

## **Yellow Fever: Disease, Prevention and Vaccine Safety**

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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 please press star 1 on your touchtone phone. Today's conference is being recorded, if you have any objections you may disconnect at this time.

Now I will turn the call over to Miss Downs. Thank you.

Alycia Downs: Thank you. Good afternoon and welcome to today's COCA conference call, Yellow Fever: Disease, Prevention and Vaccine Safety. We're very excited to have Dr. Mark Gershman and Dr. Erin Staples present on this call.

Dr. Gershman is a Medical Epidemiologist in the Traveler's Health Branch in the Division of Global Migration and Quarantine. And Dr. Staples is a Medical Epidemiologist in the Arboviral Diseases Branch, Division of Vector-borne Infectious Diseases both with the Centers for Disease Control and Prevention.

We are using a PowerPoint presentation for this call that you should be able to access from our Website. If you have not already downloaded the presentation please go to [emergency.cdc.gov/coca](http://emergency.cdc.gov/coca). Again that's [emergency.cdc.gov/coca](http://emergency.cdc.gov/coca).

Click on Conference Call Information Summaries and Slide Sets; the PowerPoint can be found under the call-in number and passcode.

After this activity the participants will be able to review the epidemiology and clinical aspects of yellow fever disease, provide updated information on the geographic distribution of disease and risk areas for travelers, discuss the risk of importation of yellow fever virus into the United States and ways to minimize the risk including prompt recognition and diagnosis of imported cases, appropriate isolation procedures, mosquito control measures and use of yellow fever vaccination.

Understand the appropriate use of yellow fever vaccine including new international health regulations and the potential for serious adverse events.

In compliance with continuing education requirements all presenters must disclose any financial or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters as well as any use of unlabeled products or products under investigational use.

The CDC, our planners and our presenters wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. This presentation does not involve the unlabeled use of a product or a product under investigational use. There is no commercial support.

I will now turn the call over to Dr. Staples.

Erin Staples: Thank you Miss Downs. This is Erin Staples. I'm going to start first by going over some of the basic epidemiology of yellow fever disease, talk some about

the clinical disease including testing and treatment and also provide some basic information on vaccination before I turn the call over to Dr. Gershman, who's going to really get into more policy-related issues and regulations in terms of the use of the vaccine - yellow fever vaccine in the United States.

For those of you following along with the presentation I'd ask you to go Slide 4 which starts with the title, Yellow Fever. Yellow fever is called by actually yellow fever virus which is a prototypic member of the flaviviral family.

This virus is transmitted to humans predominantly through - by Aedes mosquitoes though other mosquito species are involved. And I'll talk about those in a few minutes.

The disease is endemic to equatorial Africa and South America and is estimated by the WHO to cause 200,000 cases and 300,000 deaths annually. However, the vast majority of those are not recognized by the current surveillance practices and go unrecognized.

The overall case fatality for Africa is estimated at 23%, for South America it's estimated to be even higher at 50%. That is believed to be due in part to the differences in surveillance but also not really the differences in the viral strains that may be present in those two areas.

The next slide shows the distribution or worldwide distribution of yellow fever. These maps are actually - have been recently updated through a collaborative effort with the WHO and the Centers for Disease Control to try to align recommendations and vaccine policies between the Green Book which is the WHO's traveler's book and the Yellow Book which is the CDC's version.

It will be hard to notice some of the subtle differences but just to point out some of the things in terms of the new risk areas. In Brazil there has been extension eastward of the zones due to recent epidemics and activity that we've seen as well as a further extension down through Paraguay into southern Argentina.

Again that activity has been seen to increase in the last couple of years so those areas have been included with detail.

The other difference is on the Africa map. While you see that the actual distribution - it has a better - or let's just say more defined line across the northern area of Africa. That was through a lot of work with the working group to establish areas that would be at risk based off of vegetation, known mosquito vectors and other things.

So those are the most updated maps. There'll probably be a little bit more information forthcoming regarding this but that is slightly updated maps for your knowledge.

Moving ahead to the next slide, which is entitled Yellow Fever Virus Transmission Cycles in Africa but this also applies to some degree in South America. The most common transmission cycle and the one that's probably least recognized is the one all the way to the left or the jungle or sylvatic cycle.

In that the virus is maintained through a cycle of mosquitoes that reside in trees and tree-hold dwelling mosquitoes and non-human primates usually monkey species.

In Africa those mosquito species are predominantly *Aedes africanus* but in South America those species are *Haemagogus* and *Sabethes* mosquitoes. The next cycle is an intermediate or savannah cycle and that only exists in Africa.

And in that cycle humans living on the edge of forested areas come in close contact with nonhuman primates and the mosquitoes and are eventually involved in that cycle. And that's usually mediated by semi-domestic *Aedes* species including various *Aedes* species in Africa such as *Aedes (bromni)*.

The last cycle can occur both in Africa and South America and it's called an urban cycle. And that is the one that we are most concerned about in terms of the large epidemic expansions of the disease.

That cycle itself is just mediated by mosquitoes that are able to transfer the virus from one human to another human without the need for a nonhuman primate. So as you can imagine you could end up with large urban outbreaks of the disease if you have enough of the mosquito involved which is the *Aedes aegypti* mosquito.

On the next slide I actually show you some of the distribution maps for the *Aedes aegypti* mosquito in terms of the potential risk for introduction and spread of large epidemics of the disease.

You notice in the 1930s the areas that are colored in green are actually areas where *Aedes aegypti* were found to be around the area so in areas of South America, Central America, Caribbean up into the United States.

Well early on in the 1900s it was discovered that *Aedes* could be involved in the transmission of yellow fever and many countries that had problems with the disease in the Western Hemisphere implemented control programs.

So by the 1970s many countries had successfully eradicated Aedes species mosquitoes predominantly Aedes aegypti. So you can see that many areas in South America for instance were successful.

Unfortunately, however, not all countries in the Western Hemisphere instituted this policy including the United States and many countries in the Caribbean so Aedes aegypti mosquitoes still existed.

By 2007 following the cease of most of those control programs we've had repopulation of most areas and an extension of the population of Aedes mosquitoes into many other areas.

And those of you that are familiar with another flaviviral disease, dengue, will recognize that many of the dengue outbreaks that are currently occurring in the Caribbean as well as South America are in areas where there's Aedes aegypti.

With that said all of those areas could be potentially at risk for an Aedes aegypti sustained transmission of yellow fever virus including the southeastern portion of the United States.

The next slide shows somewhat of a slightly dated from 2005 but shows where Aedes aegypti usually occurs in the United States now mostly located in the southeast portion of the US so there is a little bit of activity area that was picked up in Arizona.

So there is the potential that if a person who was infected with yellow fever got on an airplane and traveled for instance into Miami and then got off and came into contact with an Aedes aegypti mosquito there is potential that that

person could be bitten and the infection transmitted to other individuals in that area.

So we do have - or we get very concerned about potential urban outbreaks and the risk of importation of the disease into the United States. There are some factors in the United States that may limit the spread including the use of air condition among other things but it is a concern for us and something we always continuously monitor.

On the next slide I get in a little bit more detail about the role of humans in yellow fever transmission. So humans, as I said, can become infected; they actually have an incubation period of approximately two to six days and Mark will touch onto the importance of that when he goes through some of the rules and regulations later on in the talk.

Now humans become viremic and they become viremic to a degree that they're capable of infecting a mosquito. So for instance with West Nile which is another flavivirus humans are not a host of the virus; they cannot sustain a high enough viremia to pass it onto other mosquitoes.

However yellow fever they can and they are an integral reservoir for the disease. So the person becomes viremic shortly before they present with a fever so you could have an asymptomatic traveler who is viremic. And then for the first three to five days of illness they also are viremic enough to transmit the virus.

With that said the virus has been found in the blood up to 17 days after illness onset but that was in an immunocompromised host and that's more the rarity than the common which is usually within the first week. Following the bite of the mosquito the mosquito will pick up the infection from a viremic human

and you end up with an intrinsic incubation period at least for *Aedes aegypti* it's somewhere between 9-12 days.

Once infected the mosquito remains infected for life. And furthermore many of the mosquito species that are capable of picking up the infection with yellow fever actually transovarially transmit the virus. The next slides shows the timeline of what I've just discussed. So essentially you have a human 1 which is depicted in blue on the slide who becomes viremic after getting bit by an infected mosquito.

While the person is viremic if they're bitten by, let's say, an uninfected mosquito which is shown here then the mosquito itself can pick up the infection or at least the virus. There has to be an intrinsic incubation period where the virus gets amplified in the mosquito and gets localized to the salivary glands so that when it feeds on another human it is able to basically transmit the infection.

And then you have an intrinsic incubation period with the onset of viremia in the second human. What we have seen and with an urban outbreak most recently even in Paraguay what that means is that you maybe have one or two cases initially and then you'll see growth and expansion with an exponential increase every time when you talk about a incubation period including the extrinsic and intrinsic incubation period.

The next slide get into the clinical presentation for yellow fever. And it's depicted here as a pyramid because in fact the majority of these infections actually never become symptomatic. And that is not unlike the other related flaviviruses like West Nile.

Up to 85% we believe of individuals who acquire the infection never develop clinical symptoms. They are, however, viremic enough to help sustain and maintain the potential transmission of the virus.

There is about 9%-10% of those individuals that do become infected with the virus that will develop nonspecific febrile illness. They could have myalgias, headaches, other symptoms that are hard to differentiate from many other infectious disease conditions.

Most of those cases, of course, the asymptomatic but also the fever cases are not traditionally detected by the surveillance mechanism. It's only when you get into the more severe presentations which include the fever, the jaundice and hemorrhage that is more of what people think about when they think about yellow fever disease do you start to get into a population where you'll be able to pick that up by surveillance.

And hence those estimates from WHO; they're using the tip of the pyramid here to back-extrapolate to how many people may actually be infected in endemic areas.

The very top of the pyramid shows the number of people that become infected who will actually die which is 1%-2%. Again on the first slide about yellow fever I talked about 23% up to 50%, and again that comes from the clinically-recognized cases that are depicted by surveillance.

This is important just to consider that the fact that many times we get the question like oh well there's no disease cases being reported in this endemic country. Well that does not mean that the infection is not there or present. So you always have to consider the use of the vaccination and I'm sure Mark will touch on that a little bit more in detail.

In terms of diagnostic testing for yellow fever, laboratory diagnosis is usually accomplished by testing of serum for antibodies. The testing can be performed here at the CDC in Fort Collins. As far as I know there is not a commercially-available assay that's out there for yellow fever.

But if you do suspect that on any traveler returning or any other individual you can get testing done usually through your state health department who will send the sample to us.

What we'll do is we'll run an ELISA to look for yellow fever antibodies either IgM or IgG. If we detect either IgM or IgG immunoglobulin, that is, antibodies we will do a confirmatory test which is a plaque reduction neutralization test; they're called PRNT.

What that is is we essentially grow up the virus, plate the person's serum or CSF in some cases that I'll get to later on, on the virus to see if it will specifically neutralize. The reason we do that is the family members, the flaviviruses in the same family, often cross react in our assays.

And that's due to the fact that the envelope protein between a lot of the flaviviruses have very conserved regions where common antibodies are raised. We can differentiate between, for instance, dengue or West Nile by giving the plate reduction neutralization test.

So we never confirm anybody based off of just the presence of IgM or IgG antibodies we go on to do the specific neutralization test. As we've already discussed humans are viremic particularly early in the illness so we also, in acute samples, can often detect virus by viral isolation or culture and we can detect viral RNA through RT-PCR work.

If there is an unfortunate case where they have died post-mortem samples can also be used to obtain the diagnosis. Frozen tissues we use to try to get viral isolation and detect RNA by RT-PCR and we use fixed tissues for immunohistochemical staining though we've had some limited success of also retrieving some RNA from those tissues.

Moving to the next slide which touches on treatment prevention and control for better or for worse there is no specific antiviral treatment for yellow fever and therefore supportive therapy is the main treatment or way to approach these patients.

There have been some preliminary studies done on hamsters which are a model for yellow fever infection that show potentially some promise with nucleoside analogs. The chance that anything will actually be ever approved for yellow fever in terms of a large clinical trial is quite limited given the sporadic nature of the cases and the areas where they occur.

But we'll have to see perhaps other antiviral agents against West Nile or dengue could provide some promise but currently there are no agents that have been shown to be effective.

So prevention and control really remain our key ways to decrease the potential that someone will contract yellow fever. So the two ways to go do that is through vaccination and mosquito control.

Well I touched a little bit earlier on that slide about *Aedes aegypti* how there can be a successful mosquito eradication program but the hope for that particularly with ongoing dengue epidemics is quite small. Many of the mosquito species have adapted to the insecticides and potentially are resistant.

So then it really relies on individual personal protective measures of using DEET or having long sleeves, sleeping under a mosquito net to minimize their chance of getting exposure to the mosquitoes. All of those things can help minimize the risk.

The risk of course can be further minimized by the use of a vaccination which I'll talk about in just a few minutes here.

In terms of immunity to yellow fever we believe that natural disease provides life-long immunity. And I'm currently on Slide 14 if people are trying to catch up. The sporadic disease occurrence however and the deadly nature of the disease does not really allow an endemic area for high levels of immunity to be obtained.

Many areas actually have no previous immunity for instance in the United States. And there is minimal cross-protection immunity to yellow fever despite the cross reaction in our assays. Previous flaviviruses have not routinely been shown to be protective though there's some evidence to say that they may be in areas with multiple flaviviruses such as Western Africa.

So again 17D vaccine or yellow fever vaccine and I'll talk to you a little bit more about the name - is really the main way to create a level of immunity and potentially prevent the introduction and spread of the virus in certain areas.

Yellow fever vaccine is a live attenuated viral vaccine and it's generally given every 10 years.

Moving onto the development of the 17D vaccine the actual viral strain was obtained from a patient that's shown here, (Asibi), who's a man from Ghana. It was passaged several hundred times to become attenuated. First passages were through mosquitoes biting monkeys and back and forth.

Then they passed in mouth embryonic tissue, then chicken embryonic tissue and then chicken embryonic tissue with neural tissues removed. After all that passage essentially two strains were derived, they were actually a few more but only two are currently still in use.

There's one referred to as 17DD. It was separated at passage 195 and then subsequently passaged almost 100 additional times. That is currently the strain that's used in Brazil.

The other one which is used more widely is 17D-204. And as the name kind of denotes it was separated at passage 204 and then passaged somewhere between 30 more times depending on which vaccine you use. And again that is the strain used outside of Brazil and places like the United States, France, Dakar, Switzerland, Russia and China to name a few.

In terms of all of the different vaccines that are available they are all produced in eggs and that gets into a role when we talk about anaphylaxis. They do differ slightly in the sub-strain passage level and stabilizers, salts and diluents so they're not exactly all the same but they do perform very similar when compared in clinical trials.

They are all a heterogeneous mix of virion subspecies. So in other words if you did clonal - if you played it out and picked clones of the actual vaccine virus you would notice that there are subtle nucleotide changes within the viral strain. In general it's pretty well conserved but it is a kind of a mish-

mosh of different viral strains in there and it's not just one single viral strain in the vaccine.

With the yellow fever vaccine there was a seed-lot system created which limits the vaccine lots to a single passage from a secondary seed. Secondary seed has to go through very stringent testing to show that it performs how it's supposed to, that it works well.

The reason a seed-lot system was created is that in - early on in the vaccine's use, in 1941, people were continuing to passage the vaccine beyond the original levels that were established. And what they found is the vaccine actually redeveloped a neurovirulence and the many individuals who received the vaccine developed encephalitis-type picture.

With that known they limited the passage. So again they have to go through kind of strict criteria to establish a secondary seed and are only allowed to develop one passage after that with development of the vaccine.

I've seen actually the vaccine produced; it's a quite labor-intensive process, usually still done by hand if you can believe that, with individuals inoculating the individual eggs. And it is grown into a chicken embryonic stage before it's harvested so in fact people that have allergy to chicken proteins which is rare but people that do will potentially have an allergic reaction to that vaccine and you need to keep that in mind.

The next slide shows the list of currently available 17D vaccines. The first three are WHO pre-qualified. What that means is WHO has gone through a process, has written up kind of rules and regulations for successful establishment of a 17D vaccine.

And then they have - the places that get approved for pre-qualification they basically go through almost an annual process of the WHO going there, making sure all the process and standards are.

Why does this matter? Well these vaccines can actually be purchased by UNICEF and PAHO for distribution in endemic countries. So there is a reason for the pre-qualification.

There are also vaccines that are produced at a local level which includes the one that's used in the United States. It's produced by Sanofi Pasteur in Swiss Water, Pennsylvania and is referred to as YF-VAX which is shown up here in the picture. It is used in the United States and Canada.

There is also a laundry list of vaccines that are on there, I won't go through all of them. But in most clinical trials which either have compared vaccines that are on this list or even just looked at the vaccine individually all the vaccines appear to give you a good immune response with similar reactogenicity profiles or side effect profiles.

So what does that mean to you? Well that means if someone is coming to you from West Africa and had received a vaccine or for South America and received a vaccine you should assume that that vaccine is effective and that you do not need to re-vaccinate that individual.

The only word of caution with that is that's assuming that the cold-chain was maintained because this vaccine does need to be maintained cold.

In terms of yellow fever vaccine requirements, again, I'll touch on this briefly but Mark will talk in more detail about it, most endemic countries require proof of vaccination for all travelers coming from other endemic areas. So the

United States is not considered endemic so potentially US travelers do not need to show that.

While many of you have had experiences that perhaps say otherwise we know for instance that Bolivia is requiring it for all individuals coming. That is when - what Mark will get into kind of the recommendations and requirements in a minute.

However there are certain countries mostly in Asia where there are vectors that are able to transmit the disease so the risk is there. and they have gone ahead and asked for proof of vaccination again from travelers coming from endemic areas. The United States has no vaccine recommendations for yellow fever or any other vaccines for that matter for entry.

Moving on to Slide 19 in terms of the indications for yellow fever vaccine; it is indicated for persons greater than equal to nine months of age planning to travel to or resident endemic countries also planning to travel to a country with an entry requirement.

And the vaccine needs to be given 10 days prior to arrival in endemic area. And that is because it takes about 10 days for about 90% of those individuals who are vaccinated to become protected so that is considered an acceptable level.

Now re-vaccination is currently set at 10 years. There have been studies to suggest that immunity perhaps lasts longer but there were some initial studies to suggest that 10 years is probably a conservative estimate but a good one for the interval between vaccinations.

On re-vaccination the person is considered to be immune so you do not need that 10-day waiting period. In terms of the use of 17D vaccine since it was first developed in 1937 which that is the only time a Nobel Prize was awarded for a vaccine development, to Max Theiler, up until 2008 over 500 million doses of the vaccines have been successfully given to humans.

Surprisingly enough there was never a placebo controlled efficacy study and now it's probably unethical to do one of those for the vaccine itself. But what they did find is when they started using the vaccine that the incidents of yellow fever among laboratory workers in endemic areas declined after the vaccination began.

There were non-human primate studies done to determine what would be considered effective levels - protective levels of antibodies. In the CDC assay that's considered to be a titer of at least - greater than or equal to 20 is considered to be protective.

I'm just going to touch briefly on adverse events before I turn it over to Mark. In terms of common adverse events people will complain of fever, of headaches, backaches, usually three to seven days after vaccination, about 5%-15%.

That is the period of when the person is viremic and they're developing an immune response so those are not uncommon to suspect. There is some injection site inflammation that occurs again usually within the first week. Depending on the study is it as low as 1% up to 30%. Sometimes that associated with the additives that are in the vaccine.

There is one study that showed mild neutropenia; one study that showed AST elevation but I'm talking about one study out of at least 28 that I'm aware of in

the literature since 1958. There is variability within studies but in general most of the vaccines have these common side effects.

The last thing to touch on is serious vaccine adverse events. There are three primary serious vaccine adverse events. If you take them all together the overall reporting rates based off of the vaccine adverse event reporting system which is active here in the United States called VARS, the data was actually - it has been published now in Vaccine and we can provide a more specific reference if people want that.

But the overall rate is 4.7 per 100,000 doses administered. So in terms of the three primary serious adverse events as I've already kind of alluded to; egg allergies, chicken proteins and perhaps even gelatin may lead to anaphylaxis in individuals; that rate is seen about .8 to 1.4 per 100,000 doses.

Then there's neurologic disease and viscerotropic disease which I'll talk about in more detail. Neurologic disease is slightly more common than viscerotropic disease but is thankfully relatively rare at a rate of .4 to .8 per 100,000 doses administered while viscerotropic disease occurs in .3 to .4 per 100,000 doses administered.

Touch base on neurologic disease and we - many of you may have heard of it as neurotropic disease but we're kind of trying to use neurologic disease to be a little bit more appropriate and I'll talk about that in just a second.

But the absolute number of cases unknown - we don't believe that reporting is quite as frequent as the severity of this can be quite variable. The onset is - for the cases that we do know about is about 11 days following vaccination but the range has been 2-28 days.

The most common presentation is meningoencephalitis which is really the neurotropic disease part of it where the vaccine virus actually crosses into the cerebral spinal fluid or into the central nervous system and causes viral vaccine meningitis or encephalitis.

Other neurologic diseases are Guillain-Barre Syndrome, acute disseminating encephalomyelitis, bulbar and Bell's palsy. Those are actually believed to be autoimmune mediated and that in fact that is more of a neurologic disease than mediated by the actual vaccine virus itself versus the immune system responding to the vaccine.

From what we know from cases where we do have information we do believe it's more common following initial vaccination. I'm only aware of one report that has yet to be confirmed of a case occurring after repeat vaccination. So this occurs after the person's first vaccination regardless of their age and time.

Neurologic disease is rarely fatal. I've listed a few descriptions of the fatalities but relative to the absolute number of cases that occur that is quite uncommon. There is some morbidity associated with it with some prolonged periods needed for recovery from the different neurologic events but we do believe recovery is full when it does occur.

And then moving on to viscerotropic disease this is the one that we worry about most. This is Slide 24. This is severe illness which is very similar to wild-type disease. And what happens is the vaccine virus proliferates out of control in multiple organs leading to multisystem organ dysfunction and in some cases multisystem organ failure.

As far as we know there's been at least 40 cases reported since it was first recognized in 2001. Interestingly enough in retrospective review of some old

viral databases they have identified the vaccine virus as causing death as early as 1975 so it may be that this was a condition that's been present for a while but unrecognized.

The onset of this is usually quite rapid and was usually within a week of vaccination with an onset typically within three days. So far, again, with the information that we have on the known cases we've only see this side effect following initial immunization of yellow fever vaccine.

We have seen this side effect reported after most 17D vaccines so the 17DD strain from Brazil as well as the 17D-204 strains produced by multiple manufacturers have led to this complication so it does not seem to be vaccine-specific.

I've shown you the age and sex distribution on this slide. There is a male predominance for it but you either are basically dealing with slightly younger females or older males though the age ranges are similar. This side effect is, unfortunately fatal in approximately 53% of the cases that we're aware of so it can be quite deadly. And is something, again, that we fear most about this vaccine.

This is the last slide I'm going to cover and then I'll turn it over to Mark to talk a little bit more about the indications and rules and regulations about yellow fever vaccine and that's the diagnostic testing for serious vaccine adverse events.

In terms of neurologic disease it can be confirmed if you have detection of the vaccine virus the RNA or through isolation of the vaccine virus or yellow fever-specific IgM antibodies in the cerebral-spinal fluid. If you find IgG

antibodies in the cerebral-spinal fluid or IgM or IgG antibodies in the serum that is not diagnostic.

The serum antibody response just tells you that the person appropriately responded to the vaccination. We believe due to the size of IgG that it can leak across the - from the CSF into - sorry - into the CSF and therefore it's not diagnostic.

IgM we believe is only locally produced but admittedly there's never been a study done of healthy vaccine recipients who were willing to give a cerebral spinal fluid following vaccination to determine how much or if there's an IgM.

But we can say from the case reports that we do get and the testing that we do do that we don't always find that present and that tends to be in correlation with those that have the autoimmune phenomenon not necessarily the meningitis or encephalitis.

DBS and ADEM are actually a diagnosis of exclusion because we have no way to test for an auto-antibody mediation. In terms of viscerotropic disease detection of the vaccine virus in the serum either greater than seven days - because again most people will be viremic within the first week and it will go away.

And then also having very high levels of vaccine virus exceeding three logs of plaque forming units per ML is also indicative of viscerotropic disease. There can be in the unfortunate cases post-mortem detection of the vaccine virus in many dead tissues; that's also considered diagnostic.

And antibody testing, again, is not diagnostic because the antibody response is usually intact in these individuals with viscerotropic disease. So we do see good antibody responses so that does not seem to be the mechanism or failure of that to get the vaccine virus under control.

We still do not know what causes viscerotropic disease. We are trying to collect information on cases and to develop a database so that perhaps when we become a little bit more clever about potential mechanisms we may be able to elucidate what is the cause specifically for either viscerotropic or neurologic disease.

With that said I'm going to turn that over to Mark.

Mark Gershman: Thanks, Erin. So I'm going to continue from - I think with Slide 26 called Special Interests just so everybody can follow along with continuity.

So there are situations of special interest concerning the safety of yellow fever vaccine used in the live vaccine, pregnancy particularly. There has been experience in Brazil with large mass vaccination campaigns where pregnant women were inadvertently vaccinated because it wasn't known that they were pregnant.

A fairly recent study of 340 infants showed no increase in major malformations of those infants born to mothers who were accidentally vaccinated. There was a small increase in minor malformations including skin nevi. It's not clear what the significance of that is or if it was really a causal relationship.

Another fairly recent study of 480 pregnant women again who were inadvertently vaccinated in a Brazilian campaign show that 98.7 developed a -

98.7% developed a protective immune response. Traditionally it's been felt that pregnant women might not respond with a full immune response because of a relative immunodeficient state during pregnancy.

However a prior study done in Nigeria, I believe, showed a poor immune response to - for seroconversion to yellow fever vaccine in pregnancy. So studies are a little bit conflicting and there aren't that many studies but that's sort of a summary of what we know.

Breastfeeding is also another area of concern. Up until recently the concern was more theoretical for transmission of yellow fever virus through breast milk however in the last year to two years there's been an unpublished report from Canada of breastfeeding as a likely route of transmission to an infant whose mother was vaccinated while she was breastfeeding.

And the infant was exclusively breastfed. It has not been published yet but the data seems fairly convincing. And there may actually be another case from Brazil fairly recently.

HIV of course is of concern because it's a potential immunocompromised state for many individuals even if they're not symptomatic. There are no well designed prospective studies of the safety of yellow fever vaccine in HIV infected persons.

But this is of particular interest I guess for all these situations because more and more people are traveling to more and more remote parts of the world so we're seeing more people who have HIV who are on medications who feel well enough to travel, more pregnant women and breastfeeding women are traveling. So these are questions that we get all the time.

Limited studies suggest that yellow fever vaccine may actually be safe in HIV infected persons especially if the CD4 count is greater than 200. But also these patients have a lower rate of seroconversion than non-HIV infected persons.

And so it's - even though we don't know exactly what that means it certainly suggests that they may not have full protection from the vaccine. However, as Erin mentioned, and this is a key fact, that the one - one of the only two reported cases of yellow fever vaccine associated neurologic disease, a case of encephalitis that was fatal was in an HIV infected man in Thailand who post-mortem was found to have a CD4 count of less than 200.

So this tends to be the driving force for conservative recommendations for yellow fever vaccine use in HIV infected people.

And lastly immunosuppressant medication where traditionally we try to avoid and it is recommended that people on immunosuppressant medication do not receive live virus vaccines including yellow fever vaccine, however there are newer and newer drugs being developed.

And drugs such as immunomodulators are not clearly immunosuppressant drugs. We just don't know if and to what extent they might be immunosuppressive. These include drugs like the tumor necrosis alpha factor - tumor necrosis factor alpha inhibitors used for rheumatologic disease, interferon therapy used for various diseases.

We just don't have any studies out - available. And again in the absence of that we tend to be more conservative with recommendations.

Next slide, so to summarize some of the things that Erin talked about and I talked about in terms of special populations and side effects - serious side

effects and putting this all together yellow fever vaccine is clearly contraindicated in certain situations.

These are contraindications you'll find on the package insert which is an FDA-approved document. It's contraindicated in infants less than six months of age due to the increased risk of vaccine associated encephalitis at this age group.

It's also contraindicated in anybody with a history of acute hypersensitivity reaction including anaphylaxis but not only anaphylaxis to any vaccine component especially eggs, chicken protein or gelatin.

It's contraindicated in anybody who is immunosuppressed from illness or drugs. Immunosuppressive illnesses would include things of course like leukemia, lymphoma, generalized malignancy, symptomatic HIV infection or Aids for sure.

Immunosuppressive drugs would include corticosteroids, alkylating agents, antimetabolites, other cancer chemotherapeutic agents, tumor necrosis alpha factor - tumor necrosis factor alpha blocking agents in the absence of any different information than what we now know and of course transplant related immunosuppressive drugs which are very immunosuppressive.

Also it's contraindicated in anybody with a history of thymus disorder which would include thymus disease or a thymectomy, for cases of viscerotropic disease I think all of which were fatal were recognized in the reports of the first 40 or so cases where the patients had all had thymectomies for thymomas.

And also anybody on current radiation therapy should not receive the vaccine. Current radiation therapy also has to be considered in immunocompromising state potentially.

Next slide. There are precautions to the use of yellow fever vaccine in certain situations which you might think of as more of a relative contraindication as opposed to an absolute one.

We have to be cautious about giving to adults 60 years of age or greater, because even though I don't think Erin went through age specific risk rates the risk of a serious adverse events including viscerotropic disease and neurotropic disease go up with age, clearly over 60 and even much more so over 70. Especially in primary vaccinees, as she had mentioned.

For infants six to eight months of age, this is a gray zone. Again I mention it's contraindicated in infants less than six months of age. It's indicated by the FDA in this country for use in nine months or older of age. So the gray zone is infants six to eight months of age.

And the ACIP, the Advisory Committee on Immunization Practices and the WHO recognize situations in which vaccination of an infant six to eight months of age might still be considered such as unavoidable residence in or travel to a yellow fever endemic area with their family.

Asymptomatic HIV infection, so again not people with Aids, Aids-defining illness or constitutional symptoms from an HIV infection but asymptomatic HIV patients could conceivably receive yellow fever vaccine if there's established laboratory verification of adequate immune function and we tend to use CD4 counts in greater than 200 at this point in time to establish that.

And of course if they cannot avoid a potential exposure to yellow fever virus if travel to endemic area could be postponed or canceled that might be preferable.

Pregnancy and breastfeeding I touched upon those; those are precautions. Again we'd rather not vaccinate pregnant or breastfeeding women unless absolutely necessary. But if the itinerary to a yellow fever endemic area or residence in that area cannot be prevented then a yellow fever vaccination could be considered if the risk is considered higher - or the benefits is considered higher than the risk.

For all of these precaution situations the provider and the patient really must weigh together the risk and benefits of administration of a live virus yellow fever vaccine against the destination specific risk for exposure to wild-type yellow fever virus.

And of note is the fact that pregnant patients and asymptomatic HIV patients may have altered immune function resulting in a suboptimal serologic response to the vaccines so just vaccinating them doesn't mean they're ready to go on their happy way and feel safe.

Considerations should really be given to serologic testing if time allows to document that they've mounted a protective antibody response prior to their travel to a yellow fever endemic area.

Next slide, the Advisory Committee on Immunization Practices or the ACIP, periodically reviews and provides recommendations for yellow fever vaccine use in the US. The last ACIP guidelines for yellow fever vaccine were updated in 2002 and were published in the MMWR.

The URL link is provided here for that document if you want to find that. The ACIP yellow fever vaccine working group is currently updating those guidelines and it's anticipated that revised guidelines will be available in late 2009 or early 2010.

Next slide. So sort of to summarize what I've been talking about in conjunction with risks of safety of the vaccine that Erin was talking about, considerations for the risk versus benefit of yellow fever vaccination which is a common conundrum that providers run into often with a vaccine that has these concerns.

These considerations include that the risk of acquiring yellow fever for travelers in Africa would be estimated, again, these are all crude estimates but it's the best we have - might be estimated at 50 cases per 100,000 travelers per two-week stay during the peak transmission season which is July through October.

Realistically spread out through the year the average annual risk is probably closer to 10 per 100,000 per two-week stay because there's really a lower risk during the off season.

In South America the risk because of the difference in transmission cycles the risk is felt to be about 10 times lower so it's about 5 per 100,000 per two-week stay. Compare this to the risk of yellow fever vaccine associated serious adverse events for persons greater than 70 years of age who are the ones who probably have the highest risk rate.

For any serious adverse event person over 70 has a risk of 12.6 per 100,000 doses. For yellow fever vaccine associated viscerotropic disease it's 2.3 per 100,000 doses and remember that viscerotropic disease is at least 50% fatal.

Next slide, the International Health Regulations of 2005 allow countries to require proof of yellow fever vaccination for entry. The goal is to prevent importation and indigenous transmission of yellow fever virus.

Even though a country might already have the virus and be considered an endemic country the virus may not be uniformly distributed throughout the country. So a traveler who is not vaccinated could go into the bush, acquire yellow fever infection and even be asymptomatic and translocate that to a city where they could start an urban epidemic when they travel back to the city to fly out of the country.

So translocation within the country is a big concern even if yellow fever already exists there.

Proof of vaccination must be documented on the yellow card or the International Certificate of Vaccination or Prophylaxis. ICVP is a lot easier to say so I'm going to try to refer to it as that from here on in.

Yellow fever vaccine is the only vaccine currently required under the International Health Regulations. In the past cholera and small pox were required but because of public health advances and changes in thinking those are no longer required.

And under the IHR a traveler without proof of vaccination can be detained for up to six days in a destination country. Six days in the incubation period for yellow fever disease.

Next. This slide shows the front of the current yellow card of the ICVP for use in the US. This was last revised by the CDC Traveler's Health Branch at the end of 2007.

And next. This next slide shows the section of the yellow card which is the certificate proper. This is really the only part of the whole folding card which is required and prescribed by the International Health Regulations. The top section has spaces to enter the patient's name, other demographic information and the patient's signature.

The table has multiple rows each of which can be used for a new administration of a required vaccine or prophylaxis under the IHRs. And conceivably other vaccines or prophylaxes other than yellow fever might be required in the future as situations dictate.

Each time a vaccine or prophylaxis is prescribed and administered the clinician needs to fill out a new row in the table. Each row consists of all of the following fields starting from the left, the type of vaccine or prophylaxis, the date of administration, the signature of the clinician, the vaccine manufacturer and lot number, the dates of validity of the certificate and the official stamp of the yellow fever vaccination center which goes in the large block on the right.

And again to repeat what Erin already stated, the validity of the vaccine - of the certificate is 10 days after vaccination for first-time vaccination. And the validity lasts for 10 years. Now if a person is being re-vaccinated the International Health Regulations state that the validity starts on the day of vaccination only if the repeat vaccination occurs within that 10-year period.

Theoretically if it's outside the 10-year period you'd have to 10 days again but I doubt if anybody is checking to that degree of detail at a border post but you never know.

Next slide. Regarding yellow fever vaccine confusion is sometimes engendered and the use of the term's requirements and recommendations. Requirements are permitted by the International Health Regulations. Again they're established by individual countries for entry.

And the purpose is to prevent importation and transmission of yellow fever virus within their boundaries. It's really to protect themselves. And they are subject to change at anytime as practitioners find out.

Recommendations on the other hand or advice given to prevent yellow fever infections in travelers, these are based on the best available yellow fever epidemiologic data. They are also subject to change depending on disease conditions which change from time to time as there are outbreaks, epizootics and epidemics.

CDC and WHO have had small differences in their recommendations over time in the past. Currently we're working hard to harmonize those recommendations and we are almost there at this point in time. The working group is continuing its work.

Next slide. Medical waivers for yellow fever vaccination are allowed by the International Health Regulations. If in a provider's judgment the yellow fever vaccine is medically contraindicated the provider should complete the medical contraindication to vaccination section on the yellow card of the ICVP.

In addition it's recommend they give the traveler a signed, dated and stamped exemption letter on the physician's letterhead stationary. That's sort of to hedge their bets to give sort of two documents. You never know what the receiving country is going to be looking for.

Also it's important they inform the traveler of the increased risk of yellow fever disease without vaccination. Just giving them a waiver doesn't protect them; they need to know they're vulnerable to acquiring the disease. They should council the traveler about mosquito prevention measures which should be followed as rigorously as possible.

And it's important to advise the traveler that issuance of a waiver does not guarantee it's acceptance by a destination country. Unfortunately the acceptance of the waiver is up to the whim of border personnel at a port of entry in any country and that's beyond anybody's control.

The traveler might also consider contacting the destination country embassy for further guidance about waivers in that particular country.

And next slide. This slide shows the medical waiver section of the yellow card which is titled again, Medical Contraindications to Vaccination. It has spaces to fill in for the name of the disease for which vaccination is being waived, the name of the traveler and the medical condition or conditions which necessitate the waiver.

And next slide. Again I may have touched on this but mosquitoes do not read medical waivers. A traveler with a medical waiver for yellow fever vaccine is free from risk from vaccine-associated adverse events but they are not free from risk of yellow fever disease. So it's not as simple as just giving a waiver.

Unvaccinated travelers going to endemic areas could be a significant risk of contracting yellow fever and for example during the period of 1970 to 2002 nine cases of yellow fever were reported in unvaccinated travelers. They were western travelers from the US and Europe going to endemic countries. Eight of these nine cases were fatal.

So to summarize there are three basic options for travelers with contraindications - medical contraindications or precautions to yellow fever vaccine. The provider could give the yellow fever vaccination and the patient could travel to the endemic area. This involves risk from vaccine which could be a large risk depending on the particular situation.

The traveler could get a waiver, a medical waiver, and travel to the endemic area. This entails risk of acquiring yellow fever depending, again, on which country. In West Africa that could be fairly significant.

Or the third option which I think people might forget is a real option is the traveler doesn't need to go there. They want to go there but often they don't need to go there. So not to give vaccination and convince the traveler to either postpone their travel, or if their conditions are permanent to consider travel to another area but not go to a yellow fever endemic area.

This entails no risk of yellow fever disease and no risk of yellow fever vaccine associated adverse events.

Next slide just gives a list of all the personal protection measures to prevent mosquito bites which everybody should following going to a yellow fever endemic area whether they get vaccine or not.

Nothing in this world is 100% and even though yellow fever vaccine is very good there actually is a documented case of a Spanish traveler who contracted yellow fever and had been vaccinated. Now of course we never know if the vaccine was good or if they were vaccinated properly but it is a documented case that somebody who was vaccinated who got the disease.

And certainly anybody on a medical waiver traveling to an endemic area needs to take rigorous mosquito bite precautions. Vaccination of course is the best if the person can get it. Using insect repellent on exposed skin is also essential. DEET is the most studied and probably thought of as the safest because of the long track record.

Also other alternatives are picaridin, oil of lemon eucalyptus and IR3535 which I believe is some incense Skin So Soft products. Wearing long sleeves, long pants, hats and socks is important although not always easy in a tropical area but important because it minimizes target areas of unexposed skin from mosquitoes.

Treating clothes with permethrin also very effective and staying in well-screened or in air conditioned accommodations.

Next slide. The CDC Traveler's Health Website for which the URL is shown here, [www.cdc.gov/travel](http://www.cdc.gov/travel). This is a comprehensive information source for traveler's health. For anybody who might not be familiar with it it has information on traveler's health by destination, by disease. It has information on vaccinations.

It also has a search tool for finding a traveler's health clinic in any given patient's locality. It's continually updated with travel health notices and news.

And it contains an online version of CDC's Health Information for International Travel. The latest version is 2010; this is the CDC Yellow Book.

And lastly there is a yellow fever provider training module being developed by the CDC Traveler's Health Branch currently. It's going to be a Web-based and free educational module. It'll take about two to three hours to complete with continuing education credits being offered.

It's expected to be available by the end of 2009 and probably at the latest early 2010. The plan is to distribute this to the various state health departments for over study and distribution within their jurisdictions. And it's hoped that they might incorporate this into a process for certifying providers and giving them a yellow fever stamp to administer the vaccine and possibly and hopefully for may recertifying them periodically.

And that's the end of my talk and our presentation so thank you and we're a little bit over on the time for the talk. I'm hoping there'll still be time for questions. I'll leave it up to the operator and the moderators. Thank you.

Coordinator: Thank you. If you would like to ask a question please press star 1 on your touchtone phone. You will be prompted to record your name; please do so so I may introduce your question. To withdraw you can press star 2. Again to ask a question press star 1. It'll be just a moment.

Okay I do have a question, your line is open.

Question: How many times does one get vaccinated if you've had two or three intervals over 10 years? Do you still have to continue to meet the requirements?

Mark Gershman: I guess I'll answer that one since it seems to be what I just talked about. I think if a person, you know, I think you're implying that you could probably assume the patient is - has protective antibodies at that point. And that may well be the case based on the few studies we have that immunity is longer than 10 years for the most part although there are only a few studies.

But the problem is there are the International Health Regulations. So unless the person has a medical contraindication in the view of the provider I think if they're going to a country that requires a vaccine they have to get it if it's been 10 years to get in.

And as far as giving a medical waiver that's always a judgment call. If the patient is under 60 I don't think it would be necessarily a wise idea to give a medical waiver just because you feel they're protected and they've gotten a number of them before.

If they're over 60 then you can always make a case that age introduces a medical contraindication so it's really a judgment call. But the International Health Regulations do have to be addressed when helping a traveler plan to a yellow fever endemic area.

Question cont'd: Okay.

Mark Gershman: And, yeah, that's - I guess that's all I'll say on that.

Erin Staples: And this is Erin just to add one other thing; there have been occasions where people have received previous vaccinations and now are facing an immunocompromised condition where you wouldn't necessarily want to vaccinate them.

In certain circumstances often after talking to me we can coordinate testing that person for an antibody response which may provide piece of mind both to you and the traveler in terms of whether or not they still have maintained a productive immune response.

And again that's handled on a case to case basis but we have done that because we do offer testing to check for an appropriate immune response in an individual.

Question cont'd: Thank you Erin.

Erin Staples: Yeah, thanks.

Coordinator: Thank you. Next we have Michelle, your line is open.

Question: Hi. Quick question. With co-administration with other live vaccines so for example the oral typhoid if you have to give it at the same time the oral typhoid is given over a week. And my understanding was that I just need to clarify whether or not that's good or not or should you delay giving the oral typhoid?

Mark Gershman: I can answer that. Oral typhoid is not the same as other oral vaccines because it only acts in the gut topically. And it is not a problem giving the oral - the timing with oral typhoid and yellow fever vaccine is not an issue; you can give them any time relative to each other.

However other live virus vaccines administered parenterally by needle or intra-nasally like the live influenza vaccine we don't have a lot of data so in the absence of data it says otherwise.

There is the theoretical risk of interference; giving one - well - not giving them on the same day so it's recommended for all of the other live virus vaccines to administer them on the same day as yellow fever vaccine, and if they cannot to wait a month. That's the ideal.

That always doesn't happen when travelers walk in at the last minute to traveler's health clinics or any provider giving travel health vaccines. And so again that's the ideal to separate them by a month. But if that can't be done then you just do the best you can.

There isn't specific information to say it will cause an untoward event it's just a theoretical concern so it's certainly better to give the vaccinations at less than ideal timing than to not give one of them. That would probably leave the patient more vulnerable.

Erin Staples: And there has been one study with MMR particularly since that is co-administered in endemic countries at nine months of age. And they did show that there was a little bit lower immune response though it was not statistically significant when you had a time delay between the live viral vaccine, meaning a week or two weeks by three weeks to four weeks that immune response seemed to be better but it was not statistically significant.

The only other thing to think about and add just related to co-administration is you do have to be cautious of tuberculin skin testing. Because of the interference that's been shown with MMR and tuberculin skin testing, again, you either need to administer them together or you need to optimally delay 28 days between the two of those.

Question cont'd: Okay. Thank you.

Coordinator: Next we have Diane, your line is open.

Question: Hi. Does the yellow fever book or the vaccination by a physician or can it be (unintelligible) by a nurse or nurse practitioner.

Mark Gershman: Yeah, I couldn't hear that one, the volume was quite low. Can that be repeated?

Question cont'd: Sure. Can the book be signed by - if the vaccine is administered by a nurse or nurse practitioner or physician assistant can the book be signed by those professionals or does it need an MD signature on it?

Mark Gershman: I believe it can be signed by the person - and should be signed by the person administering the vaccine.

Question cont'd: Right and - okay.

Mark Gershman: As long as it has to be stamped by the official stamp. And in most states a physician - only physicians are allowed to be stamp owners. And I know that's not uniform; some states allow non-physicians. But, yeah, the person giving the vaccine should sign it.

Question cont'd: Okay. So that's a state by state requirement?

Mark Gershman: As to who can own the stamp?

Question cont'd: Yes.

Mark Gershman: Yes it is because states really regulate their own vaccination policies.

Question cont'd: Thank you.

Coordinator: Next we have Joseph, your line is open.

Question: I have a question on the Slide Number 12, Diagnostic Testing for the Yellow Fever. And for the laboratory diagnosis (unintelligible) should have through the ELIZA and I think (unintelligible) about the confirmatory testing but I think I was told that you need the virus to be in the blood to take that confirmatory test.

And however the (unintelligible) is not a viremia at that time and if you have a positive ELIZA test do you - if you have a negative confirmatory test do you say that that ELIZA test is negative or it's positive?

Erin Staples: I think I understand your question. There was a...

Question cont'd: Yes.

Erin Staples: ...little bit of static on the line. In terms of the confirmatory testing it is specifically looking for antibodies. So if your plaque reduction neutralization test does not give you a titer amount even though there maybe antibodies detected through the ELIZA either IgM or IgG that would not be considered to be specific antibodies and it would be considered either cross reactive or non specific depending on it.

For instance an individual with MS could be tested for instance on cerebrospinal fluid; we've had this occur where they do have a lot of antibody production. However the neutralization test is negative. So we always try to recommend the neutralization test.

You do not need virus in the blood for the neutralization test. However you do need, for the neutralization test adequate time to develop an antibody response. Usually we use the cutoff of seven days. So seven days of illness onset if you have that length of time to develop an appropriate antibody response.

If the person was negative within the first seven days we would ask you to send in a convalescent sample because we cannot definitively rule out the diagnosis if our testing is negative.

If a testing after seven days for instance on eight days to, you know, 21 plus days is positive we would go do the confirmatory testing to tell you whether or not those are specific antibodies and we think the person was infected with yellow fever virus.

((Crosstalk))

Erin Staples: ...we can try to detect the virus itself. So within that first seven days however it's not an absolute so if we do not detect the virus and we do not detect the antibodies we'll still ask for a convalescent serum particularly if you feel that this is clinically warranted or another diagnosis has not been determined.

Question cont'd: I see. And in the case of the yellow fever (unintelligible) you have life-long immunity so you only get yellow fever once.

Erin Staples: That is the thought process and that is based off of some studies in Africa but it's a little hard to differentiate because you could have asymptomatic infections as well as nonspecific febrile illnesses but it's not believed that individuals could get infected.

Now the biggest problem for us in terms of laboratory diagnosis of yellow fever disease is we cannot differentiate by our testing the difference between an antibody generated - sorry, a vaccine generated antibody response and a antibody response to the natural virus.

So the person has been previously vaccinated we will be able to tell you for instance the level of protection but we will not be able to rule in or out the potential that they could have been infected.

Now that would have occurred because not everyone forms an appropriate immune response to the antibodies but we will not be able to tell you the difference in those circumstances unfortunately.

Question cont'd: Thank you.

Coordinator: Thank you. Next we have Alisa, your line is open.

Question: Hi, my question is about filling out the yellow fever booklet. Did I understand you to say that the validity date should be dated 10 days after the actual administration of the vaccine?

Mark Gershman: Yes, correct. That's what the International Health Regulations say for first time vaccinee. So this person has never had a vaccination before. That certificate is not valid until 10 days after the date of vaccination. That's because a country with an International Health Regulation permit of requirement doesn't want people coming into the country who aren't protected from getting yellow fever.

And they're not felt to be protected until 10 days after vaccination. So that date is the date that the immigration person or border guard is going to be looking

for wanting to make sure that that person is not entering the country before the date that the - the ICVP and therefore that the vaccination is valid and vaccination is being effective.

Question cont'd: Okay. And can I ask one other question?

Mark Gershman: Sure.

Question cont'd: On the viscerotropic disease the mean age for people to have gotten that for males was 58. Why is the age limit 60 or older or even worse 70 or older when the mean age was 58 for more serious side effects?

Erin Staples: This is looking at cumulatively all - the chance for individuals for all serious adverse events as well which incorporates viscerotropic disease, neurologic disease as well as there are some other circumstances where adverse events were deemed by the physician reporting it to be life threatening to an individual.

So in fact that, you know, is not a specific recommendation necessarily for viscerotropic disease but for all serious adverse events where older people based off of the best information we have available, which is again through a passive reporting system of the vaccine adverse event reporting system, that we make those estimates from.

Question cont'd: Okay. I guess I was having a hard time differentiating from the slide that said the mean age was 30 for females and 58 for males for viscerotropic disease on the actual VIS, vaccine information sheet, it says, you know, it gives the older age limits for that particular side effect.

Erin Staples: Right and the VIS will be updated with the new recommendations which will have some of these newer risk estimates which were done off of a review of vaccine adverse event reports from 2000 to 2008.

Question cont'd: Okay thank you.

Coordinator: Next we have AI, your line is open.

Question: Hi, thanks for taking my call. I think mainly the question has been asked and answered but it has to do with the timing in between two live viruses. I had somebody - or live virus vaccine - somebody who came in with yellow fever and then two weeks later had a MMR vaccine. And the question is, you know, is there a necessary problem in developing the immunogenicity for either of the vaccines?

Erin Staples: Again the information on that is limited. But I'd point people out to a study that again we could try to disseminate but it's a study that was done in vaccine. Again it was in younger children and it was primarily to address the issue of concomitant vaccinations because at nine months of age both MMR and yellow fever is given in endemic countries in South America as well as Africa.

So the first author on that is Stefano - STEFANO - and it's a vaccine paper from 1999. If you have problems locating it that's one of the few - there are some very early studies before the vaccine formulations were done but that is the only one that we have any definitive information about the potential thwarting of the immune response given the timings of live viral vaccines specifically yellow fever vaccine and in this case MMR.

Mark Gershman: And I would just add if I heard correctly the person - this is pertaining to a case where the person received yellow fever vaccine first and then MMR two weeks later?

Question cont'd: Yes.

Mark Gershman: Yes, so I would think - and Erin, you can correct me if I'm wrong - the concern is really with the MMR that the first vaccine is probably the one that they're more likely to take - the immune response is likely to take. And after 10 days 90% of individuals will be protected from yellow fever vaccine anyway.

And the only theoretical concern might be if the MMR took - and it all has to do with - it all goes back to several studies done in the 40s or 50s on interferon levels after various live vaccines that interferon is produced after the first vaccination from exposure to that live virus.

And that interferon might prevent a full immune response to the second vaccine because the virus isn't allowed to replicate enough to stimulate the immune system. So the second vaccine is one - the one with more concern.

So I would say in that situation it's probably likely and you can infer that they're protected from yellow fever vaccine but of course we don't know for sure. Would you agree Erin?

Erin Staples: Yeah, no, I would agree. I mean if there are special circumstances, again, as already alluded to, if there are situations that can't be avoided or there is a concern that could be residual, we can test -- at least here in our laboratory -- for yellow fever specific antibodies if that becomes an issue or a question.

Particularly if the traveler will be going to an area he has not gone yet or will be a repeat traveler to high risk areas.

Question cont'd: Thank you.

Coordinator: Next we have Debra, your line is open.

Question: Hi. I'm actually still thinking back to the slide where you had listed some cases of folks who had died following receiving the yellow fever vaccine. And one of the cases was a three year old child. And I don't recall if you said or not was that child - did that child have some other risk factors or underlying health issues prior to vaccination or do you know?

Erin Staples: That was a report in the literature from a three year old that happened - it was reported in the 90s. And when in fact they actually looked back at the child they did not find - I think if I remember correctly and I'll have Mark correct me on that if I'm wrong - there wasn't any significant factor in the child. But however in this one case and this one case alone they did find that there was a vaccine viral strain that was pulled out of that child which the deletion and alteration in that vaccine strain would have led to an increased propensity for encephalitis.

So in that only one case are we aware of a specific nucleotide change which led to amino acid change which influenced the narrow virulence of that particular vaccine. However other individual with that same lot did not develop that and why that occurred we're unaware.

Question cont'd: Thank you.

Mark Gershman: Yeah, just to add actually the virus had been - the isolate had been saved and the viral studies were done in the 90s. The case was actually and unfortunately a three year old girl who at that time was felt to be totally normal. It was reported in (Gema) in 1966.

And just from a review of other papers and I'm a family doctor not a pediatrician but I've taken care of kids and Erin is a pediatrician. But what has become apparent to me and it's the scary thing in vaccines is that, again looking at other vaccines that have had serious adverse and fatal adverse events with kids, is that at the time these vaccines are given, especially routine vaccines in early childhood, infants and children may have a serious immunocompromising condition that has yet to develop.

So maybe genetically programmed but it doesn't manifest until a later time. And they may receive the vaccine and have a serious or fatal event and they are somebody who has the underlying propensity but hasn't been clinically manifest and clinically diagnosed. But they still have the immune defect.

And I think that's the problem with serious adverse events in kids. And so maybe this child by laboratory techniques and molecular and DNA techniques available today would potentially be identified as somebody with some subtle immune defect. But in the 60s and maybe even in the 90s if they - I don't know if they tested for immune defects in the serum samples, nothing was recognizable then.

But again with all these fatal adverse events we think that it has to do with subtle immunogenetic defects that we're just not able to identify.

Coordinator: Thank you. Next we have Angela, your line is open.

Question cont'd: Yes, regarding the medical waivers; is age alone enough to give a medical waiver for over 60 or over 70 without any other conditions? And if so is it likely to even be accepted by the host country?

Mark Gershman: I think that's the \$1 million question. I don't know the answer to that. I think the International Health Regulations just say that it's in the judgment of the provider the vaccination is medically contraindicated and I'll read the wording from the International Health Regulations.

"If the supervising clinician is of the opinion that the vaccination or prophylaxis is contraindicated on medical grounds the supervising clinician shall provide the person with reasons written in English or French," blah, blah, blah, "...underlying that opinion."

So I think the International Health Regulations are vague. I follow the ISTM with listserv and I think you see opinions going both ways on that. And I don't practice travel medicine clinically myself. Unfortunately I don't think there is any one answer to that.

I think if the data is there to support that age over 70 a person with other comorbidity too is at risk for a severe vaccine adverse event and the provider and the patient just feel they don't want to give it I think based on what I read here you could give a medical waiver.

Now I'm not sure - I don't think anybody should ever lie on a document but I'm not sure if you're right that the medical reason is age that it will be accepted. We don't poll border, you know, it's impossible to poll every country, you know, there are 250 or 280-odd countries in the world and many of those have yellow fever entry requirements one way or another.

And even if you could poll countries you couldn't poll every border guard who may change their approach on a given day depending on what mood they're in. So it's really an unanswerable question.

But to be safe if there's a way around placing age in words as the reason and you can come up with another medical reason without lying that may be a way to increase the chance it's going to be accepted because - but we just don't really know the answer as to how waivers are received. It's only anecdotal when we hear about it in emails and on the ISTM listserv.

Erin Staples: And this is Erin. Just to add to that and something Mark already said but it's important to take the message that you really need to weigh the risks and benefits of vaccination. And just because a country may not be reporting yellow fever cases doesn't mean the risk is trivial.

We can provide some additional guidance if there's particular cases. The other thing to keep in mind also is that we do notice again more severe adverse events in primary vaccination. So if you had a 70-year old gentlemen who had respectively received multiple yellow fever vaccinations, I think, you know, you have to again interpret that risk as being perhaps lower than your newcomer to yellow fever vaccination who presents to you with 70 years.

So every patient needs to be individually, you know, advised as to the risk and the benefits of that in understanding where they're traveling to, the risk that might present for them and potentially the risk for the vaccination depending on their history including their medical history as well as with the previous vaccinations.

Question cont'd: Thank you.

Alycia Downs: I want to thank our presenters for providing our listeners with this information. I'd also like to thank our participants for joining us today. In the case that you didn't get a chance to ask your question or if you have any additional follow-up questions please send an email to [coca@cdc.gov](mailto:coca@cdc.gov) - that is [coca@cdc.gov](mailto:coca@cdc.gov).

The recording of this call and the transcript will be posted to the COCA Website at [emergency.cdc.gov/coca](http://emergency.cdc.gov/coca); again that is [emergency.cdc.gov/coca](http://emergency.cdc.gov/coca) within the next week. You have a year to obtain continuing education for this call.

All continuing education credits and contact hours for COCA conference calls are issued online through the CDC Training and Continuing Education online system, [www2a.cdc.gov/tceonline](http://www2a.cdc.gov/tceonline).

Thank you again for participating and have a wonderful day.

Coordinator: Thank you. That concludes today's conference. You may disconnect at this time.

END