A Primer of New Advisory Committee on Immunization Practices Guidelines on Human Rabies Prophylaxis

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Coordinator: Good afternoon and thank you for standing by. I would like to remind all parties that your lines have been placed on listen only until the question and answer portion to today's conference. At that time if you wish to ask a question please press star 1 on your touchtone phone and be sure your telephone is unmuted and clearly record your name at the prompt. Your name will be necessary in order to introduce your question.

Today's conference is being recorded. If you should have any objections please disconnect at this time. It is now my pleasure to introduce your first speaker Miss Conne Ward-Cameron. Thank you ma'am. You may begin.

Conne Ward-Cameron: And thank you (Emily). And good afternoon. I'm delighted to welcome all of you to today's call from COCA, the Clinician Outreach and Communication Activity of the Emergency Communication System at the Centers for Disease Control and Prevention.

We're very pleased to have Dr. Charles Rupprecht, Chief of CDC's rabies branch with us to provide a Primer on New Advisory Committee on Immunization Practice Guidelines on Human Rabies Prophylaxis. Tough one to get out, sorry.

You will hear Dr. Rupprecht referring to slides in his PowerPoint presentation for this call. The PowerPoint is available from our Web site -- that's

emergency.cdc.gov/coca/callinfo -- all one word. The link for the PowerPoint can be found under the call-in number and pass code there.

The objectives for today's call are that you as participants will be able to discuss the Advisory Committee on Immunization Practices recent vaccination changes for post-exposure prophylaxis to prevent human rabies.

You will be able to explain the rationale for reduced doses in human rabies vaccine and you will be able to identify exceptions to the recommended human rabies vaccine protocol.

If you have any questions Dr. Rupprecht will take those at the end of the call. Remember that dialing star 1 will put you into the queue for questions. And we suggest given the large number of people on the call today that if you have questions go ahead and get into that queue relatively early so that you'll be able to get in and speak with Dr. Rupprecht.

There are a few disclaimers I need to give you for those of you who are listening for continuing education or contact hour credits. 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 any unlabeled product or products under investigational use.

This presentation will not include any discussion of the unlabeled use of a product or products under investigational use. CDC, our planners and our presenter wish to disclose that we have no financial interest or other relationships with the manufacturers of commercial products, suppliers of

commercial services, or commercial supporters. There is no commercial support for this presentation.

Our presenter this afternoon is Dr. Charles E. Rupprecht who has been the Chief of the Rabies Program here at CDC since 1993. He is also the Director of CDC's World Health Organization Collaborating Center for Rabies Reference and Research.

For almost two decades he has served as a consultant to the National Association of State Public Health Veterinarians on the Compendium of Animal Rabies Control Committee. He is a member of the Human Rabies Vaccine Working Group of the Advisory Committee on Immunization Practices. And the author of more than 200 scholarly papers.

Dr. Rupprecht earned his VMD from the University of Pennsylvania School of Veterinary Medicine and his Ph.D. in Biological Sciences from the University of Wisconsin.

Thank you for being with us today, Dr. Rupprecht. And for our participants if you're following along on the slides you should now be on Slide 6. Dr. Rupprecht.

Charles E. Rupprecht: Thank you, Conne, and good day to all of our listeners. It's my pleasure to be able to discuss some recent changes in the Advisory Committee of Immunization Practices as concerns human rabies prophylaxis. And you should now be on my title slide - be on Slide 7 if you're following along.

In the late portion of 2007 we were given some information about some changes in the availability of human rabies biologics, specifically vaccines as part of a routine facility upgrade. And being dutiful, that manufacturer tried to predict recognizing that human rabies post-exposure prophylaxis is not a reportable event to try to predict how much product they'd actually need over the ensuing two year period when they would be out of production.

One also has to recognize that these are not drugs, these are biologics that need a fairly long event horizon to produce. And so to try and predict - guess a relative unknown quantity of biologics was obviously a less than ideal guesstimate, particularly when one considers the zoonosis that we're dealing with as a disease of nature is always somewhat unpredictable and will have various peaks and troughs. And when you have peaks locally, regionally, nationally, that will entail more exposures and hence more use of product.

When you similarly have, through the routine regulatory environment, lots of products that may not pass approval, the combination of a manufacturer that is trying to predict how much product should be used with a disease of nature and then having tertiarily another manufacturer whose lots were not immediately available were the makings throughout 2007 to 2009 for a very interesting time in regards to rabies management in the United States.

When the situation became obvious to us and in lieu of a stockpile of such critical biologics as a preventable disease we came up with management plans and entered into many interactions with a variety of groups of people who deal with the business of rabies and its prevention throughout the United States, not the least of which was getting back to basics as well as ensuring

that our first responders, diagnosticians, animal control officers, et cetera, minimally had pre-exposure vaccination on board.

It soon became clear to us that there were going to be times when risk assessments and engagement of everyone involved in human rabies prevention was a necessity, part of which included the need for coming up with scenarios if in fact we hit a shortage.

Luckily we never came up with a true shortage of human rabies biologics in the United States which operationally defined meant that individuals who were in need of prophylaxis would not have biologics made available to them. We came close, but luckily we never actually passed that particular criterion which entailed then quite a bit of dutiful involvement of dealing with the availability of products that we had at hand and what we would do in case a shortage were to loom.

On the basis of that a variety of strategies were developed. And when some of these were brought forward to the ACIP for consideration, in case a shortage ever occurred members, then asked that for some of those suggestions why not consider them for routine use rather than just in a shortage? And if in fact there was available bona fide evidence further consideration in an emergency situation that we should be considering these for more commonplace.

This is the back fill for those of you who have not lived through those 2007 and 2009 contentious times that oftentimes came to conflict between the art of public health and the practice of medicine as it's defined in the United States, and helps fill the necessary background moving into Slide 8 for the members of our ACIP Rabies Work Group which was made up from our prior ad hoc

informal management team from throughout the United States and on to Slide number 9. Those of us in HHS who also served on that ACIP Work Group up until the present time.

As well as up on to Slide 10 a variety of international consultants that such adjustments were discussed over this period of time both formally and informally both in person as well as by phone and in e-mail as well as at our 2008 Rabies in the Americas Conference that was held here jointly with USDA.

In person we had a workgroup with some of these individuals who not only serve as technical advisors to the World Health Organization and other non-governmental organizations as well as members - the technical advisors for industry for the individuals who are commercially producing the only two rabies vaccines licensed in the United States.

Moving on to Slide 11. The terms of our reference was to review the objective evidence for a reduced schedule of human rabies postexposure prophylaxis, namely the reduction of consideration of five doses to four vaccines in PEP. To provide these data to the ACIP committee for the discussion, consideration, recommendation of the dropping of that last dose. And if in fact it was so recommended to revise our prior 2008 ACIP statement.

Slide 12. The source of the evidence that we used was both peer reviewed literature as well as things that were unpublished as well as things that may have been supplied in the files to the Food and Drug Administration. Not only in regards to the biologics themselves in the clinical trials but obviously the scientific basis behind rabies virus pathogenesis which then supplies all of the

factual reason for exposures of definitions and management of exposed individuals.

Basic immunization kinetics and response to potent biologics such as rabies vaccines, surveillance data not only here in the United States but also in our role with the WHO collaborating center in consultations with many, many partners that we have thanked profusely in the past and again reiterate.

Slide 13. The rationale for having this discussion was to engage before any true shortage was become evident. Obviously considering all the discussions about the utilizations of any biologics from an evidenced-based approach for ACIP, to minimize any adverse biomedical events from additional doses of vaccines that are received as evidence any of you living in America the current discussions about health reform and concerns and unnecessary health expenditures if in fact they are not needed based upon the evidence, a legacy for the development of any future biologics as to the evidence as to the minimal number of doses that should be utilized as opposed to the current products, and obviously the application of health effectiveness research and the application of an evidence-based approach to vaccinology in regards to these ACIP statements.

Slide 14 is just a tiny review that we have always been reviewing these in one way or another since the time of Pasteur as to the kinds of biologicals and the numbers of doses that are used and their application.

And as one can see that from the utilization of initially nerve tissue-based vaccines up to the advent of cell culture and tissue culture-based products there's been a gradual diminution from somewhere between 14 and 23 doses,

some of which are still used unfortunately in the developing world, all the way to the reduction of only four doses but what was used previously in what's been referred to as the 2-1-1 application. That both the 2-1-1 and hence four doses as well as the traditional (unintelligible) scheme of five doses which is what's been adopted in the U.S. broadly since the 1980s onwards and that there's always been a gradual reduction.

What some fail to understand is that they don't seem to appreciate that the prior schedule of five doses was not as if one had objectively looked at the use of rabies immune globulin with one dose compared to two doses compared to three, four, five, six, et cetera in any sort of comparative, concomitant clinical trial.

These were done on the basis of any gradual reduction from 14 is ideal. And then on the basis the evidence presented it seemed to be immunogenic as well as meeting the criteria for licensure when those vaccine doses were so utilized.

Hence there was a long history of support around the world as well as in the United States for this gradual decrease that would help set up the backdrop for such a consideration in the 21st century.

Slide 15, thinking about our etiological agents. We're talking about negative stranded RNA viruses, lyssa viruses that cause an acute progressive encephalomyelitis. These are the quintessential neurotropic agents.

And if you think of the basis, the rationale for why we do things the way we do them, we want to try prudently, relatively quickly and appropriately, to be

able to neutralize and activate and push towards clearance that local insult of viruses that are being deposited in a wound after a bite at neuromuscular junction.

Luckily for us it does take time for those locally deposited virions to gain access to the correct receptors, the correct cell types, to gain access to those cells, for them to replicate and start to move in the peripheral nervous system to the CNS between the time when an exposure occurs and when one is able to actively institute prophylaxis.

Hence the combination of wound care and debridement for the removal of viral load there in the periphery. And hence the key focus upon wound washing in the treatment of any animal bite. The infiltration locally of rabies immune globulin to help neutralize the virus until such time that active immunity begins to help build with the combination of passively administered immune globulin if you do this as early as possible.

Obviously it's prudent and conservative to try and intervene before access into the peripheral let alone the central nervous system, the prime predicator of what drives appropriate and timely post-exposure prophylaxis as opposed to things that occur fairly late, i.e., issues to deal with at or about day 30 that is what was the day 28 dose administered. Obviously in bona fide exposures we're much more concerned about interventions that occur shortly after exposure as opposed to the long one.

On to Slide 16. Just capturing that basic discussion of the generalized viro-pathological scheme that we've seen time and time again in humans and other animals. And recognizing a median of about a month of incubation period

seen in the United States. Suggesting it's the interventions that occur much before that time that are critical as opposed to the ones that occur relatively late in the game when the virus may be actually ensconced within the nervous system and the difficulty of trying to intervene once in the CNS.

Slide 17. One of the large body of data, of course, and the recognition of the kinetics of rabies biologics that just about all immmunocompetent subjects mount an active immune response detectable on or about day 7 to 14.

Reiterating that there is no seroprotective level for humans and other animals. There are arbitrary levels that individuals have used on the basis of evidence among reference laboratories of what constitutes the detection of virus-neutralizing antibodies as far as detectability as demonstrable for an appropriate immune response.

From a review no significant differences in the availability of antibodies from either a four or five dose schedule going forward prospectively in clinical trials and hence in the comparison of those studies that used four doses when given in a regimen that included wound care in immune globulin, no unequivocal or non-equivalent outcomes were observed. As illustrated in Table 18 which is a composite from a variety of clinical trials that illustrate the relatively rapid induction of virus neutralizing antibodies by day 14 to 28.

The relatively rapid decline in human rabies immune globulin, barely detectable once infiltrated at the correct dose that tends to decline between days 21 to 30 usually to below levels of detectability. And the lack of utility from the standpoint of seroprevalence or GMT's of that last and fifth dose administered on day 28 -- from clinical trial David Newman.

In regards to surveillance, Slide 19. In the United States we've never had any postexposure prophylaxis failure since the advent of the current concomitant wound care immunoglobulin infiltration and administration of cell culture vaccines.

The recognition that the majority of individuals in the U.S. as in the world who succumb to rabies have no prophylaxis, have delayed prophylaxis or have inappropriate prophylaxis often times no infiltration or no cell culture vaccines at all.

And that a review globally of the so called postexposure failures that not only are true failures - that is of individuals who appear to have received timely and appropriate vaccination are very, very rare but that the majority of individuals have any history of vaccination at all that is delayed or inappropriate.

And often times the clear majority of these individuals demonstrate onset of rabies before day 30 or die thereafter of which case no cases were identified in which the lack of administration of that fifth and last dose of vaccine was felt to be at all relevant to prevention for that particular instance.

Slide number 20. We also recognize that the public is not compliant in the best of circumstances. That's not only here in the United States when people have been exposed to bona fide laboratory diagnosed rabid animals but also from a variety of unpublished data from engagement with our colleagues where much fewer than the five doses had been utilized and hence we know that public compliance is less than it should have been. We also know this from investigations during the limitations in supply in Puerto Rico where a

number of individuals who did not receive five or even four doses of vaccine were still known to be alive after exposure.

And hence it became clear that if at least some of those other criteria, wound care infiltration and at least a prime boost strategy, that these were the key. Also similarly based upon this lack of ideal public compliance from a variety of venues around the world.

Similarly we have to recognize - Slide 21 - the utility comparatively of animal models in forming much of our prophylaxis management recommendations. Classically from the time of how vaccines in the 19th century were first being formulated and certainly driving most of our progress throughout the 20th century. Including the utilization of immune globulin from the ‘40s to date. And similarly with the advent of cell culture vaccines the basic models that form the foundation prior to clinical trials up until the present time.

Both from the literature as well as from our own research from a variety of species from rodents to non-human primates it became clear to us that it was not the absolute number of cell culture vaccines that was important as long as prophylaxis was timely, appropriate and minimally involved a prime boost strategy behind the foundation of how rabies vaccinology works.

As illustrated Slide 22 from data generated by Dr. Richard Franka our colleague here and one of the ACIP working group members which was published last year demonstrative of what I just mentioned using a Syrian hamster model that we’ve used for many years in modeling of human response demonstrating that when compared to controls that received only diluent or animals that received vaccine only in the severe exposure model,

that when animals were exposed and given prophylaxis 24 hours later that there was no significant difference in animals that received less than five doses of vaccine when complimented with immune globulin compared to those that received only one, two, three or four doses of vaccine.

So the take home from this was as we have seen in this and in other models and other experiments that not the absolute number of vaccine doses that even against severe exposure in animal models that are important.

Slide 23. Since the evidence-based model for ACIP came into recent existence there has also been the necessity to review what the potential outcome might be from the standpoint of the health economics.

And Dr. Martin Meltzer and his colleagues from our working group were able to go ahead and do a anticipated impact in which case - from the health care payers and health care system that we recognize that the potential cost per dose of vaccine might rise, that obviously the number of visits that the patient would make for application of prophylaxis would decrease, and obviously all of those associated costs from loss of time to work, for supervision of children as well as all the potential outcomes from going from point A to point B for application of biologics, the cost of the biologic itself and the adverse health outcomes from that fifth dose et cetera, and then obviously the number of patients may increase over time as the disease of nature, more application of biologics for example in a shortage situation that there might be a larger number of patients in space and time in the future.

From the standpoint of the consumers we didn't think that the insured would see increased costs given the current health care discussions, that the

uninsured similarly would see an increase in costs to them due to the indigent care situation and obviously payers of last resort to ensure that no one in the United States who is in need of postexposure prophylaxis would go without.

Continuation of the preliminary assessments that supported the positive benefits that would accrue with a reduced schedule of rabies vaccination overall and that there was no anticipation from our standpoint that changing the previous recommended schedules of five to four doses for human postexposure prophylaxis would substantially alter the health economics of human rabies prophylaxis in this country as it's currently understood from a negative standpoint.

Slide 25. In summary from a variety of the basic pathobiology, the utilization of animal models, the review of clinical trial data, the epidemiological surveillance both nationally as well as internationally that was reviewed - that taken together there was no supportive evidence that a human rabies case would result from a reduction of postexposure vaccination schedule from the fifth dose on day 28 to the utilization of only the fourth and last dose on day 14.

Based upon these data that were presented to the Advisory Committee on Immunization Practices the committee voted to accept and make these recommendations at their June meeting of last year. This was thereafter reflected in their minutes of their meeting and were published this past month in the MMWR from CDC.

Slide 26. We recognize that throughout its history that ACIP has made recommendations to the CDC after the licensure of such products. And in fact

that there was not an unprecedented event here with the recommendation in a change from the 2008 to the 2010 recommendations to decrease from five to four doses which would have been seen in apparent conflict with the label from the regulatory standpoint.

One also recognizes that there is no expectation for there to be a label claim currently from the biologics that are licensed in the United States. We recognize that some clinicians utilize the four dose situation from the time the ACIP recommended the same, based upon the evidence. We similarly recognize that there will be some clinicians who elect not to go with the four dose schedule.

Based upon a lack of information for the immunocompromised we considered it prudent until such time that available comparative data for the immunocompromised situation were to become manifest that there would be no change in that recommendation.

And hence within the criteria that ACIP had previously defined and are in the cited literature that for the immunocompromised that they would still receive the fifth and last dose compared with similarly wound care as well as infiltration of immune globulin.

Slide 27. Based upon the situation that I just previously reviewed there's obviously been quite a bit of questions that have arisen since June of last year. And one of these is reflected, for example it's not unusual in travel medicine for individuals to have patients present that have been exposed abroad and people have asked should they receive the fourth or the fifth dose?

It depends. It depends that if in fact they received wound care and immunoglobulin appropriately. It depends upon the nature of exposure and in fact if it's an exposure at all.

It depends if we know what those biologicals were, those biologic - for example sometimes it's an unknown script. Sometime neither the patient nor can we have a trace back to what it is they received.

Alternatively there are products that do meet the WHO's precertified basis for biologics that are recommended through WHO guidelines, these biologics, some of which are produced by the same manufacturers as products that are licensed in the United States as pre-qualified products.

Some of these products appear just as pure, potent, safe and efficacious as the products that are licensed in the United States even if they aren't for example some of the products that may be produced in Vero cell vaccines commercially.

And so often times you may have a bona fide exposure that occurs abroad that is similarly given prophylaxis and good wound care with human rabies immune globulin and the patient may have received one or two or sometimes even three doses.

So that when they come back if in fact they're not immunocompromised and they seem to meet these criteria of bona fide biologics then it would seem reasonable to go forward with the ACIP recommendations and that patient would receive only the ensuing number of biologics and in the schedule based upon when they received the last dose.

Conversely if one has no idea of what they've received it's not unusual at all to begin prophylaxis de novo starting if fresh and warranted proper wound care infiltration and the full course of four doses and of course if the patient is deemed to be immunocompromised under those clinical definitions operationally would receive five doses.

To start all over again and go to four or fifth if the patient is immunocompromised all the way to just continuation with the requisite number of doses up to four if those biologics meet from an investigational standpoint the criteria so described.

So Example Question Number 1 it depends and is perhaps one of the more variable ones since we don't control the scenarios, the diagnostics, the surveillance nor necessarily the biologics that patients may receive abroad.

Example Question Number 2 for Slide 28, oftentimes elderly and immunocompromised patients may present. And for example in this scenario one that's not uncommon in the United States having a bat in the household as opposed to the non-living quarters.

And in the situation where it's fairly clearcut meaning the animal is in hand, the animal is diagnosed as rabid, the exposure is obvious, then it should also be obvious what one should do for Example Question 2 for which I should not have to point out since it should be intuitively obviously given how much we've belabored this point about utilization of 2008 in the immunocompromised situation ACIP guidelines as opposed to the four in a non-immunocompromised situation.

Turning to the next slide, 29, for Example Question Number 3, previously vaccinated individual has an exposure from an animal that's not available. What type of prophylaxis should be administered under the new guidelines if in fact the individual is healthy, not felt to be immunocompromised.

In a situation like this depending upon the epidemiological circumstances as local public health authorities would deem based upon the investigation then the current 2010 ACIP with wound care infiltration of immune globulin as much as can be administered, 20 IU per kilo, at the site of the wound and the four doses administered.

Obviously the only time this would vary would be if in fact animal control officers were able to appropriately find, confine and diagnose as needed and if the animal is not found to be rabid.

And in fact being an urban situation as we see now currently in Central Park with over 100 rabid raccoons recently diagnosed over the winter that epidemiological situations change and even in relatively previously quiescent situations where perhaps the risk mitigation would be that such an individual would not receive immunization would be different here if it was unvaccinated.

Since this was a previously vaccinated individual nothing changes, the individual would receive two doses on Day 0 and three only if it was an unvaccinated individual would the four-dose schedule be relevant. So a bit of a trick question for Question 3.

This is not affected by the current recommendations. The individual was previously vaccinated and if it's deemed to be a rabies exposure the individual would receive doses at Day 0 and 3 intramuscularly unaffected by the current recommendations.

I didn't mean to throw anybody, just seeing if anybody's paying attention after this period of time.

For additional references there's certainly the citations for the currently published ACIP recommendations which we feel are fairly clear cut. Tried to use those last three examples of putting these in the perspective as well as in the written handout for your consideration.

And above and beyond the citations that are in the ACIP recommendations certainly there is for the academically inclined the nice review in Stanley Plotkin's current edition of vaccines particularly along the lines of the historical evolution of human rabies biologics and prophylaxis in the United States.

And with that I believe we should be up to Slide 31, thanking you for your time and attention and turning it over now with ample time for questions to Conne and the rest of our staff. Thank you.

Conne Ward-Cameron: Thank you Dr. Rupprecht, thank you for sharing that deliberative process that went into making those revised recommendations and even throwing in a trick question to see if we were on our toes.

And now it's time to see if our audience is on their toes. Emily, do we have anyone in the queue for questions for Dr. Rupprecht?

Coordinator: Thank you ma'am. At this time anyone wishing to ask a question or make a comment please press star 1 on your touchtone phone. All questions will be taken in the order that they're received and you'll be announced by name when we're ready for your questions.

Once again anyone wishing to ask a question or make a comment please press star 1 and please be sure your telephone is unmuted and record your name clearly when prompted. One moment please.

Our first question comes from Jackie Hopkins.

Jackie Hopkins: Hi Dr. Rupprecht, thank you so much for a very informative summary. I'm actually back on Example Question 3 with regard to the feral urban cat. I understand that the booster doses on Days 0 and 3 with no RIG would be appropriate. And that - maybe you touched upon this - that that would be given if the local health service jurisdiction feels that the situation warrants it.

As an example in San Diego County, California, we don't have terrestrial rabies so we wouldn't necessarily on feral urban cats recommend. We typically leave it up to the victim and the provider. Do you have any comment about that?

Charles E. Rupprecht: Thank you, excellent point. You're right on the money. For example if this was in Hawaii, no concerns. Similarly there are many parts of the US that are fairly quiescent and in many large urban areas even in which the surrounding

areas have not had any enzootic rabies for many, many times, prophylaxis decisions are always made based upon the animal in question, its availability, the circumstances of the event, the exposure or not, i.e. contact, was it actually a bona fide exposure, and not least the epidemiological situation.

These are always done on a risk assessment basis. And so for example if this was in a quiescent area and the animal was otherwise healthy because it had a collar on it and no fleas and was in good flesh.

And because the officer in this situation maybe squeezed it a little too tightly in getting it out of the trap and it was a scratch rather than a bite, the animal otherwise seemed normal and went away back into the neighborhood potentially into the arms of its owner that shouldn't have let it out to begin with - sorry for the editorial - then obviously local jurisdictional risk assessment is always a key. And in many situations for dog and cat exposures would not deem prophylaxis to be necessary.

Versus situations that things change, stuff happened, Central Park now and in fact due to the activities that are going on perhaps a different situation. If this was a very aggressive animal, no collar, active parasite ridden, that as it ran away ran in a rather sinuous pattern suggestive of ataxia perhaps one would err towards a different side of management.

Jackie Hopkins: Great, thank you.

Charles E. Rupprecht: Thank you.

Coordinator: Thank you. Our next question comes from (Marsha Golodft).

Marsha Golodft: The ACIP document on immunization practice overall has several categories of immunocompromised. There is a group such as diabetes, renal failure and (espania) where additional vaccines are recommended for bacterial diseases. Would this group be included as immunocompromised for the purposes of rabies postexposure prophylaxis?

Charles E. Rupprecht: Thank you, Dr. Golodft, excellent point. And we believe that if in fact they call into the category for other considerations such as you point out for additional vaccines then operationally and clinically when such a patient presents under those circumstances that they could in fact be deemed relatively immunocompromised.

And until such time that other evidence presents itself, i.e. from serological comparisons, that perhaps it would be prudent to engage those individuals that administer the fifth dose.

Similarly we have to recognize having said that that the committee felt strongly that in no way would we be putting such patients at risk based upon the evidence.

For example, given the conditions that you suggest are fairly broad and given that compliance is less than ideal, given that such conditions are all the more exacerbated abroad, given that even for those jurisdictions internationally for which the burden of HIV is fairly high, that we have had no postexposure prophylaxis in areas in which surveillance is approaching the ideal due to even severe immunocompromised and for which compliance and the lack of perhaps the fifth IM dose has been provided.

Similarly we know that there's a relative degree of immunocompromised in the geriatrics and in fact even with rabies vaccines, clinical trials have shown that there is a overall lower GMT in older patients compared to the young, adolescents or middle aged.

Nevertheless one has to recognize that this not a lack of response and that there are no known cases of geriatric patients being quote/unquote relatively immunocompromised and not responding as well has to be differentiated from not responding at all.

So I think it's conservative and prudent for the patients that you've mentioned to be considered for the fifth dose recognizing however that if it's deemed clinically that they are not I don't feel anybody believes strongly on the weight of the evidence we have, limited as it is to date ,would significantly put those patients at risk, that the primary ones tend to be wound care, human rabies immune globulin itself if one looks back at the animal models of what RIG in and of itself may do combined with the prime boost nature of these very, very potent biologics. Thanks for your question.

Coordinator: Thank you ,sir. Our next question comes from (Karen First).

(Karen First): Yeah, hi. Thanks for taking my call. This is a little bit off the subject but because of the information that -outside the United States there have been occurrences where people have gotten vaccinated and still developed rabies due to a deviation from the recommended prophylaxis, it's become common among practitioners - many practitioners - to assume that if somebody misses one of their doses that they have to start the whole series all over again.

And I didn't know, are there any circumstances that you would recommend that they start all over again? What I'm - what I've been told is that they just should pick up the series wherever it is that they dropped off but not repeat the whole series all over again. But I just wanted some clarification on that.

Charles E. Rupprecht: Sure, excellent question, thank you. And it happens more often than I think people wish to admit. About the only times when it might be warranted to start entirely over again meaning both rabies and immune globulin administration and cell culture vaccine from Day 0 onward would be when you absolutely have no idea what it is that they received or there's some question in the veracity of what it is.

Oftentimes you might get a script that is almost indecipherable and in another language or tongue. So there are some situations where you elect to begin all over again due to a lack of accurate information.

There are other situations however where based upon educational level, based upon outreach and recall that - and the CDC is here to assist in such situations as a WHOCC - to help try and investigate such circumstances where quite a bit of information is able to be had.

Oftentimes one may even figure out pulling back that an exposure never really occurred. So there are some situations where you can believe what has occurred, there is no need to start over again. And so for example either because they've gotten RIG and bona fide biologic XYZ, say they received only Dose 1 and they've shown back up.

Well, the day they present to you and if they're not immunocompromised and you feel strongly or know what the biologic is, you would finish out the series with vaccine doses 3, 7 and 14. And the only time that you wouldn't was when you felt uncomfortable or had no information to be able to proceed along those lines. So keep the interval as best you can recognizing that a day or two is not critical in regards to those schedules in the prime boost scheme.

(Karen First): So the subsequent vaccines you base them on Day 0 or you base them on the day that they came in for their dose 2?

Charles E. Rupprecht: So for example if they present to you today, today would be Day 0. And if they got Day 0 - let's suppose for example they were in Mexico, were exposed by a dog that got away, got a cell culture vaccine and RIG in Mexico and now show up in Texas, New Mexico, Arizona, California to your office on Day 3.

They would receive the Day 3 vaccine dose assuming that you can verify that they actually received qualified biologic. And you would administer the second dose on Day 3, the third dose on Day 7 and the fourth and last dose on Day 14.

(Karen First): So they go to our emergency room and they get the first and the second dose and then they disappear for a while and then they show back up in our emergency room and now they're like three days late for their third dose.

Charles E. Rupprecht: Give them the third dose.

(Karen First): And then when do you count the fourth dose, off of Dose 0 or...

Charles E. Rupprecht: One can keep the interval the same. Recognizing that the scheme that was chosen and from a comparative vaccinology sense recognizing there are few other biologics that we go to this extreme primarily due to abject fear and ignorance associated with this historically, that the kind of scheme and the spacing of this was a best guesstimate of pacing of biologics presented to the immune system, recognizing that a day or two in terms of the basic kinetics are not going to vary that much. And on the basis of what we know from the recognized prospective clinical trials that that kind of spacing seemed to be okay as far as the patients responded appropriately and no human cases occurred thereafter. That until such time that other evidence presents it would seem reasonable to continue the spacing of that biologic from the time the present back to you after the missed as opposed to the original Day 3 schedule which they're already off.

(Karen First): Thank you very much, that was very helpful.

Charles E. Rupprecht: Thank you, ma'am.

Coordinator: Thank you. Our next question comes from (Barbara Locke).

(Barbara Locke): Yes, hi ,thank you. My question is, are there any good studies to show local infiltration of the wound versus simply giving the RIG IM?

Charles E. Rupprecht: Thanks, excellent question. Certainly there were the original studies that demonstrated the utility of infiltration. One can demonstrate experimentally again using animal models, the utility of local infiltration as opposed to elsewhere.

There's also the epidemiological recognition of human cases when immune globulin has not been infiltrated into the wound as opposed to elsewhere, the potential immune complex formation and interference when immune globulin is not infiltrated into the wound and placed in or about the same spot that the vaccine is administered.

And lastly from the standpoint of the academic if one thinks of the need, the utility, the action of immune globulin and oftentimes we use the ink blot or the diffusion idea, most of your viral concentration is going to be localized similar as a concentrated amount of dye would be in a drop - say into a fluid - in that one site and it will only begin to spread gradually thereafter.

Similarly when you're thinking about infiltration the most temporal spatial concentration of that immune globulin is where it should be and that should be at the site that should take the greatest action.

When one, for example, has an exposure in the head and one would go ahead and administer immune globulin in the gluteal not only do you have the problem of deposition potentially into adipose tissue but one has then diluted the relative amount of that and has to have the physiological time for the diffusion of that product from (adipo) to the place for which it is intended to act locally.

So there are a variety from both the theory as well as the experimental support in animals as well as the empirical epidemiological data as to why infiltration locally is the best practice particularly in severe bite situations and particularly in those multiple and severe ones to the face and head with the relative proximity to the CNS.

(Barbara Locke): Thank you.

Charles E. Rupprecht: Thank you.

Coordinator: Thank you. Our next question comes from (Robert Edmond).

(Robert Edmond): Hi, I have a question back to your slide on the traveler if a person comes back from let's say Asia or wherever and they've received - they had a definite exposure, they had good wound care, they got a rabies immune globulin and got two doses of a vaccine which we don't use in the US such as Verorab or (Rabipure) is it okay then to give the last two doses with one of our two vaccines, Immovax or RabAvert?

Charles E. Rupprecht: Thanks, excellent question. As long as one feels comfortable in the veracity of the administration and by that I mean for example there's been a quite a bit in the news lately of certain countries producing or providing counterfeit vaccines. There are certain situations and certain venues where you might feel uncomfortable regardless of what's told you from any biologic standpoint.

However if it comes from a locale that we have quite a bit of experience with - it could even be a developed country for which that product may not be licensed in the United States but is utilized there to effect and without incident over many years and is on the prequalified list that I think it would be reasonable to consider only the administration of the subsequent two doses from the product here.

It's like many things in rabies and its prophylaxis, it depends. And in certain situations you will feel comfortable; in other situations you may never feel comfortable.

(Robert Edmond): Well, the second part of the question is how much nerve tissue vaccine is still being used?

Charles E. Rupprecht: You mean abroad?

(Robert Edmond): Yeah.

Charles E. Rupprecht: In developed - I'm sorry, did you say nerve tissue vaccine?

(Robert Edmond): Yeah, like Fuenzalida and are they Semple?

Charles E. Rupprecht: Oh yeah. In many parts of Latin America countries are still producing nerve tissue-based vaccine. Since the 2005 WHO consultation, even before that, the utilization of nerve tissue vaccines was no longer supported. I know the Pan American Health Organization has had quite a bit of outreach to countries in the region.

I know our own staff are having quite a bit of technical consultations and have to those countries that are still producing and using nerve tissue-based vaccine. We know from personal experience there are still unfortunately countries in the world that are not producing suckling mouse brain vaccine but adult nerve tissue-based vaccine that hearken back to in essence the (fenol)-based inactivation of the 19th and early 20th century.

And we know that there's still residual virus found in that material based upon the way that they titrate that material and it still kills animals from intracerebral inoculation.

So unfortunately there are still some places throughout Latin America that are using the safer suckling mouse brain vaccine recognizing that's "safer" only in comparison to these other residual nerve tissue-based adult vaccines that have actual live virus associated with them such as that are still unfortunately used in parts of sub-Saharan Africa and in other developing resource-limited countries in Asia.

(Robert Edmond): Okay, thanks very much.

Charles E. Rupprecht: Thank you for the question.

Conne Ward-Cameron: And Dr. Rupprecht and Emily we have time for one more question.

Coordinator: Thank you. Our final question today comes from (Steve Englander).

(Steve Englander): Thank you, Charlie. Excellent presentation. I may have missed in your discussion of Slide 26 and you may not be in a position to comment but are you aware of any revisions on the package inserts from Sanofi or Novartis, the US manufacturers? Reason for the question is that in many smaller local health departments their medical direction may come from individuals who are more comfortable with what the package says than ACIP?

Charles E. Rupprecht: Thank you, excellent question. And it was a major bone of contention as you might appreciate. Obviously the working group including the outreach to

the technical points of contact for both producers of human rabies vaccines licensed in the United States and similarly from review of the files in FDA that no one found any evidence to feel insecure that any of the recommendations that would go forward would be to actually jeopardize public health.

That's a far cry from then trying to suggest, nor mandate which they can't, a label claim; that label claims are done on the basis of the manufacturer. And there are a variety of reasons why it was put forward and discussed at ACIP that subsequent labels would not be changed.

Some of them ranged from they felt this would be a dangerous practice and did not feel comfortable which obviously conflicts objectively with their own technical consultants who knows something about rabies all the way to we have many other decisions to make, we have limited resources and we wish to put those resources into other useful products. It covered the gamut there.

And so recognizing that one cannot compel label claim changes, recognizing that obviously why would we want to make recommendations on the basis and the weight of the evidence it would jeopardize or cause a human case, and recognizing the substantial benefit from an evidenced-based approach to utilization of vaccines from a public health capacity that this would be a useful thing.

Nevertheless it's one of the reasons why I tried to include that slide. ACIP simply does not rubber stamp and that obviously this is an individual decision. We all recognize that not everybody just does label-based medicine today. And that this is a potential conflict between how one interprets and utilizes

evidenced-based approaches from a variety of sources regardless of what the label clearly states.

This is the reason that we not only included that slide and I thank you as a very important last question but similarly felt strongly that that be put into the MMWR so that individuals recognize this potential perception of a conflict.

Conne Ward-Cameron: Thank you, Dr. Rupprecht. Thank you (Emily) for facilitating our call today and thank you again, Dr. Rupprecht for sharing the practical use of this information through those excellent questions from our participants so thanks also to you for participating today.

If you have any additional questions for our speaker - and I'm guessing that there are still people in the queue who did not make it through - please email us at coca@cdc.gov and that's C-O-C-A@cdc.gov and we will be glad to get those questions to Dr. Rupprecht so that we can forward them and he will be able to respond to you. Again the email address is C-O-C-A@cdc.gov.

The recording of this call and the transcript will be posted to the COCA Website at emergency.cdc.gov/coca within the next week. You'll have a year to obtain continuing education credits for this call if you wish. All continuing education credits and contact hours for COCA conference calls are issued online through the CDC Training and Continuing Education online system.

That email - excuse me, that Web address is www2 -- the number two -- a.cdc.gov/tceonline/. And that information is, again, at our COCA Website. Thank you again for being a part of today's call. We look forward to talking with you again soon.

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