatic medication. But if you didn't -- if you aren't the one that prescribed the medication you could consult with the provider that did prescribe the medication and just get a sense from them whether they consider their patient immunosuppressed on this medication.

(Patty): Yes, to talk to their pulmonologist or whatever, okay.

(Dr. Andrew Kroger): Right.

(Patty): Thank you.

(Dr. Andrew Kroger): You're welcome.

Coordinator: Our next question comes from (Deb Berlekamp).

(Deb Berlekamp): Hello. I have two questions. The first one is if you have a patient, say that is using Methotrexate weekly for, you know, even rheumatoid arthritis or Crohn's disease, what would your recommendation for live vaccines be there?

And the second question is a similar question to one that we had last week about patients who say they get the flu from the inactivated vaccine. As far as adverse drug reaction reporting, if we hear that so often should we, you know, encourage them to report those adverse reactions?

(Dr. Andrew Kroger): So, I'll take the first question first. I've traditionally, if I hear Methotrexate, I've traditionally applied our general three month rule to that drug because, you know, often times - for a while there we did not really tease out the dose. But now with one particular vaccine -- and it only applied to one, Zoster vaccine -- there is a specific dose cut off for defining Methotrexate as a immunosuppressive. And I do apply that exception to Zoster vaccine.

It can be challenging to apply, even if at the low dose, it's tough to apply the exception to the other vaccines. And I traditionally didn't do it before the Zoster subject matter expert came up with this dose parameter. But again, I'm going to opt to talking with the provider that, you know, actually administers the medication.

I think it's a good benchmark guideline for low-dose versus high-dose. But I know that in print we only apply that exception to Zoster vaccine with respect to Methotrexate.

And for the second question about flu and reporting, so you know, the inactivated influenza vaccine can't cause the flu. It can cause other symptoms. So I guess if something is concerning to you as a provider, usually the person doing the reporting is going to be the person that experiences and witnesses what's happening in the patient.

So it could be the provider, it can be the patient themselves, it will take reports from both and as many people as want to report it as well. We'll de-duplicate the records and everything.

But yes, I mean if it's clinically concerning report it. I think by definition it can't possibly be what we call influenza disease, because the vaccine can't cause that. But the symptoms can be caused by it. And if it's a concern to you, it's fine to report it.

We'll take the next question.

Coordinator: Our next question comes from (Don Cooley) from West Virginia.

(Don Cooley): Yes, (Dr. Kroger), my question is regarding the valid doses and minimum interval. I understand we're supposed to repeat the valid dose after the minimum interval from the valid dose, except with expired vaccines -- inactivated, expired vaccines. We can repeat it as soon as possible. Could you please explain the difference?

(Dr. Andrew Kroger): Yes. Absolutely. It's a great question. It's actually the definition of what is causing the invalidation. So when I talk about forecasting a minimum interval before giving a repeat dose that is specifically in the context of the invalidation being a shortened minimum interval.

It does not - that rule does not apply to "expired dose", it does not apply to "temperature-deviated" dose, it does not apply to wrong route -- like if, you know, some of the vaccine squirts out of the syringe. So that rule only applies to your interval was shortened too much.

Now that being said, of course there are other rules that we apply for live vaccines for those other types of invalidation. But the rule where you take the minimum interval that occurred before the invalid dose, and forecast it so that you have to wait Beyond the invalid dose applies specifically to when the interval gets shortened. So it wouldn't apply to expiration date. And that's why.

Now, I'll say a little bit more. The expiration date -- the 28 day live vaccine rule we apply -- when a live vaccine expires, we're concerned about potential live virus still being present, whether its interferon or antibody, we will say 28 days for expiration. But it's not the same rule. It's not that rule that applies to both inactivated and live vaccines where you have to apply the minimum interval that came before the invalid dose.

The reason for that rule in the first place has to do with kind of the original programming of our registries and our CoCasa system. We wanted to really impart to the provider that we do not accept compressed schedules. And so, you know, not only do we invalidate the dose but we actually require some waiting before, you know, before giving the next dose. Kind of expanding the series a little bit. So that's kind of the reason. It's mainly programmatic. It's hard to justify the reason for the rule for inactivated vaccines with a scientific explanation, but that rule does exist for programmatic reasons.

(Don Cooley): Thank you.

(Dr. Andrew Kroger): You're welcome.

Coordinator: Our next question comes from Dawn Klink of Oneida County Health Department.

Dawn Klink: Yes, I'm wondering if the four day grace period also applies to the flu vaccine if it was given too soon.

(Dr. Andrew Kroger): We apply the four day grace period to essentially any vaccine that it appears in Table 1 of the ACIP General Recommendations. I think it's A13 for the pink book -- the table of all the minimum intervals for every dose of every routinely recommended vaccine. We allow the grace period for those intervals and those ages. So yes, the short answer is yes. It would apply to two doses of influenza vaccine.

Dawn Klink: Thank you.

Coordinator: The next question comes from (Pamela Sherman Burnett).

(Pamela Sherman Burnett): Good afternoon. I just have a question about the stem cell transplant in regards to restarting the vaccination. Just to confirm, are you to restart the whole series?

(Dr. Andrew Kroger): I believe - the question was is it necessary to restart the whole series of vaccine with post-HCT transplant? And essentially the answer is yes. Following the transplant the patient is considered to be completely naïve, in the published schedule in the ACIP General Recs and the IDSA recs, they may not be the same full schedule of doses as that exists for infants, but they are multi-dose schedules and generally require the full series of this multi-dose schedule. So essentially it is like starting the series over. So yes..

(Pamela Sherman Burnett): Okay, thank you.

(Dr. Strikas): Operator, we have to close out the questions now. Unfortunately we've had a long program and we need to close out and also give our listeners the

information they need for continued education. So you've seen some of this flashing up ask questions were being asked and answered.

So thank you very much for attending today's program. I'll remind you, for continued education credits please go to the website you see up on the slide now. Also the course number for this net conference is EC 2064. That's E as in Edward, C as in cat, 2064. The verification code is EPI-general, g-e-n-e-r-a-l, with no spaces. The CE credit for this net conference will expire on August 17 of this year.

Once you become familiar with the online CDC system you'll find it pretty easy to use, and a great way to keep track of your CE credit earned from CDC training programs. If you're having any difficulty or are new into the system you can get assistance by phoning 1 (800) 41 TRAIN or train. That number is 1 (800) 418-7246, and it's available for assistance by phone between 8 AM and 4 PM Eastern Time.

To get help by way of email you can contact ce@cdc.gov. We received many helpful questions today to clarify the program's information. If you did not get to ask your question today, or if you have other questions related to this net conference, you can contact us at email question and answer service at the address nipinfo@cdc.gov.

And also, if you saw on a previous slide, we'll have a repeat Q&A session on today's topic, General Recommendations on Immunization, Part 1, on July 23 in eight days at 10 AM Eastern Daylight time. Registration information will be at the website where you see the information about registering for these net conferences.

Another where you can ask questions is to contact the CDC INFO or info program. You can call 1 (800) CDC-INFO between 8 AM and 8 PM, Monday through Friday. Another way to contact that program is to go to the CDC homepage, www.cdc.gov, and click on the CDC info link at the bottom of page. This is a general question and answer service that handles immunization related questions in addition to other public health related questions.

Here's a listing of additional CDC resources which can help you navigate the many complex immunization topics we've covered today and will cover in the future. These include the pink book, the CDC vaccine homepage, I resource guide for healthcare providers, and our Twitter account.

I really want to thank all of you for joining us today, with special thanks to our subject matter expert, (Dr. Andrew Kroger). Please join us next week for discussion to complete the general recommendations on immunization that is part two, and on vaccine safety in the next conference. Thanks very much, and goodbye from Atlanta.

Coordinator: This concludes today's conference. Thank you for your participation. You may now disconnect.

END