COCA Conference Call – Human Rabies Prevention: Trouble Shooting Prophylaxis
Dr. Charles Rupprecht
September 5, 2007

Coordinator: Welcome and thank you for standing by. At this time, all participants will be in a listen-only mode. To ask a question during the question and answer session, please press star 1 on your touch tone phone.

Today's conference is being recorded. If you have any objections, you may disconnect at this time. I would now like to turn the call over to Alycia Downs. You may begin.

Alycia Downs: Thank you and good afternoon. And thanks again for joining us for today's COCA Conference Call on human rabies prevention, troubleshooting prophylaxis.

We are pleased to have Dr. Charles Rupprecht present on this call.
Dr. Rupprecht is the Director of the World Health Organization Collaborating Center for Rabies Reference and Research at the Centers for Disease Control and Prevention in Atlanta and the chief of the Rabies Program Division of Viral and Rickettsial Diseases National Center of Zoonotic, Vector-Borne and Enteric Disease here at CDC.

The objectives for today's call are for clinicians to review salient features of rabies epidemiology, pathogenisis and transmission, to gain familiarity and current recommendations related to human rabies pre- and post-exposure prophylaxis and to discuss selected case examples of rabies prophylaxis management.

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

Charles Rupprecht: Thank you ma'am. It's a pleasure to be with you this day in celebration of our first annual World Rabies Day – week, and what we'll do is go through about a third on introduction and review, [a] second part on issues related specifically to rabies pre- and post-exposure prophylaxis, and then ending with issues of some selected case reports, based primarily upon some calls that came in as early as this morning and as late as the last week [to CDC].

[These are] some common issues that we'd like to address, and then end the conference with some Q&As, if we could.

Rabies is an acute progressive encephalomyelitis, and it's one of the oldest infectious diseases that we're aware of. It's been reported in just about every major culture [or] civilization for approximately the last 4,000 years.

And because of its case fatality rate, which is the highest of any infectious disease, it obviously carries much public health significance, as well as veterinary issues. And given its both public health and veterinary concerns, as well as economic [concerns] around the world, it is obviously a major emerging infectious disease, [not just] an historical agent.

Next, on to the etiology slide. We're talking about etiological agents in the family *Rhabdoviridae*. These are single-stranded negative-sense RNA viruses. The Lyssavirus genus is the most important taxon in the family.

We have, besides rabies, which is the type species of the genus, at least six other taxonomic species or genotypes. And to show that evolution is dynamic, historically about one new *Lyssavirus* was described almost every decade since the 1950s, and in the 21st century alone, we have four new *Lyssaviruses* that been described.

And beyond taxonomic significance, this is of concern because almost all of the major human and domestic animal rabies vaccines in the world are all traditionally based upon true rabies viruses, and the further we get biogenetically from those, obviously, they raise some significant issues as regards cross reactivity.

Next please.

In regards to distribution, with rare exceptions, rabies is found all over the world. We don't have any reports historically in Antarctica and without having any true terrestrial mammals, that's not surprising.

It's rather interesting to us that even as late as the mid 1990s an entire continent, Australia, was reported to be rabies-free. And then, because of issues related to surveillance of Hendra virus, our Australian colleagues were able to diagnosis the first reports of other Lyssaviruses; not rabies virus, but other Lyssaviruses found in bats. So, we have an entire continent that joined the fold in the late 1990s.

When you look at [the] distribution maps, we have to recognize that surveillance is very biased for zoonoses in general and, not surprisingly, for rabies.

Often times, this is skewed towards clinical descriptions in people or some diagnostics in domestic animals, but recognizing that wildlife and, in particular, bats, are the major both predominant evolutionary reservoirs, as well as significant public health concerns in developed and developing countries, it's not surprising that surveillance is less than ideal. Often we don't have adequate submissions nor do we even have adequate surveillance systems.

This is a dilemma for travel medicine, because people always want to know "What about the rabies-free areas?" Well, there are self described "rabies-free", countries.

We can talk about areas that certainly have been able eliminate dog rabies, which is our greatest concern. These are most developed countries today. Dog rabies persists in most developing countries.

Most Pacific Oceania islands are rabies-free, so this is the largest geographic area we can describe as being rabies-free.

For example, Hawaii in the United States, most of the islands in the Pacific, New Zealand and, with the exception of four in the Caribbean - Cuba, Puerto Rico, Granada and Haiti/ Dominican Republic, a lot of the islands in the Caribbean are purportedly rabies-free.

Now, we might have to take that with a grain of salt, stepping back and thinking about the issues of rabies in bats. [Since bats are] volant [able to fly], certainly islands in the Caribbean are no small feat for bats to reach.

And so, often times, if it's an issue of dog rabies, it's relatively easy to resolve in the Pacific or in the Caribbean with the exception of those four island nations that I mentioned in the Caribbean.

It's less clear or less obvious from the issues of bats and so, obviously, one would be concerned of a bat bite anywhere in the world, as far as potential rabies exposure.

Clearly, globalization issues, as we've known since the days of monkeypox translocation, are obvious ones. And so we would hope that with electronic reporting today, that change in a country's status would be readily recognized and reported and one would be aware of it [quickly].

But one, hopefully should be aware of this problem of translocation and the ease of transportation of rabid animals today, both domestic and wildlife, as far as trying to call any areas truly "rabies free". So this has to be taken in context.

Next, in regards to hosts, we're really talking about all warm-blooded vertebrates. Yes, even birds are susceptible. But, luckily, only mammals are of public health concern in nature.

We have had no recent documented cases of rabies in birds. That's merely a historical issue, and certainly is one in context as far as the development of rabies biologicals, avian species have played a very important part.

We've known about rabies in mammals for several millennia and we can talk about two large groups of mammals – Carnivora and Chiroptera. Taxonomically carnivores are those mammals who have specially adapted teeth for eating meat.

Within carnivores, we're talking primarily about the canids, the raccoons, the skunks, etc.

The other group is the Chiroptera, that is the bats, not only the very small bats that most of us are familiar with, the microchiroptera, but also the megachiroptera, the large bats, the flying foxes, for example, in the Old World.

Next, in regards to burden. One has to appreciate that the burden of [rabies as a] disease is not just measured in regards to bodies [or fatalities alone]as concerns rabies.. We think there's a minimum of at least 55,000 human cases [in a year]. And in the [time we've been talking today], we have had at least one human case in the world.

We have to recognize that [rabies is] obviously underreported and under-diagnosed. We have to recognize that there are a wide variety of other encephalites out there.

For example, a recent report in EID [The Emerging Infectious Diseas journal] where several cases that were misdiagnosed as cerebral malaria actually turned out to be rabies cases; but we take that 55,000 as a [rough] average.

Most of that burden is found in Asia, then in Africa, and finally in parts of Latin America, and even developed countries because of the issues of rabies in wildlife, the issues of rabies in bats, we still have our human cases as well. So we may have [many more] tens of thousands of human deaths.

And when I talk about a rabies case, by and large we're talking about a fatality, whether in humans or animals.

More importantly, anytime anyone is exposed to an animal, we're talking about tens of millions of individuals exposed per year. If we think of just the burden of emergency rooms in the United States alone, that if we have 1% or more of people reporting because of dog bite issues. Luckily, the vast majority of these do not have anything to do with rabies.

But the specter of rabies needs to be raised anytime we have a mammalian bite . We've been able to control and, in cases, eliminate canine rabies, but wildlife are especially important in developed countries.

Next slide please.

In regards to rabies pathogenesis -- We're talking about highly neurotropic agents. These are probably the quintessential neurotropic agents, introduced by a bite into the periphery, entry into the peripheral nervous system by a retrograde flow in the axoplasm, and then into the CNS.

For example, if we think of a small child's head and a large dog's mouth, sometimes we can have direct introduction into the brain and replication at the level of the central nervous system.

And thereafter, this centripetal passage to the CNS, centrifugal passage to innervated organs [occurs]. Most importantly, those portals of exit being the salivary glands where we have then secondary rounds of replication, whereby we can have a virus excreted into the millions of virions per milliliter of salvia and hence, the cycle repeats itself.

Now, often times, rabies is thought of to be a poor parasite in terms of parasitic models in general, but we have to recognize that by the time clinical signs develop in the host, the virus is already past many of its replication cycles and is being excreted actively in the saliva.

And hence, it's a very good host because it is able to adapt to a very privileged spot, immunologically speaking, and ensconce itself within the mammalian central nervous system. And [rabies virus] actually, affects its own transmission well before the host appears ill and, certainly, before it dies.

From a viral standpoint, the host is excess baggage. This is one of the reasons why we have observation periods in animals for which we understand their pathobiology, most notably, the dog. And, in cases where it [canine rabies] has been controlled, observation of the dog, obviously, saves many [human] prophylaxis cases otherwise.

Next please, in terms of diagnosis.

Really [diagnosis] is fairly simple when based upon a history of a bite by a rabid animal for which we have laboratory diagnosis, as well as a compatible encephalitis in a patient.

And we're really talking about inclusion that, at least historically at the turn of the last century, those intracytoplasmic, inclusion bodies, the negri bodies, were recognized. Today the gold standard is the direct florescent antibody test, for which there's been a new national protocol [developed] and for which we undergo regular training.

The United States has objectively perhaps some of the best surveillance [systems] in the world, primarily, because of decentralization. We have over 100 diagnostic labs spread throughout the country and have anywhere from 100,000 to 120,000 submissions per year of which, luckily, only 7,000 to 10,000 turn out to be positive.

So, many people exposed, many samples sent in, and, yet, relatively few in comparison actually turn out to be rabid.

In humans, we can talk about antemortem diagnostics. In the U.S. we receive about one case, a suspect case, in humans per week. This past week I believe

we had three or four. And so often times these go in peaks and valleys, often times before holiday weekends.

We request postmortem diagnosis in animals. The tissue of choice is CNS tissue, particularly the brainstem.

In humans, we're looking for serum, cerebral spinal fluid, a full thickness skin biopsy at the nape of the neck and saliva.

Next, in regards to clinical stages we can think about five classical ones that occur after exposure. The incubation period, for which diagnosis is not possible, by and large. This is the period whereby a virus is moving into the CNS.

And, in worse case situations, we can think [it takes] about a week. These are going to be dependent in part upon dose and route and severity. And so in very severe situations, relatively short incubation periods [occur].

Also we have some very prolonged incubation periods for which we do not have adequate explanation. In fact, some of the best objective documentation of long incubation periods in excess of a year, as long as six years, have been documented in the United States.

On average, most of these incubation periods [are] on the order of four to six weeks.

Thereafter we have a very non-specific prodromal phase, where the host appears with almost flu-like signs, thereafter progressing into an acute neurologic phase. Often times at the site of the bite there may be suggestions of tingling or puritis from dorsal root ganglion [infection], for example.

We also have progressive hallucinations, odd acting behavior, cranial nerve deficits, progressive paralysis, ataxia, etc.

Often times, historically, people talked about a more furious stage or maniacal behavior, versus a more paralytic [presentation].

Often times this is complicated, not just by the variant of rabies virus, but perhaps just as much on some host attributes, because in having different individuals bitten, for example by the same rabid animal, one may manifest with more furious centralized signs as opposed to others with ascending paralysis and more of a paralytic phase.

Often times, historically, it's been suggested that vampire bat rabies in Latin America presents as more of a paralytic phase.

Relatively soon thereafter, the patient progresses into coma. And relatively soon thereafter, into death. Obviously, recovery from rabies is very, very, very unusual.

Next please.

We have had only five documented historical recoveries from human rabies, in people who had had vaccine on board, before the demonstration of clinical signs. Most of the time, once signs manifest, there's relatively little that can be done.

We have only one historical survivor, which through heroic medical care, that also involved induction of drug-induced coma, anti-virals, etc., have we had one relatively recent survivor in 2004.

Next please.

Human rabies in the United States: we have anywhere from one to eight cases over the last five years - so it's relatively uncommon. Even though the burden of rabies in [humans] is not common, rabies is not a rare disease in [other] animals. In the United States, we live in a [relative] sea of rabies and, hence, that's what results in 20,000 to 40,000 potential [human] exposures per year.

Often times, we don't know if these are real exposures, because the animal may not be available for diagnosis, and so one errs on the side of caution.

When we had dog rabies that was rampant, post World War II, we had somewhere between 9,000 to 10,000 rabid domestic animals per year. You could imagine the number of exposures that occurred when we had enzootic dog rabies.

The United States is now free of dog rabies transmission. We're fortunate not to have a single human case in 2007 [yet]. Knock on wood. Most of our exposures still occur inadvertently because of suspect domestic animal exposures.

Thereafter, most [other] exposures are related to suspect wildlife such as raccoons in the eastern United States, skunks in the upper and lower Midwest and in California, foxes in Alaska and the southwestern United States, as well as bats that are enzootic in 49 of our 50 states.

And, we invite you to go to the [publications] page of the CDC rabies website, to look more in depth at our 2006 surveillance report.

Almost all human rabies cases are caused by a bite. Non-bite exposures are exceedingly rare as far as actually causing rabies. We have to go to some extreme examples to consider non-bite exposures. For example, in 2004, a transplantation acquired rabies. We have relatively few cases from mucosal exposure. In fact, one has to go back into literature from the 1930s to find the last bona fide case of mucosal exposure [from an animal, resulting in human rabies].

[In that situation, it] was a young girl who was repeatedly licked on her mucus membranes by a rabid dog, over several days.

Aside from that, we have some purported [cases] that were acquired in bat caves that had huge aggregations in the tens of millions of bats. These are biologically [very] rare events and, in fact, there are potentially other sources of exposure in both of those cases.

As well as at least two cases of aerosol acquisition [occurred] in the laboratory as far as humans are concerned.

Obviously, most of what we have to deal with on a daily basis, is not an exposure. Merely seeing a rabid animal, being in the same room with a rabid animal, petting a rabid animal - - even though, obviously, we don't suggest that people pet rabid animals - - is not suggestive of an exposure along these lines.

And hence if we were in an auditorium and a rabid bat was flying around us at that time, this is not considered an exposure. And, in fact, having just come from a major conference out in Estes Park we, in fact, had a bat flying about the auditorium while talks went on all that week.

Often times, we're invading their grounds instead of the other way around.

We also have to recognize that with bite exposures from carnivores, they tend to be more profound lesions that are caused, and the lesions that are caused by the small teeth of bats are often times minuscule.

Next, in regards to prophylaxis, we're really talking about two major forms, pre-exposure vaccination as opposed to post-exposure prophylaxis or PEP. In the old days, we used to refer to this as post-exposure treatment.

Obviously, it should be clear that we're trying to differentiate prophylaxis or preventative before clinical science as opposed to treatment or experimental treatment modalities such as we've been experiencing ever since the 2004 Wisconsin event. And hence, PEP, as opposed to PET.

The other reason is that people often times may not seek prophylaxis if they hear about post-exposure treatment, because they may think. "Oh, I can be treated for rabies" and often times they take this out of context. So you'd be surprised what a difference a word makes.

Why do we give pre-exposure vaccinations? Well, there are, obviously, occupational groups that are at risk of Lyssavirus and, hence, rabies exposure, such as diagnosticians, rabies researchers, veterinarians, cavers, etc.

And so the reason one provides rabies vaccination is in theory to provide some level of vaccination of immunological support to individuals at risk who may be inadvertently exposed.

Obviously, not every veterinarian gets boosted every time they're bitten or scratched and they obviously aren't euthanizing all their client animals with the multiple of times that this occurs.

In addition, because these individuals are at risk, it simplifies post-exposure management by and large. So, it's not as if we believe that this is a magic bullet and that one is provided protection per se, but obviously being good Pasteurians, we understand these are highly potent vaccines, these are some of the best biologicals we have in both human and veterinary vaccinology, as far as their potency.

And, at least from the animal end, these are some of the few veterinary biologicals that are actually licensed in regards to efficacy, not just in regards to immunicity.

As far as post-exposure prophylaxis, it is as it implies. It is for the naive individuals who are exposed or potentially exposed. It consists importantly of wound care.

We often forget this, but, obviously, this takes out a lot of the potential viral load, the viral burden, that's been inoculated into those wounds, as well as a whole variety of foreign substances, including bacteria.

We're very much concerned about flora in different animals' mouths, so one would think at a minimum the standard 15 minutes of wound washing, at the very least with water, if not soap and water.

Whether or not one provides virucidals is really open to speculation. We'd be happy if it's adequate soap and water or whatever the modicum is for common wound care at the current time.

In addition, the infiltration of rabies immune globulin. Infiltration means at the site, as opposed to in the buttocks, if one thinks of why we're providing rake.

And if we go ahead and combine these three: wound care, rabies immune globulin and the first of multiple doses of rabies vaccines, survivorship is virtually assured if it is both prompt and proper.

The biologicals that we're talking about, they're the same as far as vaccines that are used for both pre- and post-exposure prophylaxis and rabies immune globulin is used only in PEP.

Next please.

We have three rabies vaccines licensed in the United States. Unfortunately, the RVA vaccine previously manufactured by Michigan Department of Health, Michigan Biologicals, Bio Port, is no longer available, which means we only have two currently [available] vaccines.

We're in relatively good shape compared to most of the world where nerve tissue based vaccines are still being used. We have two, the classical human diploid cell vaccine, which first became licensed on or about 1980, and shortly thereafter, the purified chick embryo cell vaccine, with both of their proprietary names listed on the slide.

Intradermal application by HDC used to be available for pre-exposure vaccination. This was a relatively effective and economical way to get relatively large numbers of individuals, such veterinary students, who were at

risk, vaccinated relatively inexpensively. Unfortunately, that is no longer available.

Often times because of the economics involved, post-exposure prophylaxis intradermal [application] is often times routinely practiced in many developing countries.

Next please.

In regards to rabies immune globulin, this is plasma that's taken from human volunteers. There are two products that are licensed, both Imogam, as well as Hyperab.

Both are supplied in vials of 150 IU per milliliter and these are supplied, at least in regards to the dosage administrations in both adult, as well as pediatric vials, two mil [ml] versus ten mil [ml] vials.

For pre-exposure vaccine, the next slide, vaccine is given on days 0, 7 and 21 or 28. Serology for those who are at risk occurs every six months [or every] two years.

For example, [for those] individuals such as ourselves who are exposed on a continuous basis, meaning we're working with rabies virus on a daily basis, [serology] would occur every six months, as opposed to most individuals at common exposure levels such as veterinarians [for whom] it would occur at every two-year intervals.

If one has an adequate titer, then no routine booster is needed. When one's virus neutralizing antibody titer falls below a minimum they would receive a single intramuscular booster.

Now I don’t know how it got taken out of context, but there are no such things as rabies protective titers. We can talk about immuno-protective complexes and obviously protection against rabies is complex.

When we go ahead and vaccinate, we’re talking about a whole suite of cytokines beyond virus neutralizing antibodies. All we’re looking for is an adequate titer that’s been internationally defined, and the bar is set relatively high because at the time, as a legacy, that people were first learning how to measure serologically virus neutralizing antibodies, laboratories were having problems in regards to backgrounds and baselines.

In the United States, a minimum titer is complete neutralization at a titer of one to five. At the WHO level, that’s 0.5 international units per mil [ml].

If a previously vaccinated person is ever exposed, two vaccine doses are given intramuscularly. No need for RIG. These are given on days 0 and 3.

Again, because of the excellent potency of these biologicals and what we know historically, that if people have a history of vaccination of either of these licensed products, or having had a cell culture product elsewhere or a demonstrable titer elsewhere, by and large these are very, very long-lived antibodies and, certainly, one is primed.

And, hence, we get questions all the time about well I received a vaccine in 1980, I don’t know what my titer is. Should I get a titer or do I need to get RIG-ed?

If one is a normal healthy adult and based on that timeframe, we know that cell culture vaccines were in use in the United States, then one does not need RIG or multiple doses beyond those two.

Next please.

In regards to post-exposure prophylaxis, the importance again on proper wound care. Why does one infiltrate rabies immune globulin at the site of lesion? Well, in theory, that's where most of the depot is in regards to rabies virus.

Taken another way, if we think of a bottle of distilled water and an ink drop. As you drop that concentrated, for example, blue or India ink into that water, it begins to defuse, but the most concentrated aspect of that is exactly where that ink first hits the water.

It's the same relatively simple context in regards to rabies immune globulin. We want most of that infiltrated in and about the lesion itself. And, yes, we recognize a problem.

For example, on fingers, noses, appendages such as the tip of the ear, whereby we want to avoid compartment syndrome, but often times you'd be surprised that up to a mil [ml] can be carefully infiltrated actually into the wound itself.

We also recognize that rabies immune globulin is probably the only biological, other than local anesthetics, that's infiltrated locally.

And, so, often times, people feel uncomfortable about that if one can't infiltrate as much as is necessary because it's administered on a per weight

basis and we recognize the obesity epidemic that's going one, then obviously, one should administer the rest of it in lean muscle mass.

And so, for example, if one was bitten on the left finger as much as possible should be infiltrated into the left finger and then the remainder in the left deltoid with vaccine being administered in a different syringe and in the right deltoid.

We try to avoid large fat depots such as the buttocks. And vaccine is administered on days 0, 3, 7, 14 and 28.

Next please.

Obviously, we're concerned about rabies and the post-exposure management and the epidemiological record. Since rabies immune globulin came on board with cell culture vaccines post 1980, we have not had a single post-exposure failure in the United States. Recognizing many of these are not bona fide exposures, but recognizing that many of them are.

And so, this is a huge track record demonstrating the efficacy of these biologicals when appropriately applied. We have to recognize this as an urgency. We don't want to either become lackadaisical, meaning wait, nor do we want to go ahead and consider that they have to be done right now.

And so, these are urgencies as opposed to emergencies. The true emergency, if you will, is the first aid in regards to the wound washing. And so, if a patient happens to call, obviously, that first aid measure of soap and water should be done immediately.

Post-exposure prophylaxis obviously is going to depend in part on the species of animal, the epidemiological situation in that particular area. For example what you would do in Georgia is different than what you might do in Hawaii. It's also based in part upon whether we have the ability for enhance surveillance and the rapidity for diagnostic follow up or observation of the biting animal.

And then, obviously, consultation with many of your colleagues in the local and state health departments is suggested because they are the ones who hold the best latest information in regards to the local epidemiology of rabies.

Everything that we're aware of on a national or regional basis, we have to depend upon the local reporting and the enhanced surveillance of the local level to know what is going on.

And the reason the surveillance reports are behind, is because we don't close the surveillance year until March of the year thereafter to allow time for the localities and the states to get their final tallies together.

Next please.

In regards to adverse reactions, again, these are very, very safe biologicals compared to nerve tissue based vaccines or even the products we had in the 1950s and the 1960s. Most exposure prophylaxis should not be interrupted for mild local or mild systemic signs and, obviously, becomes a gray area when they appear at least on a temporal basis to be more serious.

These are handled always on a case-by-case basis. Often times, over-the-counter medications can be used to control pain, fever, etc Any suggested

potentially serious adverse reaction should be reported to the vaccine adverse event report reporting system or VAERS.

Next please.

What I'm going to do next is go through a series of case reports. Ideally, what I'm trying to do is go through these on a rhetorical basis to allow us at least 15 minutes for questions at the end, either for anything that I may have said that was unclear or to allow questions about any of the case reports that we'll go through or any other questions that might be pressing out there.

The advisory committee and immunization practices the 1999 human rabies prevention document is a living document and the broad guidelines that are out there really have not changed beyond some of the things that we've already discussed this afternoon.

A lot of these things, if the weird can happen, it does in regards to nature and living in the U.S.A. and we that people get exposed to rabies.

So in a lot of the situations that we're faced with it's first trying to define if they're exposures or not and what the relative severity may be. A lot of times it has to do with what kind of animal the exposure occurred with and whether or not it's a dog or a cat or a ferret and it is amenable to observation.

And, hence, wouldn't negate the necessity for post-exposure prophylaxis, as well as corrections when the patient doesn't appear on time or when delivery errors occur.

Next please.

First case report is one that happens all the time. Somebody's jogging and they're bitten by your neighborhood mu– I'm sorry your neighborhood wonderful AKC registered dog.

And often times we get into semantics whether it's provoked or not. Well, from the dog's standpoint, it was provoked. From the person's standpoint, it may not be.

In a situation like this, where you've got a multiply vaccinated dog in a relative well-heeled neighborhood and establishment, probably good local animal control authorities and that animal can be observed, is one concerned? Well, I mean, beyond treating the animal bite wound, I would not be concerned about rabies in this situation.

One would hope that in the vast majority of situations of dog bite in the United States, that the animal is available for observation. We know both from laboratory studies, as well as epidemiological observations, that dogs, cats and ferrets can be observed for a period of ten days. If the animal shows no signs of rabies during that period, the person is not deemed to have been exposed to rabies.

If the animal shows any clinical signs of rabies based upon inspection by a competent veterinarian, the animal is euthanized, its head is removed, its brain is extracted and it is sent to the diagnostic laboratory [which] should be able to give you turnaround time in 24 to 48 hours to allow you to make your decision.

If the animal remains normal over that period, obviously, no post-exposure prophylaxis is needed. These are some of the easiest, most obvious ones and yet we often forget about this situation.

Case Report No. 2 is one that just occurred last week and I spoke with length with the clinician in Mississippi. This is a different situation. Different not only geographically, but also in substance because here you have a very experienced person in terms of knowing his animals and knowing his trade.

And he was very concerned about the demeanor of this animal. The animal was not vaccinated. It was quite unruly. And even though Mississippi is somewhat highlighted as being one of the few states in the U.S. only to have, knock on wood, rabies in bats, this individual was very concerned about rabies, thought the animal acted in a very unusual manner.

Unfortunately, it ran out into the street, which in theory could be part of prodromal acute neurologic phase, was obliterated by a tractor-trailer and, thereafter, the animal was buried.

Now, under ideal conditions, could this animal be exhumed and if in fact they'd be able to identify central nervous system, could we come up with a definitive diagnosis?

One would hope yes, but in this situation it wasn't possible and if one considers probably many of the people on this call who have administered prophylaxis for much less.

Given the circumstances of the exposure, meaning the way the animal presented and the individual themselves, that they know their trade, that they know this particular animal, it'd be a much different situation in regards to recommendation of prophylaxis, if for no other reason [than] for palliative reasons to ease the peace of mind of this particular individual who was exposed.

Case Report No. 3, happens again a lot. Seemingly normal animals by well-intentioned individuals cat scratch. One is very hard pressed to go into the literature and find a bona fide documented - - and when I say documented I mean a competent laboratory who actually documents it - - the animal in question had rabies.

Bona fide demonstration of rabies acquisition by scratches. Most of the time if we are concerned about scratches it is within felids because of their grooming situation. Often times in rabies, animals will stop grooming and so that situation becomes could the animal have contaminated its claws with some of that ropey saliva.

Well, the theory, yes, if that was the case then given that rabies in cats outnumbers rabies cases in domestic dogs in the United States, one would have thought by now acquisition of scratch would have been documented.

Hence, in an area of the country such as the Pacific Northwest which for the most part is quiescent, except for rabies in bats, and in an otherwise provoked situation, that is well-intentioned person and in an otherwise healthy cat that's not available, it would not be unwarranted not to prophylax and beyond providing wound care in this situation.

And discussion over both the epi and situation of non-bite exposures rarely causing rabies, it would not be unwarranted not to administer prophylaxis in Case Report No. 3.

In Case Report No. 4, often times people are new, who it might be their first night on the job and rabies could be considered something new and exciting and mysterious and often times many of us are arithmetically challenged.

And also along a similar line of this case report, in some children that were recently exposed, an ER person who could not find a lesion since it was alleged to have been a bat exposure, went ahead and administered 20 plus small doses of RIG all over the child's body in trying to be dutiful in thinking that there could be a bat bite somewhere.

In a situation such as this whereby RIG and not five doses of vaccine were administered, one is often times faced with what to do. One is usually suggested to take a course of grain approach and that is what's the nature of the exposure.

In situations like this, whereby someone is potentially exposed and bat exposures, potential exposures, are some of our most contentious, often times, it has to do with some public health communication with the patient. And, often times, the ACIP recommendations are taken out of context and, often times, it gets repeated incorrectly to us.

Well, CDC says that when a person's in a room with a bat, they should receive prophylaxis. No, that's not what that ACIP says, nor was that ever our intent throughout the 1990s nor to date.

That is most bats are not rabid, even those obviously suggestively ill bats that are submitted, only 5 to 14% of the obviously ill bats that are submitted come back rabid.

What the suggestion is, and particularly in situations like this where we're invading the bat's turf, as opposed to we never have bats in our house and a bat was found there and was squeaking and banging into the walls and vocalizing, etc.

In situations where a person wakes up and sees a bat - particularly at this time of the year, [with] drought conditions in many parts of the country, [it's a] normal time of the year for young bats to be trying their wings, situations where they're not acting abnormally and in situations where we can get an adequate history, that is, the person is not overtly somnambulant.

This is not an individual [with] a crying baby waking up with a down bat in the room that is discarded, not someone who is celebrating the last few days before going back to school and is otherwise intoxicated or under the effects of any medication.

If we can get a competent history and if we can talk to the person and we recognize that some people are adverse to taking any risks, both physician and patient, and that, often times, we don't have in care management, a lot of time to discuss these issues and referral and discussion and dialogue with people in public health, it may be quicker to write a script.

That at least in the vast majority of cases, when we discuss, put things into context, discuss what we know about the facts about rabies in bats, the epi data where they exist and ask individuals, "Are you an otherwise normal individual? Would you have awoken if you had a sharp prick as you might get from a pair of forceps?"

Most individuals say, "Oh yeah, I don't think I'm at risk." They may elect for their children, even after thorough examination and not being able to find small lesions. Often times, healthy competent adults will elect not to receive prophylaxis.

And so this is a judgment call. If any of those pre-conditions exist and the individual says, “Oh, I’m a real deep sleeper. Oh no, you know, we had a couple of six packs.”

Or, “You know, I did find this couple of small lesions and I’m really a deep sleeper and wouldn’t have noticed it.” You’d probably go one way, as opposed to after trying to put some of these things context, somebody may elect not to receive prophylaxis and that would not be a bad judgment call in this gray area for No. 4.

In regards to Case Report No. 5, this has to do with what happens when somebody started on something potentially bizarre abroad. Well, unless you know that these people have rabies antibodies on board because you’re at a state that can do a stat serology, often times in a situation like this, where you don’t know what they got started on, it’s best to go ahead and initiate prophylaxis from scratch.

Meaning, if there’s still a wound, [initiate] wound care, infiltration of RIG and vaccines particularly [if the person is coming] from a dog enzootic country.

Case Report No. 6, this always happens. It’s usually a long weekend. Diagnostic turnover should be rapid to support the initiation of prophylaxis or not. One should not be waiting five to seven days for diagnostic results, particularly, in an unprovoked bite from a recognized reservoir.

And so, in a situation like this, where you know there’s going to be more than a 24 to 48 hour period of time, it certainly is sound to initiate prophylaxis whenever you strongly suggest or believe rabies may be the case as in this situation from a skunk bite.

In terms of No. 7, what happens when the person doesn't come back on time. They may have been mixed up in terms of their prescription form, bona fide bite by a rapid animal.

What you should do is initiate vaccination on the day they appear and then continue the series. And so, for example, when they appear on Day 21, you give them the fourth dose and have them appear 14 days later. So keep the interval spacing the way it is by and large.

Case Report No. 8, we are not concerned about rodent bites. Again, I'd be a rich person if I had stock in prophylaxis for everybody bitten by rodents.

Rodents are not reservoirs. We don't really understand why. Tens of thousands of rodents have been examined. Occasionally, some will be found rabid. For example, situations such as groundhog and beaver, relatively large bodied rodents, unprovoked situations.

However, most routine rodent bites such as this, they're not reservoirs, there are no "documented" cases of human rabies acquisition after rodent bites. So prophylaxis is not warranted most often after routine rodent bites.

In terms of No. 9, somebody comes to you with an ELISA titer of one to five, that is less than one to five, two years after primary tree, you go ahead and give them a booster.

Well, number one, an ELISA titer versus we've been talking about rabies virus neutralizing antibody titers of 0.5 IU internationally or a complete neutralization at one to five.

And so one would want to know what is their rabies virus neutralizing antibody titer before you would make a decision. If the VNA titer comes back higher than complete neutralization at one to five, obviously, they wouldn't need a booster as opposed to if it was lower, they would.

In the last case report, No. 10, the person comes in with vaccine A a long time ago and now they've cut themselves during a necropsy on a suspect animal.

Well, if you can get diagnostic results, that will help determine your decision. If the animal comes back positive, you need to go and find RVA vaccine, no.

And so if they know they've gotten Vaccine A and you have access to licensed Vaccine B, you would, if warranted go ahead and administer two booster doses in Case Report No. 10.

I think at this point, in the interest of time, we'll open it up to questions, either from anything from the case reports or the presentations or for any burning questions people may have. Thank you.

Coordinator: Thank you. To ask a question at this time, please press star 1. To withdraw your question, press star 2. Once again, to ask a question, please press star 1.

First question. Your line is open.

Question: Hi Dr. Rupprecht. Thanks for that discussion on bats. That was actually really helpful.

My question is, when you find a bat out in the hallway outside of a sleeping person's open door, do you have the same discussion with them or do you consider it sort of irrelevant because it wasn't found in the same room?

Charles Rupprecht: Thanks very much. That's an excellent gray area question. And, in fact, we actually had that happen with our previous NCID director. They actually found the rabid bat outside [the bedroom in] their hallway.

His wife was not concerned. He was relatively concerned. Upon a great deal of discussion, when one goes through the issues of normal healthy adults, somnolent or not, medications on board, etc., even in situation like that, a majority of people after a consultation, you can put them at ease, [and they say], "No I think I would feel a bite such as that if I was asleep."

Often times, when we're thinking about the bat scenarios, most often we're thinking about same time, same place. And so then it can go from the hallway to the next floor, the floor to the basement, etc.

It really, by and large comes back to the same situation when you have the bat in hand and it's found positive, are you concerned about the ability of that individual to able to detect a bite exposure? If you are, prophylaxis [may] be the case. If not, a lot of these people, you'd be surprised, you can [discuss with them and they calm] down.

Question Cont'd: Great, thank you very much.

Charles Rupprecht: Thank you.

Coordinator: Our next question . . . you may ask your question.

Question: Yeah, I have a question about bat biologists. If the question has come up how often they need a booster every time they're exposed or get bitten, which, of course, isn't the case. But I answered their question by saying they need to get

their titers checked and every two years at least and then act on that basis. Is that correct?

Charles Rupprecht: Thanks. That's an excellent question and this is another huge conundrum. Certainly, this is a population at risk that we certainly would recommend highly that they have routine titer testing and routine boosters when they're titers fall below a minimum.

We realize they're a special population, I am/was one of them - - and that they consider personal protection equipment (PPE) such, at least, as a glove on one hand or a glove as a baffles [on the other] because often during a busy season, they will be sometimes, bitten repeatedly on a single night or in the course of several days.

One would also be surprised often times they're a pretty good judge of behavior of what seems abnormal to them,– and to submit the animal for diagnosis. Often times animals can act completely normal or be in a prodromal stage, and will be excreting virus.

So in situations like that, routine titer testing [can be used to make sure levels are adequate for antibody levels related to occupational exposures , and] boosters when this is out of the ordinary, meaning this is usually a very good person that's handling [but] an animal bites them. Bite to an experienced bat biologist is a concern and [suggests greater] encouragement of PPE.

If this is something that continues to occur, that is, despite advising serological testing, boosters, PPE, etc., some remediation [may be in order], particularly in graduate student situations [or with novice handlers].

Obviously, in democracies and with adults, we realize that there's relatively little that can be done, but in academic settings, and in settings where people are using bats for research, when this happens, particularly in the novitiates, in the people who are being trained, and their supervisor is responsible for safety, then certainly, one may need to take some other administrative action to make sure that we don't wind up with a [recurring] case.

Thank you very much for the question.

Question Cont'd : You bet.

Coordinator: Our next question.

Question: Hi Chuck. Excellent presentation. Have a question regarding infiltration of rabies immune globulin in or around the site of the bite.

Considering the rabies virus moves centripetally about a centimeter a day, does it make sense to infiltrate proximally to the site of the bite or just in the site of the bite?

Charles Rupprecht: Thanks that an excellent question. And certainly, if there were multiple bites, say from a finger to a hand and an arm and on to the deltoid, that's what one would be doing anyway.

Part of the problem, I think, in particularly in children, say with a finger bite by a bat, if one goes ahead and infiltrates locally and then one goes ahead and administers, based on what volume you can into the deltoid, at least you've caught it at it's inception and potentially at a place that it's going to go and move and diffuse anyway.

Part of the problem with going proximal, for example on the lower arm, is having enough muscle mass. So you certainly would if there were lesions there, but aside from that, perhaps most infiltration, and I know we get into active discussions with a lot of our colleagues in developing countries saying they can always infiltrate the maximum amount in a finger.

Well, with a 100-kg person and say a bat bite or a cat scratch on the finger, that becomes relatively difficult, I think, to put multiple ml in and around the finger. [The] deltoid would be a next best site.

And I really haven't heard of anyone, even though it's come up for discussion multiple times, as to whether or not it would be administered appropriately whether the muscle mass in the lower arm would be able to accommodate what you would otherwise administer say up in the deltoid.

Question Cont'd: And should we be now avoiding the gluteous for the remaining RIG that cannot be infiltrated locally?

Charles Rupprecht: Very much so. Whatever one can try to avoid administration, particularly with the obesity epidemic, in those out adipose pockets into the gluteals would certainly be well served.

Question Cont'd: Thank you.

Coordinator: Our next question. Your line is open.

Question: Yes, hi. I have two questions. The first question is if somebody's received all five doses of the post-exposure prophylaxis and they have an exposure say two years later, what kind of follow up is needed for them?

Charles Rupprecht: Two doses, zero and three.

Question Cont'd: So, okay, always zero and three. The other is more of – is an exposure that want an opinion on. It actually happened in my family. We had a bat in the backyard. I have two dogs and a cat. Don't know if any of them were exposed. Brought them in.

And, you know – but it was right up to the house. Bat did test positive for rabies. It was animal control picked it up, tested it. They quarantined my animals for 45 days and no one could give us any specific information as to whether we needed post-exposure, because they didn't take the animals for at least a week until…

Charles Rupprecht: You should have called your state health department or given us a buzz.

Question Cont'd: Oh, we called everybody.

Charles Rupprecht: The animals should have been properly boosted and observed for 45 days if they were previously vaccinated.

As far as you're concerned, unless you guys had direct exposure to the bat, you're not considered exposed and often times a lot of prophylaxis goes on for the person who touched the dog that fought with the bat, that, you know, lived in the house that Jack built.

Certainly, we are concerned about the individual animal exposure, if they developed rabies, [as to] exposures to family members. But there have never been any documented cases of indirect, non-bite exposure that have resulted in cases in humans anywhere in the world.

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Question cont'd: Okay – and so basically, on those kind of situations with a positive bat and an animal that is current on rabies, it's normal for them to go ahead and quarantine those animals?

Charles Rupprecht: Immediate booster vaccinations and 45-day observation period. It varies from state to state, locality to locality as to the seriousness of the confinement.

A lot of my colleagues would just say, just be aware of it and when they're confined that means you're not [under strict confinement]– well, one should never be letting your animal stray, but that should be under [at least] leash confinement. Some people suggest confinement in the home.

Confinement is very liberally interpreted in the 50 states of the U.S.

Question Cont'd: Okay, okay, thank you.

Charles Rupprecht: Thank you.

Coordinator: Our next question, your line is open.

Question: Yes, I recently saw a young lady who rescues bats. She was bitten by a rabid bat. She had a 5.35 ELISA titer, approximately one year before the exposure.

I gave her rabies immunization on day zero and day three and she asked me how long can I go without a booster if I get bitten by a bat over the next two or three months?

Charles Rupprecht: Excellent question and I know most states that allow rehabilitation of suspect reservoir or vector species demand that [if there are] any bites, those animals [should] be summarily euthanized and submitted for testing.

Question Cont'd: The bat was submitted and was rabid.

Charles Rupprecht: And in situation like that, we hope, very similar to the previous question, we hope that these individuals are using appropriate PPE, as well as remedial training if these things continue to occur, one should suggest a change in avocation, in my opinion.

But as far as how long one waits, it obviously strains the credibility if this were to occur say on a daily basis for a week during a busy season, as opposed to every six months or every season or every year, then one would still administer boosters.

But you're not going to be administering boosters every day and so we've got to be able to interpret beyond the recommendations of offering adequate prophylaxis, while understanding immunological terms that we're only going to booster to a particular point and, thereafter, one may not boost.

And, in fact, thereafter, we run the risk of heightened adverse events and potentially sensitization, such as that people who would be at risk and may no longer respond. And we know of documented non-responders because they got boosted too often.

So in a situation like that, it's a real gray area and I think you've got at least a couple of things at your disposal. We have to recognize that although virus neutralizing antibodies can be very, very long lived, we also all have to recognize that there are a whole suite of other immune effectors, such as

cytokines that should be taken into account and, since they're may be more shorter lived, we get an anamnestic response when a booster occurs.

So boosters, when exposures occur, not strive towards the ridiculous.

Question Cont'd: Okay. She does wear gloves. This is a baby bat and it's the first time she's been bitten with years exposure so. Thank you.

Charles Rupprecht: I hope it doesn't occur again.

Question Cont'd: Thank you.

Charles Rupprecht: Thank you.

Coordinator: Our next question. Your line is open.

Question: Hi, thank you. A question about pre-exposure vaccination. I am a pediatrician and run a travel clinic. We have a lot of children visiting friends and relatives in India.

And would you recommend vaccine the pre-exposure vaccine for those children?

Charles Rupprecht: Excellent question., You know, it's a special case for children. Part of it depends. If their relatives are the sort that they know they're only going to be going from the plane to the taxi, the taxi to a condo or a house, that's one thing. If they know, they're going to be true tourist, they're going to be out and about in the streets, then we know what's going to happen.

They're going to be normal kids even though we tell them not to touch, we know what often will happen, they will touch and they may not tell us. So, in situations such as where you know that they are going to be out and about, being tourists in a developing country, with hyperendemic rabies, dog rabies such as in India, it may be warranted to offer pre-exposure, particularly to children.

And, at the same time, have the normal dos, don'ts, since we know an awful lot of our tourists invite prophylaxis themselves.-'Oh let's take a picture with a monkey on our shoulder' situation.

Question Cont'd: Right. And have you encountered in your experience many travelers or kids with rabies returning to the U.S.? Working in travel, I'm aware of some cases around the world, but what's your experience in the U.S.?

Charles Rupprecht: There was one very celebrated case. This was a very well traveled woman who was in Nepal and, of course…

Question Cont'd: Right.

Charles Rupprecht: Woke a sleeping dog, got bitten. Traveled to Thailand, unfortunately, did not receive prophylaxis even though we have the excellent Thai Red Cross there in Bangkok.

Thereafter, traveled to Australia, which did have biologicals, but she didn't wait. Came back to the U.S., and when she described the situation, again, because of some confusion, she understood her physician said it happened X period of time ago, , you should have had rabies by now, and may not need to worry.

And, unfortunately, she did develop rabies.

Question: Yeah, thank you.

Charles Rupprecht: Thank you.

Coordinator: Our next question. Your line is open.

Question: Hi, Dr. Rupprecht. Thanks for having this program.

I wanted to ask you, I know we've actually talked about this before, but just maybe you could clarify again for me and for everyone else. You were talking about misadministration of RIG in particular, not wanting to put it in hand wounds and so on, when we find out – and, unfortunately, this is too common here - - that a physician did not infiltrate for any of those reasons, gave the vaccine.

It's now one, two days later and we find this out. What do you recommend? Is it worth going back and infiltrating that wound? Where is the balance there? And, actually, on the heels of a previous question from a caller about RIG in the gluteal, if we find out that they actually did that, would you ever recommend re-administering the RIG?

Charles Rupprecht: Sure, thanks very much, excellent question. Depending of the severity of exposure, if we know we've got a bona fide rabid animal, we've got multiple severe lesions and particularly when we have them about the face and head or highly innervated areas, such as a hand, and it's early on, i.e. you caught it within a few days, certainly, within those first few days, it would be customary perhaps to consider reinfiltration of the wounds, if they weren't

properly infiltrated and certainly if the RIG went into a potential depot such as in the gluteals.

If it occurs, you know, after seven days, we've already got virus neutralizing antibodies starting on board from your immunizations from [days] zero, three and seven, so it probably would be less warranted.

So, really, depending on severity and location and timing when one discovers it, there are relatively few times when you would consider restarting in a situation such as you suggest, but particularly severe wounds in some locations such as those, one may be warranted to re-infiltrate in those first few days with bona fide bite exposures.

Coordinator: Our next question.

Question: Yes, hello. Thank you very much for your presentation. I have a question.

If someone had a pre-exposure series in the past, is it true that no matter how much time has past, they're re-exposed, they only – still need only two doses of the vaccines on days zero and three?

Charles Rupprecht: That's correct by current ACIP and even WHO standards, if it is with the current types of cell culture vaccines. And so, if one were to tell you 'oh I was vaccinated back in the military in 1945…'. Well, you know, all bets are off in a situation like that.

As opposed to if you know what country they're and they're from a developed country and it's post 1980 in particular, we know in the clear majority of cases in developed countries that only cell culture vaccines were licensed. In

situations like that, it's certainly true as long as you know you have a normal healthy adult.

Now if there are situations where you're not sure, it's always better to err on the side of caution unless you can have a titer taken. So either with the knowledge of a previous rabies virus neutralizing antibody titer that can be documented at anytime, documentation of what type modern cell biological they received and as long as that person appears for all intents and purposes to be a normal, healthy immunocompetent adult, if that is true, the individuals would receive 2 boosters after exposure….

Coordinator: Thank you. A coordinator will assist you momentarily.

Charles Rupprecht: Pre-exposure prophylaxis back in the 80s, you would still only administer two doses, zero and three.

Question Cont'd: Okay, thanks very much. I do – a quick follow-up question. Let's say in that case you weren't too sure and you want to take a blood titer, is it also true that no matter how long it's been since they got the pre-series that or a post-series, a post-exposure series, that you can trust the blood titer results?

Charles Rupprecht: Again, if you're going to a CLIA-certified laboratory, you should be able to appreciate those results. And, in fact, often times they'll be sky high.

Now, if it's an issue of health, if it's a question, for example, they were Peace Corps volunteers and received intradermal vaccinations, cell culture vaccinations, if they had a variety of other immunizations, anti-malarials on board at the same time, that certainly may be taken into question.

But, at least in our experience, the vast majority of times, cell culture biologicals in normal healthy adults, with intramuscular administration, rarely have we found people to fall to an inadequate level.

And, certainly, if we look at people such as our staff here, we have never had anybody in our rabies groups since I've been here fall below an adequate titer.

Question Cont'd: Okay, thanks very much.

Charles Rupprecht: Thank you.

Coordinator: Our next question. Your line is open.

Question: Is there any information about the risk from a possum bite as a marsupial?

Charles Rupprecht: Yes, a very good question. While possums, even though they are quite widely distributed up from south and Central America into the U.S. and now into parts of southern Canada, possums are very peculiar. They're relatively resistant to rabies.

In fact, in a comparative – one comparative study, you can put in 50,000 times the amount of rabies it took to kill a fox and possums are still laughing at you. We only have relatively few opossum cases that are found positive every year.

And so given the relative distribution and abundance and how relatively few possums that we find positive and they relatively resistance even to experimental challenge, it wouldn't be common for one to recommend prophylaxis in situations with a possum bite.

Obviously, it's always best if one can to submit [for diagnostic] tests, but when that animal's not available, I don't believe the majority of people are recommending prophylaxis as a routine possum bite, particularly, when the animal bite was provoked seemingly or they appeared otherwise, "normal", although that obviously strains the imagination in a possum.

Coordinator: Our next question is. Your line is open. You may ask your question.

Question: I apologize for revisiting this, but this question of re-exposure actually comes up all the time and I feel like maybe I could use a little bit more clarification.

So we have someone who's just finished their post-exposure series and they are then bitten again by let's say a confirmed rabid animal. Now, you know, six months later, I would say, okay, certainly they need to get another – they need to get boostered.

But what if it's a month after they just finished their original series. You know, they are an immunologically normal adult. How long a time would you say that that first series is probably good for?

Charles Rupprecht: Excellent question and there's a couple of different ways to approach this. From a medical-legal standpoint, in a situation such as you described, previously vaccinated, one month later, one should follow the letter of the ACIP and booster.

From an immunological perspective, if this was an otherwise normal, healthy adult, there's relatively little good that boosting does within a month period of time when we know they either just got the full post-exposure prophylaxis series or the complete boosters after a prior full series or a pre-exposure on board.

So one is caught between the situation of the medical-legal versus the immunological. If one would hope that this is a rare event in that individual, meaning we're not talking about the animal rehabilitator, this is an individual that, for whatever reason, just recently got exposed, I think one should probably err on the side of caution form a medical-legal standpoint alone, because we can't control sometimes for the severity of the exposure whether or not in fact frank virus could be introduced at or directly or near nervous tissue.

We can't control for the variant and we certainly know that for example let's suppose this was abroad, as opposed to the United States, there are variants throughout the word that relative cross reactivity with traditional biologicals is less than ideal.

So, you know, I hate to say it but it depends, but I think when pressed and this is a unique situation for that individual, it may be best to err on the side of caution.

Question Cont'd: Thanks that actually helps a lot.

Charles Rupprecht: Thank you.

Coordinator: Our next question. Your line is open.

Question: Thank you. Doctor. My question comes to you and I believe it was briefly touched on earlier about concomitant administration of the vaccine with anti-malarials, as you can imagine, we have going on down in this area.

So our question – my question to you is do you need to wait a certain period of time before you give the anti-malarials after the pre-exposure or can you give them concomitantly?

Charles Rupprecht: Thank you, good question. And this came up earlier historically when lower relative amounts of antigen were being administered intradermally and it certainly is still relevant in many parts of the world where intradermal vaccination with rabies is still practiced.

However, since we no longer have licensed products for ID [in the USA], we have not had documented interference with intramuscular doses of vaccine. They're the only ones that are currently licensed in the U.S. and so there should not be a cause for concern with concomitant use of anti-malarials and intramuscular doses of currently licensed human rabies vaccines.

Alycia Downs: Hi, I want to apologize to anyone who is not able to ask a question. For those of you who still have questions or if you want a clarification, please email us at coca@cdc.gov and we will try to connect with Dr. Rupprecht, get those questions answered for you.

And I just really want to thank Dr. Rupprecht for providing our listeners with this information. I think this was a wonderful talk and I know that everyone gained a lot of valuable information. So thanks again and remember that's coca@cdc.gov.

Charles Rupprecht: Thank you.

Coordinator: Today's call has concluded. All parties may disconnect.

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