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OPTIMIZING POST-EXPOSURE PREVENTION OF INHALATIONAL ANTHRAX: ISSUES AND OPTIONS

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C O N T E N T S

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P R O C E E D I N G S

DR. HENDERSON: It is a pleasure to welcome you all here. We're very grateful to the National Academy of Sciences for making this marvelous room available. We do have, I think, a very interesting program, a very complex subject, and I think we've managed to assemble those who know this subject best to examine it with you today, and to look at what our options are at this particular time.

We're most concerned at this time about those who have had an unusually heavy exposure to anthrax spores. Most of these people are now approaching the conclusion of their 60-day course of antibiotics, and the question we ask: Is there anything more that they might do to avoid the development of inhalation anthrax?

It has been recommended, as you know, that those who have been exposed should take antibiotics for 60 days. None who have followed that recommendation have developed disease. Thus, we continue to feel confident that that recommendation

is pertinent for most who are exposed, but our principal question today is the question of whether some few who we now believe might have inhaled a large dose of spores, whether they might continue to be at risk for a longer period than 60 days.

I know that you as well as we would like to have definite knowledge as to what we could expect to happen to those who have been exposed to anthrax spores and what different types of treatment might achieve.

Unfortunately, but in more ways fortunately, there have been so few cases of inhalation anthrax that much of the information we would wish to have is not available. I will remind you that there are only 18 cases of inhalation anthrax in the United States during the whole of the 20th century. Most of those cases occurred before antibiotics even became available.

There was one outbreak that occurred in central Russia in 1979 as the result of organisms escaping from a biological weapons factory. All that we know about those cases was provided more

than ten years later by relatives of those who died and by physicians who tried to remember the cases and their treatment.

The KGB confiscated all clinical records, and even today, those records have not been made available. There are a few studies in monkeys, but it is difficult to know how applicable these are in man. Because of these factors, it has been difficult to provide definitive recommendations that are backed by real experience. That we don't have all the definitive answers is frustrating for all of us.

The reason for our meeting today reflects that uncertainty. We are concerned that the risk of infection for those who may have been heavily exposed might extend beyond 60 days, perhaps to as much as 90 days. Studies done this year in Canada indicate that far larger than expected quantities of anthrax spores than we had ever imagined could be expelled from an envelope and inhaled by those in the immediate area.

Certain other observations have caused us

to wonder whether those who inhaled a great many spores might be at risk for a longer period of time. Possibly they might, although it is hard for us to know that.

Rather than asking some designated group of experts to decide this question on their own and without participation of others, we decided to share publicly the information that we have so that the problem and the options could be better understood.

If the risk were to be not 60 but perhaps 90 days for those who have experienced a heavy exposure, what might be done about it? And there are three possible options.

The first would be for those at risk to be aware of the risk and to simply keep in close touch with their physician and at the first sign of illness to see them right away.

The second would be for those at risk to continue to take antibiotics for an additional 30 days or more.

And the third might be for them to receive

three vaccine injections at two-week intervals during which time they would be covered with antibiotics.

Protection based on monkey studies would develop four weeks after taking the first injection, and antibiotic treatment might then be stopped. This possible third option of making anthrax vaccine available is now under consideration. Vaccine has recently become available, but that available supply is very limited.

To date, the vaccine has been used only for prevention of anthrax infection, that is given before the people were exposed to the challenge of the spores. It has never been used in this manner. That is a treatment or prophylaxis after the time later on after the individual has been exposed. Thus, its use in this way would necessarily be experimental and would be under an investigational new drug use.

Today, you will be hearing reports of what we know and what we don't know about the risks to

those who may have inhaled unusually large quantities of spores and what we know and don't know about possible mechanisms for further protection of those involved.

As I note, we cannot provide clear-cut, neat, definitive answers to many of the questions. However, we believed it was best to share these with you. We do not have expectations today of achieving any sort of consensus as to what might be the best alternative. As you will hear, there are risks and benefits in each of the alternatives and what might be perceived to be best for some may not be best for others.

For example, someone who has had severe side reactions to the antibiotic may simply opt to keep in close touch with his or her physician should symptoms appear.

Recommendations regarding possible experimental use of the vaccine will be provided to the Secretary early next week and a decision then reached as to its possible release.

At this time, I should like to introduce

Dr. Jeff Koplan, who you all know is Director of the Centers for Disease Control, who indeed will be introducing the next session, and providing opening remarks. Jeff.

DR. KOPLAN: Thanks, D.A., and good morning to you all. Just to add a little bit to D.A.'s comment and to summarize, we're focusing today on looking at what we know and what we need to do about post-exposure prevention of inhalational anthrax.

For those of us interested in public health decision-making, you realize that many decisions are made over the years with inadequate data, where all the facts aren't known and you attempt to plug them in over subsequent years, but rarely do we have all the information we need when we have to make public health decisions.

In this particular case, we clearly do not have adequate scientific information to drive us towards any one of a number of options towards the best course of post-exposure prophylaxis, and what we're trying to do here is assemble our combined

knowledge of many folks present with different areas of expertise, experiences, potentially viewpoints, and try to incorporate those in the best course of action for post-exposure prophylaxis and that best course may be different for different subpopulations, as D.A. just indicated.

In considering the risks and benefits and balancing them all, what we need to take into account is clearly, one, the extent of disease risk given assumed routes and degrees of exposure, the likelihood of preventing disease by various options for intervention, the side effects patients will face, the patient's and public's perceptions of these risks and benefits, the limited supply of vaccine available, and other considerations that are going to be raised in the course of discussion today.

And to summarize at least three options that we might look at today and consider and keep these in mind as these discussions are unfolding and as pieces of information are added to this is, one, basically holding the current course, which is

60 days of antibiotics, with close medical monitoring thereafter, option one.

Option two, and, of course, these are somewhat arbitrary, or quite arbitrary, including the initial one that we're following now, again, based on rather limited animal and observational data. But option number two is 30 additional days of antibiotic treatment without vaccination.

Option three is 30 additional days of antibiotic treatment coupled with vaccination. So that's what we're focusing on. There may be variations of even those options discussed as we go through the day, and certainly all of us are open to any suggestions and ideas that are brought forth in today's meeting.

Without taking further time, let me introduce co-moderator for the first session, Dr. Ivan Walks, who is the Commissioner of Health of the District of Columbia, and has played an important effective leadership role in the bioterrorist event here in the D.C. metropolitan area. Ivan.

DR. WALKS: Good morning, everyone. I think that the work that we have to do today is critically important work in at least two areas. The one that has been mentioned so far is the work with respect to keeping people from getting ill. The other one is building a relationship with the public that will allow us to work closely with them, not only with respect to this particular anthrax concern, but as we go forward.

We've had some very interesting occurrences here in D.C. with respect to how people respond to the advice we give them. We know that people take medication with varying levels of compliance. We've seen some significant schisms, I think is probably the best word to say it, in our population that we are trying to treat.

So any decisions that we make today about how we will address these safety issues need to be made in the context of a very diverse population and a population that responds with great diversity to the advice we give them.

We've had compliance issues that have been

profound in certain parts of our treatment population. We've also had some very diverse responses to our advice from the practicing health care community. We've had doctors who refuse to stop swabbing. We've had hospitals that refuse to send people back to where the lines from Dr. Eisold and Dr. Walks were forming to get medication, and I think those challenges need to be addressed.

So as we hear the science that's put forth today, we also need to think about that with respect to the diverse cultures that are going to be affected and how we're going to get them to comply. The thing that's particularly concerning to me about this--we're talking about anthrax, and so with anthrax, it may be just the individual who is noncompliant who is at risk.

If we're talking about more infectious agents down the road, it may be all of us that are put at risk if we don't learn how to communicate one concise message across a diverse population with consistent results. Thank you.

Oh, we have a panel to introduce.

DR. KOPLAN: We do.

DR. WALKS: Okay. Go right ahead.

DR. KOPLAN: I'll give the warning and you do the panel. We're going to try to really keep to schedule so we're going to be obnoxious and difficult, but please all the speakers keep to your allotted time because we've got a lot of presentations to make. We want to move through it, and we want to let you enjoy some your weekend afternoon.

DR. WALKS: Now what's terrific about these scientific meetings where everyone is very important is that we don't worry about CVs and bios because we know that all of them are tremendous. So let's just have the first panel. Are they sitting up here or--

DR. KOPLAN: They'll come up one at a time and present.

DR. WALKS: Okay. So, L. Pitt. See I know John Eisold. I don't know L. Pitt. Who is L. Pitt? Would you please come up and what we're going to hear about is the infectious dose. And I

think that's one of the things that I'd like to learn about. Is it 8,000 or 10? Come on up and tell us.

DR. KOPLAN: Our genetic introduction is everybody is very intelligent who is presenting and has lots of degrees.

[Laughter.]

DR. KOPLAN: Except I'm about to fail the intelligence test with this box here.

[Laughter.]

DR. WALKS: I have a watch.

DR. PITT: I promise not to speak over time.

DR. KOPLAN: Take it away.

DR. PITT: Well, good morning, everybody. This morning I'm going to present some data that's been generated at USAMRIID in the last ten years. This infectivity data was generated to support our research program which, of course, is to develop vaccines and therapies to protect the warfighter against an aerosol, biological aerosol threat.

The data, the medium lethal data and

infectivity data, is generated during the animal model development phase. Once the animal models are developed and we then go into the stage of doing efficacy testing on candidate vaccines and therapies, these animals are challenged with multiple lethal doses.

So to give you the overview of how the data is generated at USAMRIID, we have very specific aerosol conditions under which this data is generated. We use dynamic aerosol systems. The aerosols are generated from wet preparations of the biological agents, using a nebulizer, usually a Collison nebulizer. In the case of Bacillus anthraces spores, these spores are diluted to the desired concentration in sterile distilled water, water for injection.

Our aerosols are extremely well characterized and defined. The particle size of the aerosol has a mass meeting aerosol diameter between .8 and 1.4 microns. That means that the aerosols that we are generating are basically single spore aerosols. There's very, very little

clumping of two spores. They are single spore aerosols.

In terms of the aerosol parameters, it is also extremely standardized. All our exposures are of a ten minute duration. When we work with non-human primates, they are anesthetized so they are exposed in an anesthetized state. We do measure respiratory parameters of each individual animal using whole body plethysmograph so there is no use of published data or estimations. We actually measure the minute volume of that animal in the anesthetized state at the time of exposure.

That is also true for rabbits. We measure the minute volume; however rabbits are not anesthetized.

Rodents are awake as well. They are not anesthetized. However, we usually use public formulas to calculate respiratory parameters for rodents.

It is important to remember that when we calculate inhaled doses, we make no assumptions about retention in the lung. We just calculate

from the concentration of the aerosol and the known respiratory parameters and the time the animal is exposed. So the inhaled doses do not reflect retention of the spore.

In calculating medium lethal doses and lethality and infectivity of agents, we have a fairly generic study design. Groups of animals are exposed to five to seven varying doses of the agent. In this case, the Bacillus anthraces spores. Going from the lower dose to the higher dose. Again, these are well-defined animal studies so they're relatively small numbers of animals.

In guinea pigs and rabbits, we usually have about ten in a group. Rhesus macaques, five per group. We always mix males and females as close as possible to 50 percent males, 50 percent females, and we use healthy mature animals. Our vaccine program is focused towards the adult population and our animal models reflect that as well.

We calculate the delivered dose for each of the group of animals. In the case of rabbits

and macaques, each individual dose is calculated and then the group dose is an average for that group.

We, of course, record the survival data, and then the data is analyzed using probit procedure in SAS, and at that point, the LD50 and the dose response curve is estimated.

So this is the data from Bacillus anthraces. All this data is Ames strain. The three animal models, the guinea pig, the Hartley guinea pig; the New Zealand rabbit, and the Rhesus macaque.

As you can see, the LD50 for the guinea pig is about 79,000 spores. For the rabbit, 110,000, and for the monkey, 55,000. These LD50s are very, very similar. There is no difference between that between species.

What is of interest is that the probit slope is different: 2.4 for the guinea pig; 8.5 for the rabbit; and 6.3 for the Rhesus macaque. We have in recent months looked at the mouse model. We have to date done preliminary studies on four

different mouse strains. The LD50 is within the range of these other three species. However, our data is variable at this point, and not ready to be put on the table, but we hope shortly to have solid data.

The Rhesus macaque LD50 that we have calculated here for Ames is very similar to the Durit, et al. published data, and that is the infectivity to day. Can I answer any questions?

DR. KOPLAN: Could you possibly describe the significance of the probit slops for those of us who aren't as familiar with how you interpret what the meaning is of 2.4 versus 8.5 versus 6.3?

DR. PITT: The 2.4 means that the slope is much shallower. And 6.3 means it's a very steep slope. So you go from zero to 100 much more rapidly in terms of LD1 to LD99, whereas in the guinea pig it's a much longer slope over.

DR. KOPLAN: And the significance of that?

DR. PITT: It's species variability to the infection. In the guinea pigs, it means that you may be sick at a lower dose but you won't die,

whereas in the Rhesus, there's a much sharper curve between infectivity and lethality.

DR. KOPLAN: Thank you. We're going to do a clump of questions at the end. So we can clarify that.

Our next speaker is Dr. John Eisold, Capitol Hill physician.

DR. EISOLD: Good morning. As you can imagine, I'm very thankful for the people who have decided to put this conference on. It will be of great interest to me as well as Ivan Walks and other people around the country to make some clinical decisions about people.

On the 15th of October when the letter was opened in the Daschle suite, I had a very developed response plan in place, ready to go, that included post-exposure immunization. This actually had been a plan for a long time, but specifically about two weeks beforehand, there was an interagency brief at the CIA with medical personnel from the FBI, CIA, Department of Justice and several other agencies, where we validated our own response plans and

cross-referenced what we would do, and out of that conference, we all agreed that post-exposure immunization with 60 days of antibiotics would be our collective approach.

Shortly after the incident on Capitol Hill, I made preparations to request the vaccine from DoD, and was asked at that time to perhaps review my approach. And I did. And in retrospect, I'm glad I did for four reasons:

First, as things evolved throughout the country and continue to evolve, it is clear that the event I had on Capitol Hill was not in isolation, that I would be tied at the hip with the civilian health care system, and become close to people like Ivan Walks and Georges Benjamin, et cetera, I couldn't predict. But the ramifications of the actions that I would take on the Hill were far broader than I had originally anticipated. So deliberation was important.

Number two, as we looked at our exposed population further, and did more analysis, actually it did strengthen my resolve that I was concerned

about certain people under my care, and that immunization needed to be seriously considered.

Having said that, the deliberation in time also made me more reflective about who the immunization might be recommended, and this conference will help to hone that even further.

And the fourth reason is that if the vaccine is to be given, it really needs to be given under a process that's evaluative and not reactive, and so that out of a situation that we have here, if we do decide to vaccinate some people, it will be done in a process where we can learn from it.

So I think from my perspective, once again in life, it's if you listen, you can learn. And that's what we're about today, and as I said, I listened to people early on, and I'm glad I did. And I'm going to let Greg Martin, who is the Chief of ID at the combined program of Walter Reed and Bethesda talk to you about our perception of what our exposed population has at risk.

DR. MARTIN: Thanks, Admiral Eisold, and I have a few slides here just to kind to go over what

brought about our thinking on this thing, if I can get this thing to work.

This will not move at all. Isn't this always fun? I thought there might be a computer person here. This worked when we opened it up a little bit. I can't even move the cursor on this thing. Well, there is nobody here.

DR. KOPLAN: If you need to erase anything inadvertently, I can help you.

[Laughter.]

DR. MARTIN: Oh, thank you. Since everyone's presentations are on this computer, I think you'll be a popular man if you come up here and do that. Everyone will get some Christmas shopping done. There are none of the computer people here who set this up.

Okay. Okay. Well, thank you all for the assistance that many of you--ah, it did just move. It must be on this other computer. That's why. It's this one.

[Laughter.]

DR. MARTIN: Okay. What a great way to

start off. Okay. Thank you to all of the people here who helped us from the CDC, the NIH, the local community on this, but I wanted to give you a brief idea of why we came up with some of the recommendations we did.

This is actually what we are dealing with, and I think we have a somewhat different situation at the Capitol than some of the other areas. 13 of 13 people in Senator Daschle's office where the letter was actually opened tested positive at 14 hours afterwards with plates that looked similar to this.

This is a plate from our lab at Bethesda Naval Hospital. This was actually taken from someone who was down on the fifth floor office because almost all the 13 individuals up here, their plates were so covered with anthrax at 14 hours that we weren't able to tell any colony morphology at all.

So there some patients or individuals in this office who had more spores in their nose that environmental swabs were positive that closed whole

buildings. So if you consider some of these noses as environmental swabs, there were a lot of spores there.

If you then went down and looked at some of the other people in the immediate Feingold and Daschle offices, seven of 23 people in Senator Daschle's adjoining fifth floor office, and that's adjoining by a stairwell down to it, were positive.

Two of 18 people in Senator Feingold's office, which is next door to but does not have a direct connection to Senator Daschle's office. here were positive. Five of nine first responders, and I mean the Capitol police, some of Dr. Eisold's team that came in, were also positive, and one Capitol policeman who was in the hallway outside in the fifth floor was also positive, but he had one colony at 42 hours.

So you can't make a lot of distinctions between levels of exposure based on just culture plates because the technique varies so much from person to person, but we certainly can draw a nice curve out to show that if you were in the office

with the people who opened the envelope, you were much more likely to have had lots of anthrax in your nostrils.

So the CDC guidelines as we all know were for 60 days of antibiotics. Anthrax immunization was not recommended, and Dr. Eisold and I were considering our 60 days sufficient and should we immunize? We have come up with some, since 13 December was 60 days for the Daschle group, we had to make some decisions already, and we'll be looking for some other guidelines based on this.

So very briefly, Dr. Friedlander is here. Most of these studies were all done at USAMRIID. I did all of my bio-warfare there at USAMRIID so I kind of speak from many of the colleagues we have here in the audience.

Antibiotics 24 hours post-exposure prevented development of disease in monkeys for 30 days. Everyone is familiar with this data, but five of 29 animals developed fatal inhalation anthrax six to 28 days after stopping antibiotics, and none of these animals who were on antibiotics

developed antibody.

So in one sense we can be reassured that 60 days certainly covered all of these animals. 60 days, you know, the last animal died after 58 days after exposure. That probably makes us feel somewhat more comfortable.

Of course, the Sverdlovsk experience, which you're also familiar with, where about two grams were estimated to be released over a city, 96 human cases, the last case 43 days after the spore release, also makes us feel comfortable that this isn't just animal data, this is the real deal, people exposed, nobody, at least that we know of, developed inhalation anthrax after this period of time.

What concerned me more is when we looked further into this were some of the older animal data which I know we'll be going over a little more later on, and this persistence of viable spores was most concerning to us. And again, you'll notice one thing about this, that there's Henderson's all over the place. I mean they must select out for

going into bio-warfare in some sense.

But 42 days after, in these animals, 15 to 20 percent of the initial retained spores were still there. 75 days later, you had one percent of the spores there, and then 100 days later, trace, which is not really defined, were there.

Well, is this really important? I think obviously it depends on what your inoculum size was. A very small inoculum probably wouldn't make a difference if you had only one percent of those spores retained. A very large inoculum, you may be much more concerned.

Another study showed death of one animal from anthrax 98 days after spore inhalation. This is a little concerning also. And that viable spores in the lungs of all apparently healthy monkeys were found, you know, clearly in the two month period after exposure. So all these things were somewhat disconcerting to us, that possibly some of our highly exposed people may develop inhalation anthrax down the line.

Subsequently received a copy of this

Canadian study that was done last summer, strangely enough, and in many of the people are also familiar with this study. It has not actually been released out of draft form that I know of, but they looked at a related spore forming, non-pathogenic species, Bacillus globigii, that they put into a room that was ten by ten by 18, surrounded a person with monitors. He opened up an envelope in a very controlled situation with a letter opener, pulled it out, put the envelope down on the table, and these sensors were all taking levels of how many spores were coming down.

And they found that there was significant number of spores aerosolized within seconds. Most of these were fairly small so we're talking about ones that would get down into, potentially down into the alveoli and cause real disease. And there was an estimate of somewhere between 480 and 3,000 LD50s depending on what size dose, number of spores were in that envelope.

Now, remember, we're talking about .1 or one gram of spores. It was estimated that in

Senator Daschle's letter that there was about two grams of spores potentially in there.

And part of their conclusion was that the aerosol would spread quickly through the room to other workers and would likely they would inhale some lethal doses. So this had us very highly concerned that should we immunize?

The inocula in Daschle/Feingold suites were potentially quite high. The duration and clinical significance of these viable spores in human lungs after 60 days of antibiotic prophylaxis is really unknown. Those studies have never been done, and although never tested for post-exposure prophylaxis in humans, we do know that we have a safe FDA approved human vaccine that is available, albeit in not great supplies and not readily available, but it is out there.

So the last slide is our conclusions, and we recommended immunization to the 70 individuals who were in the Hart suites with positive nasal swabs, whether they were swabbed positive or negative. We've had to move on on this already.

We have not had immunization available, so we recommended that an additional 30 days be given to those individuals, and that's where we are at this point.

People who were outside of those offices, we are only recommending the 60 days and stopping it. So we are looking at 70 individuals or so that we have extended therapy out to 90 days. And that's all I have. Thank you.

DR. KOPLAN: Thank you very much. Brad Perkins.

DR. PERKINS: Is the control for the timer sitting next to you?

DR. HENDERSON: You've already started and you're already finished, Brad.

[Laughter.]

DR. PERKINS: Oh, good. Can I sit down now because this is actually a hard talk to give? I've been asked to talk about exposure risk across the other affected populations outside of the Capitol Hill population, following the recognition of the first case of anthrax in Palm Beach County,

Florida, over the next seven weeks, as all of you know, we initiated a series of five intensive linked investigations, the most recent one in Oxford, Connecticut starting around the time of Thanksgiving.

All of you are familiar with this data, a total of 22 confirmed and suspected cutaneous and inhalational cases across those five states or sites, and of the 11 confirmed inhalational cases, there have been five deaths.

That's a set-up to take a look at the epidemic curve which is very important in understanding what we think has happened. This slide shows cases by color for four of the five sites with inhalation cases represented as an arrow in a box. With each of the yellow arrows here, we've got a pulse of letters and we know of at least two letters in each of the circumstances that entered the mail system and have been confirmed to be contaminated with Bacillus anthraces.

One letter to NBC and one letter to the New York Post that we know of postmarked on 9/18

entered through the New Jersey Hamilton facility, was associated with a subsequent pulse of cases, not all of them directly connected to the known letters, but very clearly seen on the epidemic curve.

A second pulse of letters entered the mail system through the same New Jersey postal facility postmarked on 10/9. This pulse of letters associated with the larger number of cases and a higher proportion of inhalational disease that probably represents a different quality of material and a different aerosol risk.

The most recent case occurred with onset on the 14th of November and the complete explanation for this case is still unresolved. In total, there have been approximately 10,000 people we've asked to be committed to taking 60 days of antibiotics. Those courses were started between October 8 and November 25. So we've already entered the period where people are coming off those 60 days of therapy.

What I've tried to do is develop a

framework for a qualitative assessment of risk across these sites. And I identified some criteria that are not equally applicable to all affected groups or populations, but I think can frame an argument for a qualitative assessment of risk.

Higher risk for inhalational anthrax I would argue is associated with the high dose of known exposure to Bacillus anthraces containing power or contaminated envelopes.

Another important characteristic is whether the cohort of exposed persons includes inhalational anthrax, therefore defining a potential risk of disease. And I think, and this may be the most difficult to interpret, but certainly diffuse environmental contamination is concerning for disease risk.

Characteristics of lower risk for inhalational anthrax, again, not equally applicable in every situation, but I think each of these is important to consider in some situations.

That the cohort doesn't have any evidence of inhalational disease cases. Obviously, we'd

like to prevent disease before any cases occur, but when a case occurs, it does give us important information.

No known direct contact to Bacillus anthraces in an envelope or a powder.

A delayed initiation of post-exposure prophylaxis without additional cases. I think this is critical, and it speaks to the need for better understanding of the relationship between dose and possible length of incubation period, and as we move through, and I give you sort of summaries of each of the situations, I think you'll see how this plays out.

Focal rather than diffuse environmental contamination may be associated with lower risk.

A limited duration of potential. You'll see that visitors to buildings that have been contaminated, they may be at lower risk than people that were full-time occupants of those places.

And another piece of information that we need to try to use, I think, is the fact that we have relatively low adherence in some sites with no

evidence of disease, and try to fold that into our summaries of each of the situations.

I'm going to go very rapidly through these things, but I think it's necessary to understand each of the situations. In Florida, there were two inhalational cases with the dates of onset of disease listed there. We don't have an envelope. All the trash from this period of time was incinerated. There was no ability to go back and get actual envelopes, but we have at least two very suspicious letter stories that occurred in the 19th, the second day of Rosh Hashanah, and the 25th.

The AMI building was closed on the 7th and post-exposure of chemoprophylaxis was recommended for about 1,209 persons, and environmental testing showed rather a diffuse contamination throughout the building, reconstructing the track of the mail through the building.

This is important and I want you to recognize here the time between potential exposure and the time when antibiotics was started. If you

believe that all of the cases would occur within two weeks, then you might suggest that there is little need for the intervention.

However, I don't think we're in a position to say that, and we responded accordingly, and you'll see this theme run through each of the areas. This is just a map or an illustration actually courtesy of the New York Times that shows the three floors of the AMI building.

The patients' work area is up here on the third floor. The mail room is actually down here, and you can see that there is contamination. This is EPA data. It doesn't include all the testing data, but there is contamination in all three floors.

I've mentioned these two letters, and I think they're well known to all of you. And their story started in New Jersey where they entered the mail system. There were two cases of inhalational disease and a total of four cutaneous cases, five in mailhandlers and one in a bookkeeper.

I think the most interesting epidemiologic

period to look at is the night shift on the ninth when the sort of the Senator Daschle and Leahy bound envelopes occurred. There were 122 persons on that shift, three of them developed disease, giving a very intense attack rate in the area of sort of two and a half percent.

Post-exposure prophylaxis was initiated on the 20th through the 24th to employees and business visitors totaling about 1,529. Again, look at the period of exposure and the period when chemo-prophylaxis was begun because I think that's critical in trying to interpret the ongoing risk of disease.

This is an illustration of the Hamilton Center. These are the three cases that I mentioned. These are sorting machines. You can see them very tightly clustered in this remarkably large facility of over 200,000 square feet. However, the disease risk was limited here. You see that there is positive cultures from a wide spectrum in the building.

This just summarizes environmental testing

about a 43 percent positivity rate among samples obtained for various causes or for various reasons.

In D.C., in addition to the Capitol Hill, there are two scenarios I want to describe to you.

In the Brentwood Processing and Distribution Center, there were four inhalational anthrax cases resulting in two deaths, all of them with disease onset on the 16th.

In the State Department, there was an additional inhalational case with disease onset on the 22nd.

The Senator Daschle envelope passed through the Brentwood facility on 10/12, and was processed on a very precisely known sort and precise time. The Senator Leahy envelope, there is still some uncertainty about. It actually was sorted at the same time, but it may have remained at the Brentwood facility for another several days and actually may have gone to State Annex 32.

We're still trying to sort that out.

The facility was closed on the 21st and chemo-prophylaxis was initiated on the 21st. There

again a spread of I think that's 11, nine or 11 days between the intense exposure and the start of post-exposure chemoprophylaxis.

Looking at denominators in the Brentwood facility, one thing that we tried to use, we've tried to use, is looking at the different shifts that people worked on, but you see that even among the four inhalational cases, three different shifts were represented, and I've indicated the denominator of folks working on that shift, and you see that the attack rate actually by shift is fairly consistent in the area of a half or so percent, a little bit lower than what we saw in the night shift in Hamilton.

This is the Brentwood Postal Facility, again, a huge building, 300,000 square feet, and it's hard to see, but the cases, their primary working areas are distributed throughout the building. There were two cases, a case here, a case here, a case here, and one case here, as their primary working positions, and you see the intensity of red represents in each of those areas

positive environmental samples.

This just summarizes those data. In State Annex 32, there was one inhalational case. Again, look at the timing here. We don't know when the exposure occurred, but it was closed on the 25th. Actually a post-exposure prophylaxis was offered to these folks as a result of the observation in Brentwood and was being offered to these employees as the one case that occurred there was becoming ill.

So a fairly tight juxtaposition to the period of risk and when chemoprophylaxis was offered.

In New York City, seven cutaneous and one inhalational anthrax case. And this is the most dramatic example of late post-exposure antibiotic intervention. This case although her date of onset was much earlier wasn't confirmed or recognized until the 12th of October, although we think the exposures were associated with the 9/18 postmarks.

And chemoprophylaxis didn't start until after this point, so here we have almost a month go

by when USPS employees and employees of media outlets may have been exposed to anthrax. We don't know how persistent that risk was, but 3,700 people were recommended for 60 days of antibiotics

including 1,200 that were working in the area of sorters in the Morgan Processing and Distribution Center.

This is a summary of extensive environmental testing data in the New York City

area with ten of the 148 samples positive in the Morgan Postal Facility, all concentrated around the sorters on the second and third floor.

The Connecticut investigation is perhaps one of the most complicated investigations that is

being undertaken. And still has not revealed the source for exposure in this elderly lady. What is known is that an envelope processed at the Hamilton facility one minute after the first one of two of the senator bound envelopes was delivered four

miles from the case household. That envelope was recovered and was positive for Bacillus anthraces.

Post-exposure prophylaxis has been given

to 1,200 postal employees at the Wallingford Processing and Delivery Distribution Center where environmental sampling has identified about a ten percent positivity rate.

In conclusion, I would argue that criteria can be applied to qualitatively stratify risk across affected populations, and if I were asked to try to do that, applying all the criteria where appropriate across sites, I would probably rank the level of risk something like this in terms of potential risk for inhalation disease, where Brentwood and the State Annex Center I think because of the very narrow window between defined exposure risk for inhalation disease and the initiation of post-exposure prophylaxis, I think it's quite likely that additional cases would have occurred.

That, of course, suggesting that there is a high exposure. I think a similar statement can be made about the Hamilton facility. The AMI building, I think we've now been off of antibiotics for more than a week, more than ten days, and

adherence to therapy was not outstanding, as you'll hear from Nancy Rosenstein.

I think both of those things and the absence of any recognized disease suggests them to be at lower risk. And then you get to the media outlets and the Morgan facility and Wallingford, none of these places had any inhalational cases, and I think those are relatively low risk exposures.

Now, after having said that, I must admit a fair level of discomfort being an epidemiologist and not having an adequate understanding to make more quantitative estimates of risk differences between these populations, and I think you could make an argument to treat all of them similarly in regard to extension of antibiotics or use of vaccine. Thank you very much.

DR. WALKS: Now why don't we ask all of our panelists to come up so we can do a quick question and answer period. Questions. Looks like we have microphones set up so if you'd go to a microphone, we'd be able to identify you.

Now, if I can just take moderator's prerogative again, and if we can have the questions be as short as possible and the answers also be as short as possible. Dr. Siegel.

DR. SIEGEL: Thank you. Since the, as I understand the presentations, we're taking qualitative testing and making qualitative determinations based on what appears on culture plates. And so my question is since the time of the swab versus the exposure and the clearance rate from the nasal rate relate to the number of spores that then will ultimately appear on the culture plate, and the dose, and the potential for disease, isn't there some disconnect because the Brentwood cohort, for example, did not have nasal swabs done for about ten days after the exposure versus the Capitol Hill people.

So is there any real way to determine the potential lethality and exposure risk of Brentwood versus Capitol Hill given those parameters?

DR. PERKINS: The only comment I would make is that all of the inhalational cases that

have been identified to date where the incubation period has been known have occurred between four and six days, which is actually longer than when we think the most intense exposures occurred in Brentwood and the time that antibiotics were started.

So I think that that suggests that a good deal of the risk period in Brentwood passed without additional cases, although your point is very well taken, and I think it's very difficult to suggest that the exposures in Brentwood were quantitatively different than they were on Capitol Hill.

We don't have the information to make that determination. And that's why I stress the qualitative nature of trying to make this risk determination.

DR. WALKS: We'll alternate. Over here, sir.

DR. BROOKMEYER: Yes. Ron Brookmeyer, Johns Hopkins University. I think this is probably for Dr. Perkins. The question is in New York there was only one inhalational anthrax case. Most of

them were of the cutaneous form. The strains were the same, and my understanding is in New York and in the Daschle letters and so forth. Can you expand a little bit about what you see was the difference between why we saw inhalational anthrax in New Jersey and Florida but not in New York?

What qualitatively was the difference? Can we also be sure that all the inhalational anthrax cases in Hamilton Post Office were not due to any letters that went to New York?

DR. PERKINS: I think the difference in the epidemiology between the New York cases and the Florida cases versus the ones in Hamilton and Brentwood, at least the later cases, speak to a difference in the reagent that was delivered and whether that difference occurred as a result of differences in production or as a result of some damage to it en route. I don't know.

But, you know, I think they speak to a difference in its aerosol potential between the two pulses of letters.

DR. CHASE: Ken Chase. I'm a local

physician with Washington Occupational Health Associates. And I'm also asked to represent the American College of Occupational and Environmental Medicine here.

I know from firsthand experience over the last few months, and particularly recent weeks, that are a number of workers, private contractors, in particular, involved in what you might call anthrax decontamination work, and wearing PPE as outlined on the OSHA website.

I guess my question to the panel would be this: in the IND that you've received from FDA, is any distinction being made between pre-exposure and post-exposure prophylaxis? I'm aware that a lot of these workers keep coming back to get more and more antibiotics and in some cases where it's pointed out they've been on antibiotics an awful long time, and maybe they're adequately protected, they're just going to other clinics and other states and getting the antibiotics anyway.

I personally think that they would be prime candidates for the use of the vaccine, and I

would like to hear the panel's opinion?

DR. PERKINS: The IND that CDC is holding with FDA allows for the use of the vaccine in the pre-exposure as well as the post-exposure mode, and there's been active, and there are ongoing discussions about how best to use vaccine for pre-exposure protection like populations that you describe.

DR. WALKS: Dr. Pitt, did you want to make any comment on that with respect to the infectious quantity? Okay. That's a no. We'll go back over to you.

DR. GOLDMAN: Hi. Lynn Goldman, Johns Hopkins University, and I actually have a couple of questions I'll give very briefly.

First question having to do with the dose response curve and whether it's possible using the data that have been generated on dose response to estimate what a safe dose would be for people. I understand that we saw LD50s and we saw slopes and whether there have been efforts to extrapolate from those.

The second question having to do with the idea that the materials in the first wave of letters and the second wave of letters were different. Just a point. If you look at the actual monitoring data in the AMI facility, it's very difficult to be persuaded that that wasn't an aerosol given the distribution in the building, and I think that should be thought about very carefully. When you see environmental data of that sort, to then say that's not an aerosol, that's very difficult to explain that kind of distribution.

Third question has to do with the Hamilton postal facility and we saw data presented about the work locations, about three individuals on the night shift of the Hamilton facility who contracted anthrax, but there were another three individuals who are not on the night shift who also contracted anthrax. Where did they work and what shifts were they on, and what was the attack rate among the cohort that they were a part of in terms of anthrax?

DR. PERKINS: The question about environmental--let me take the question about environmental assessment data and using that to characterize aerosol risk. I think it's very difficult to do so. In fact, the environment that had the most, the highest proportion of positives, was actually NBC where there were only cutaneous cases that occurred, and there was a very long period of exposure without antibiotics where no inhalational cases occurred.

And the kind of particles that are associated with inhalational disease aren't actually the ones in the surface swabs. And that makes it very difficult to interpret the level of surface swab positivity with aerosol risk, and I think we've seen that very nicely demonstrated.

In the Hamilton facility, we attempted to look at attack rates over groups of USPS workers and did not find anything as high as the two and a half percent we found in that single shift the night that the Daschle and the Leahy envelopes were sorted.

The epidemiology for each of those other cases is slightly different and includes at least one postal handler or mailhandler that looks like they got their disease from cross-contamination, cutaneous disease from cross-contamination.

DR. WALKS: Okay. Let's just have the last question over here in the interest of time.

DR. GUIDOTTI: Yes, thank you.

DR. GOLDMAN: The other questions?

DR. WALKS: In the interest of time, I think what we're going to need to do is to ask the questions after. Sir.

DR. GUIDOTTI: I'm Dr. Tee Guidotti at the George Washington University Medical Center. I'd like to ask what consideration has been given to susceptibility states? We have many more people in the population now who are immuno-suppressed or who may well develop immuno-compromise as a result of co-morbid conditions.

Number one, how would your recommendations be modified to take that into account, and number two is have you been tracking such individuals in

the exposed populations in order to see if they have an apparent natural history of the infection?

DR. PERKINS: We think that that's a very important area to try to study. As you know, the inhalational cases look like they have a slightly older age distribution than would be expected based on the persons exposed.

However, you need to understand that it's been primarily working adults that have been the risk targets, and so we haven't seen perhaps as wide a variation in immune status and health condition as we might if a broader segment of the population would have been affected.

We are going to try to use all the data we have to try to clarify that, and we're aware of at least one or two inhalational cases that have some history of immune defect that may be suggestive of a risk factor for inhalational anthrax.

DR. WALKS: Okay. I'd like to thank my co-moderator, Dr. Koplan, and Drs. Pitt, Perkins, Eisold and Martin, and we'll move on to the next panel. Thank you.

DR. HUGHES: Good morning. I'm Jim Hughes. I'm Director of the National Center for Infectious Diseases at CDC. I'd like to welcome all of you to the second session. This session will focus on post-exposure chemoprophylaxis for inhalational anthrax. We'll have two presentations, one looking at historical data on efficacy and the second looking at the experience in the current outbreak situation, focusing on both adherence and side effects.

Let me now introduce my co-moderator, Dr. Janet Woodcock, who is Director of the Center for Drug Evaluation and Research at FDA, who will make some opening remarks.

DR. WOODCOCK: Thank you. Good morning. I just have a few brief things to say. FDA has approved three antibiotics for the specific indication of post-exposure prophylaxis for inhalational anthrax.

This indication was based on data that we've already heard about from animal studies and human exposure. While the data from the animal

efficacy was quite solid, fewer data were available on the optimum duration of therapy.

The recommendation for 60 days of prophylaxis was considered a conservative recommendation. However, we recognize that in specific instances, factors such as the size of the inoculum or the immune status the patient, as already been alluded to, will influence considerations about duration of therapy.

I also want to note that detailed descriptions of FDA's deliberations including the medical reviews and the transcripts from our Anti-Infective Drug advisory Committee on this matter are available on FDA's website for those of you would like to look at them. Thank you.

DR. HUGHES: Thank you, Janet. Let me now introduce the first speaker in this session. Dr. Art Friedlander from USAMRIID will provide an overview of data on efficacy. Art.

DR. FRIEDLANDER: Thanks very much. Once upon a time this was a favorite disease of mine, in quieter times.

[Laughter.]

DR. FRIEDLANDER: I just want to say a couple of things initially. One of the values in having very little data is that everybody can present it. And unfortunately that is the case with this issue. Now, again, a couple of points I'd like to make.

One is that with the development of antibiotics in the '40s, the previous therapy of anthrax, namely antiserum, was discarded, and antibiotics came into use. In fact, the very first study on the use of penicillin by Abraham, Chain and Flory included Bacillus anthraces. So there was, in fact, some concern about this organism.

The very concept of chemoprophylaxis for anthrax is based upon the use of Bacillus anthraces as a weapon. There is really almost no circumstance or very rare circumstance when you would even consider this under natural circumstances. So the studies that were done in the '40s and in the '50s dealing with chemoprophylaxis were in the context of anthrax

being used as a bioweapon.

The rarity of this disease, as we all are well aware, precludes generating the kind of data, and hopefully we won't generate that data, from the human population, and therefore we're required to look at the best animal model we can, and you're all, I think, well aware of all of the caveats that that involves in terms of trying to use information from animals that really are different than humans.

Nevertheless, that's the data that we have. So in considering chemoprophylaxis, I'm going to spend a few minutes going over some concepts of pathogenesis that are critical to the rational approach to chemoprophylaxis, and as you'll see, this information was well known in the very earliest studies that were done.

Now, I have to figure out how this thing works. Okay. So, in terms of pathogenesis, let's see this, there are again a couple of issues, and again I think most people are now well familiar with this, but I'll reiterate them. One is the spore. The spore is the infectious agent, and it

is the character, the very characteristics of the spore that create such an unusual circumstance in terms of treatment or prophylaxis for this disease as opposed to many other bacterial infections.

It's thought to germinate in the macrophage. The spore enters, will concentrate on the lung. It is, at least the gospel at this time is that it's transported to regional lymph nodes in a macrophage. That being the local draining tracheal bronchial node, and there there's the production of toxins, leading to edema and necrosis, and then spread through the lymph to the blood stream and then throughout the body.

Let's see here. No, no. Where is our guy? He said this or this. Oh, here he comes. Okay. Okay. Here we go.

Okay. So this is an old slide, but I like this slide because what this does is--this is actually from a pathologist who studied disease in the Middle East, and what it points out is that this is what the disease is, of course. It is not a pneumonia. It is a regional hemorrhagic necrotic

lymphadenitis.

It happens to be, when it comes in through the respiratory tract in the tracheal bronchial node, and then to the mediastinal nodes, and within the mediastinum.

Okay. And I like to read old papers. This is A. Lee Menchnikoff [ph]. This idea of the macrophage being important in anthrax goes back to the very, very first studies that were done on macrophages.

And now we can do fancier studies that who that, in fact, it is taken up in the lung and there's fusion of the phagosome with lysosomes, and we think that's where it germinates. It may be dormant there. We really don't know where it is in the lung, and this, for those of you who've heard me talk before, I'd like to point out we knew all about this disease pathologically and clinically a long time ago.

And namely that the disease is in the bronchial glands that are broken down by hemorrhage, extensive cellulitis, together with

effusion around the glands into the mediastinum and in the lungs the changes are but slight.

Okay. All right. Well, I think some of you--that was a chest X-ray. This is one of the patients from Virginia. These impressive nodes in the mediastinum and in the hilum are readily apparent. This patient has bilateral effusions, relatively clear lungs. That's the trachea, the bifurcation. That's the disease right there. This is from Sverdlovsk. This is a monkey, clean lungs, that's the disease.

Whether the spore sits here or whether it sits in the lung, we don't know. That's a brain from Sverdlovsk. That's a brain from a monkey. So we think the monkey is a reasonable model. It was initially studied in rodents by Barnes in 1947 and I think again this is an interesting paper and it basically points out all that we know about the disease in terms of the approaches and the reasons for chemoprophylaxis, namely that the persistence of spores in the tissues and their germination after the blood penicillin level has fallen is one

of the driving factors in terms of how to chemoprophylaxis disease, because the spore is dormant.

We know in the environment, it sits there for probably hundreds of years, and in the host, we don't know why it's cleared or how it's cleared, but we know its dormancy can be for long periods of time.

And that point is also expressed by Barnes. The conditions which govern the germination of anthrax spores in vivo remain completely obscure.

Well, we have a little bit of data now. We know what are the germination operons. That appears to be important, at least in rodents and we'll learn a great deal more about it.

This is the data that you've heard before.

I just drew this out--I don't know--about ten years ago. This is Henderson's data and it's extrapolated as a function at time zero of the retained dose in terms of lethal dose 50s, ten, on a log scale, ten, 100, 1000. And this is his data.

There are only a few data points that you heard.

This is the data extrapolated as a function of time. So one of the critical points in terms of the approach to the duration of therapy is the exposure at time zero.

If you had ten LD50s, by day 60, you're below at LD50. If, on the other hand, you had 100 or 1000 LD50s, if this data in the primate can be used, and it's the only data we have, you're above an LD50.

And you'll see the data that we generated is consistent with this, and I'll come back to that. We didn't generate it for that reason, but you'll see that it is consistent with it.

So these are the points again. The spore may persist in a viable but ungerminated state for extended periods of time, and antibiotics, the other point, don't act on the spore. They only act when the spore germinates.

So, at the time of the Gulf War, we began an experiment. The reason for the experiment, well, before I begin that, I should say that the

studies with rodents were followed by these studies by Henderson, and what Henderson showed in the non-human primate, similar to what had been shown in the rodent, is that if you treat for short periods of time--he used five, ten, and one experiment of 20 days of penicillin--the animal is protected while on the antibiotic. When you discontinue the antibiotic, the animal dies from anthrax.

He also had a group where he included a short course of penicillin and vaccinated post-exposure. Those animals survived. So we knew that.

In the Gulf War, we were asked to address the question as to whether an extended period of time on antibiotics would provide protection, and what came out of that was this study I'll go through, and that is on day zero, animals--these are non-human primates--were challenged with a relatively low dose, eight LD50s, by aerosol. On day one, they treatment was begun with antibiotics alone with vaccination alone, or with a combination of antibiotic and vaccination 30 days. The time of

treatment was extended to 30 days. At that point in time, antibiotics were discontinued.

We also looked, because we had these animals, at what the immune response was, and we rechallenged the survivors with a larger dose, 50 LD50s about three and a half months later. These are the animals. There were ten control animals. We gave them saline intramuscularly every 12 hours until they died.

There was a penicillin group. Again, this was given intramuscularly, Q12 hours. There was a ciprofloxacin group given cipro oral gastrically every 12 hours. A doxy group. And then a doxy plus vaccine, vaccine on days one and 15. There was also a group that received just vaccine.

I just want to point this out. This is not a trivial experiment. We probably learned a lot from this experiment, but there were 60 people involved in this experiment that involved essentially 60 non-human primates. There were 3,700 courses of anesthesia, there were 1,550 quantitative blood cultures. We were a little

compulsive when we did this experiment, and the animals were anesthetized twice a day to give them medication. It's not a trivial experiment. We would learn from this if we were to do it again.

All together, we only lost two animals from unknown causes, which was really remarkable given the veterinary care. I won't go through this. There was extensive blood culturing done. MICs were performed, and the blood levels were measured during the course of the experiment, and w achieved levels based upon extrapolation from humans such that we were above the MICs for all three drugs.

And these are some of the results. The control animals died within three to eight days, not unlike the human situation. The animals were ill for several days. They had in general high levels of bacteremia. They had bacteremia for about two days before death and high levels of bacteremia at death. Five of nine animals had mediastinitis. Meningitis was present in about half. Hemorrhagic in three. Very much like the

human disease. There was one animal that didn't appear to get infected.

And these are the results. The controls, nine of ten died. The vaccine alone did not protect. With penicillin, with ciprofloxacin, with doxycycline, and with doxy plus vaccine, there was statistically significant protection while the animals were on antibiotics.

When the antibiotic was discontinued at 30 days, three of the penicillin group, one in the cipro group, and one in the doxy group died from anthrax. None of the nine animals that were evaluable in the doxy plus vaccine group succumbed to anthrax.

These differences, as you might imagine, are not statistically different. In this experimental design and these results, there is no difference between antibiotics alone, and antibiotics plus vaccination.

I pointed out that we did have some animals die, and I'll show you the time course here. After the 30 days of discontinuance of

antibiotics, there was one animal that died out at day 58. If we had eight LD50s, we're pretty close to an LD50 or so. It's actually less. If you look at all the animals we were less than an LD50.

So, while they're not large numbers, the data is not inconsistent with Henderson's data, if you want to look at it from the number of animals that died. We were less than an LD50 at 30 days, after 30 days, and so the conclusions were that vaccination alone did not protect. All the antibiotics provided complete protection as long as the animals remained on treatment.

Extended treatment for a 30 day period with any of the drugs provided significant long-term protection upon discontinuance of therapy. And post-exposure vaccination combined with doxycycline treatment protected all the animals. Again, these differences were not statistically significant.

The only animals that made an immune response were the animals that received vaccine. So treatment begun one day after exposure prevented

infection to a sufficient degree to induce an immune response, which is what we would have imagined.

At three and a half months, we took the survivors and rechallenged them now, as I said, with 50 LD50s. There was an additional group of controls and most of those died. Penicillin, cipro and doxy animals died. They were not immune. The only group that was immune was the doxy plus vaccine group.

This shows schematically the experiment. Here is day zero at time of exposure. It's nice to see all the data on one slide and realize how much effort went into making that graph. 30 days of antibiotics, no animal died from antibiotics. This was an animal that died from aspiration pneumonia. When the antibiotics stopped, the animals--a few of them began to die.

When they were rechallenged, the only animals that survived were the ones that had been vaccinated and given doxycycline. The other animals most of them died.

And so the summary and conclusions. Post-exposure antibiotics which protect against an aerosol challenge with anthrax spores appear to prevent infection and the development of an effective immune response.

Animals treated in this way remain susceptible to rechallenge. Post-exposure vaccination when combined with antibiotic therapy protects animals against an aerosol challenge and leads to the development of an effective immune response. These animals are resistant to rechallenge.

The most effective post-exposure treatment of experimental inhalational anthrax consists of suppressive antibiotic therapy combined with vaccination. Thanks.

DR. HUGHES: Thank you very much, Art. Let's now turn to the second presentation in this session that will focus on adherence and side effects issues, and this presentation will be given by Dr. Nancy Rosenstein from the National Center for Infectious Diseases at CDC and has recently

spent a good bit of time in South Florida and Washington, D.C. on this investigation.

Nancy.

DR. ROSENSTEIN: Okay. So as Brad alluded to, there are approximately 10,000 individuals who were offered 60 days of antimicrobial chemoprophylaxis. The first group was initiated October 8, and so they stopped antibiotics. That's the group in Florida. And the last group began their antibiotics on November 25, and that's the group in Connecticut.

I've divided this into primarily six sites where most of these individuals are associated with, and again most of these groups are occupational exposure groups.

This is what I'm going to talk about today. This gives you some idea of what the denominators are, with the first column being the approximately 10,000 individuals for whom antibiotics were recommended broken down by site, and then were possible, I'll also try to give data on adherence in these potentially higher risk

groups that Brad Perkins described.

First, some demographics. About half of these individuals are male with as high as 66 percent in New Jersey. Very few of the women report being pregnant, and the race characteristics do differ substantially by site.

In terms of age groups, the majority of individuals are in the 18 to 64 year old age group. In at least one site up to five percent are less than 18 years of age, but these are primarily in Florida, visitors to the AMI building, and there are at least up to five percent of individuals who are over 65 years of age in some of the sites.

Our activities on adherence promotion have definitely evolved in the course of these incidents, and they will continue to evolve as we learn more about the best way to do this. There are a number of activities that have gone on and are currently going on, and this just gives you a brief summary of the activities that are going on in multiple sites.

There's been distribution of educational

materials, telephone calls to every individual who did not return to refill medication. There are small group and focus group meetings actually currently going on. We've also done health fairs where a variety of individuals with different expertise are brought together to help answer questions on a variety of topics including exposure risk, adverse events associated with antibiotics and environmental contamination.

And then there are a variety of efforts to actually do individual one-on-one counseling with individuals.

To monitor adherence, there are actually two tracks of activities, and the data that I'm going to show you actually combines these two to give you the most up-to-date data that I have.

In some cases, the proportion of individuals who are adherent is made based on individuals who come returning for refills and counting those individuals. We've also done cross-sectional evaluations in all of the sites at seven and 14 days and then again at 30 days where

individuals are given standardized questionnaires that are administered, self-administered or by nurse or by telephone.

Because of the complications of doing this type of cross-sectional analysis in this type of outbreak, participation in these evaluations is between 50 and 100 percent, and that's why I also used the data on the return refill to give you the numbers in adherence.

The data that I'm going to present is still quite new and data collection and analysis are really ongoing. So please consider it preliminary. This is a general breakdown of the individuals who are currently taking antibiotics by site at ten to 14 days and at 30 days.

You can see that in general adherence has declined over the course of the 30 days to as low as 45 percent. In Florida, the number of people who are adherent is 45 percent over the overall population of about a thousand, but in this potentially higher risk group of full-time employees and part-time employees in the building,

adherence is closer to 70 percent.

In the D.C. Capitol Hill group, overall adherence is somewhere around 80 percent, but all of the Daschle workers, as far as we know, are actually taking their antibiotics.

In New York City, adherence is 48 percent, and actually the 30 day evaluation is actually going on this week. Their preliminary data suggest that adherence is also 45 percent at 30 days, and that it's 45 percent even in the high risk group of individuals who worked on the sorting floors.

This is sort of the overall view of things. To give you a little more data, I'm going to just look specifically at two sites, at the New Jersey and D.C. postal sites, and this is the 30 day adherence evaluation.

These are individuals who filled out those questionnaires, and so of the individuals who filled out the questionnaires in both sites, about 88 percent report taking their antibiotics, but if you ask specifically about whether they took their antibiotics yesterday or take the antibiotics

everyday, you see that the numbers are actually lower, and this is still self-report data. Adherence experts tell me that when we actually count pills, the self-reporting numbers probably overestimate real adherence by as much as 20 percent, and so the real estimates of adherence taking the antibiotics everyday are obviously substantially lower.

We also looked at adherence by antibiotic, and this is again 30 days and comparing ciprofloxacin to doxycycline, and actually somewhat surprisingly the numbers on adherence actually go up very similar when you compare the two antibiotics.

I'm going to move on to talk a little bit about our adverse events monitoring. There is passive surveillance ongoing in every site to detect individuals who report adverse events, call their clinicians and want to change antibiotics, but we're also doing an active surveillance component through these same cross-sectional evaluations at seven and 14 days and 30 days.

There's initially a screening questionnaire, and then based on the results of the screening questionnaire, individuals who have potentially severe adverse events are further evaluated through patient and health care provider interviews, medical chart reviews, and now we're working to actually categorize those adverse events based on the FDA criteria.

This is again self-reported adverse events at ten to 14 days, and at ten to 14 days, as you can see, most individuals were on ciprofloxacin with only a small proportion of doxycycline.

You can see that up to 19 percent of individuals reported severe nausea, vomiting, abdominal pain and diarrhea associated with their antibiotics. The proportion of individuals reporting heartburn or acid reflux, which we expected to be more common among the doxycycline patients was actually similar between the two sites.

Between two and five percent of the individuals required this additional follow-up

because of the--the follow-up, but actually they didn't have adverse events. And I don't want to in any way minimize the impact of these symptoms on people's daily life, but when we actually investigated further, we were unable to identify anybody who actually required hospitalization or an emergency room visit for their adverse events.

And so based on the FDA criteria, we haven't detected at ten to 14 days anybody who actually would have a severe adverse event associated with their antibiotics.

And surprisingly, only three percent of individuals at ten to 14 days actually described discontinuing their antibiotics because of adverse events.

As you can imagine, the data for 30 days is actually much more hot off the presses, and again this doesn't include the New York City data which is sort of being collected as we speak. At 30 days, the majority of individuals are on doxycycline, and so those numbers have switched. You can see that in all categories, the self-reported

adverse event numbers are much higher and up to 45 percent of individuals on doxycycline are reporting severe nausea, vomiting, diarrhea, abdominal pain.

Somewhere around 12 percent of people required additional follow-up with medical chart review and physician interviews for adverse events. There are still some individuals who we're gathering data on, but I can tell you as yet, of these people who we've recommended antibiotics for, we haven't found anybody who's required hospitalization or emergency room care for severe adverse events, and so far, we haven't identified anybody who's had a severe adverse event as described the FDA criteria.

If we ask people how many of them actually missed doses, so not whether or not they discontinued their antibiotics, but whether they actually missed doses because of the side effects, the numbers were obviously slightly higher with around six to 12 percent of individuals reporting missing doses of antibiotics because of side

effects.

This is obviously ongoing work, and we have a number of things still planned. We're planning now towards an end-of-therapy/60 day program evaluation, which will be conducted in January, and among the other things assessed, we're going to assess adherence and adverse events.

Again, adherence promotion activities and evaluation of these activities are ongoing, as is surveillance for anthrax and adverse events associated with the post-exposure chemoprophylaxis among all the exposed groups. Thank you.

DR. WOODCOCK: Dr. Friedlander, can you join us here too for questions? We'll have about ten minutes of questions.

I have a question to start off with for Dr. Friedlander. Is there any scientific data on where in the pulmonary tree--

DR. FRIEDLANDER: I'm sorry?

DR. WOODCOCK: Are there any scientific data on where in the pulmonary tree the spores have to be to initiate infection?

DR. FRIEDLANDER: Yeah, there is some data. There's data from guinea pigs mainly, some data from rabbits, and that data suggests that the germination, if germination does occur, that productive germination occurs in the tracheal bronchial node or on route to it.

But these studies are done with fairly massive amounts of spores that were instilled into the respiratory tract. There are some newer data that people are beginning to look at this, as you might imagine, more carefully. The data from Henderson where they looked at retained spores, it's unclear from that data whether the spores were retained in the lung tissue per se or in the tracheal bronchial nodes.

The text says in the lung, and he describes it as being in the epithelium. But the way in which the lungs were prepared, it's not clear whether or not they dissected away. They homogenized lung tissue, but it's not clear whether they dissected away the nodes. The implication is, as I read the paper, that it's not in the nodes,

but where it actually is is not clear.

DR. WOODCOCK: I just think it's important when you're making extrapolations across species that pulmonary architecture differs quite a bit across these species.

DR. FRIEDLANDER: Well taken.

DR. WOODCOCK: All right. Over here it looks like--please.

DR. WALKS: Good morning. I first wanted to thank both the presenters, really excellent and quite clear. Dr. Friedlander, the monkey study, none of the monkeys at three and a half months, who had survived initially became sick; right? Is that correct?

DR. FRIEDLANDER: They were not ill.

DR. WALKS: Unless they were rechallenged, they were okay?

DR. FRIEDLANDER: That's correct.

DR. WALKS: Okay.

DR. FRIEDLANDER: Not that we know of.

DR. WALKS: Okay. And then for Dr. Rosenstein, the numbers of people, especially with

the D.C., seemed to be much lower than the overall number of folks who were put on medication. Do you think there is any preselection so the folks who took the time to fill out the form probably were more willing to take the medication?

DR. ROSENSTEIN: I'm sure that there's preselection, and actually in the D.C. specific, the 98 percent initial number is based on individuals who actually came back and got refills. That's why I say it's sort of apples and oranges, and, you know, the ongoing data that we're collecting in the outbreak will be supplemented by this end-of-therapy follow-up at 60 days where we're going to contact every single individual, but it was hard in the course of the outbreak with all the chaos about people getting antibiotics to get lots of folks to sit down and actually fill out a questionnaire.

DR. WOODCOCK: Next question here.

DR. SIEGEL: Dr. Rosenstein, the actual number of people from the Brentwood cohort that we put on 60 days is about 3,500 people. So you've

got about 2,500 on your slide. I'm not sure what happened to that other thousand.

The question that I have is about the individuals from Brentwood. We had about 3,100 people who had nasal swabs, all of them negative, started on antibiotics about ten days plus after exposure. Would you expect that those individuals who had longer exposure might have had an immune response and therefore might not need vaccination because of an immune response that was mounted during that period?

DR. FRIEDLANDER: It's possible. We don't know much about subclinical disease. There is some evidence to suggest that it occurs, but I think you need to take a look at the--I don't know whether serologic studies were done on those individuals, but they certainly would be worth looking at. Does anyone know?

DR. SIEGEL: There were some serologic studies done. I haven't seen any results from CDC yet.

DR. FRIEDLANDER: That would be very

informative to see whether any of those people developed an immune response for sure.

DR. WOODCOCK: Okay. Next question over here. Could people identify themselves?

DR. GOODMAN: Jesse Goodman, FDA. What we have here in a sense that you're describing with the compliance data is a natural experiment. And I was wondering if you can reconstruct the denominator in a sense? How many people who discontinued prophylaxis in various groups of risk exposure are there out there? How many person days have there been since they've discontinued prophylaxis where they haven't been getting any antibiotics?

That's the denominator. We know presumably the numerator, which is that we're unaware of any cases of inhalational anthrax occurring in such people. So I think this would be a useful number to have even with some of the caveats. If it's rather small, it means nothing. If it's rather large, perhaps it's telling us something.

DR. GUIDOTTI: I'm Dr. Guidotti from GW. Two very quick questions for Dr. Friedlander. One of them pertains to distortions of the pulmonary architecture and reduced clearance that may arise in COPD and in fibrotic lung disease. Would that in your opinion change the presentation of the disorder and might it also put those individuals at particular risk for late germination and delayed onset of the disease?

DR. FRIEDLANDER: I understand that these are extrapolations from a minuscule amount of data, but the answer is yes. I think it's my view that underlying disease does enhance susceptibility to this disease, to the expression of the disease. There is some data again from the older studies in humans as well as some data from non-human primates, and if there were focal disease in the lung, underlying disease, it's conceivable, again based upon some primate data, that that could be the source of introduction of the organism.

There were some cases that--and if there's distortion of the architecture of the respiratory

tract that interferes with clearance, you could generate an argument that that would predispose to disease.

One of the cases, for example, and there haven't been very many, in the past was an individual who had previous surgery for laryngeal carcinoma, and there are other instances where that--I mean there is evidence where that predisposes to other pulmonary infections. So it could be.

DR. GUIDOTTI: The other side of that question is that for that group, for people who discontinue their medication and for the long tail that exists in the population for late germination, has any thought been given to immuno-modulatory interventions, pharmacologic interventions that enhance the endogenous immune response as opposed to giving an increasing antibody, or antigen load?

DR. FRIEDLANDER: Just about immune modulator that you can imagine and those that you haven't imagined has been brought to the table. But unfortunately, we don't have any data. The

data will be forthcoming, I think, in animal models over the next several years.

DR. WOODCOCK: Next question here.

DR. EITZEN: Ed Eitzen from USAMRIID. My question is for Dr. Rosenstein. I was very interested in your antibiotic side effect data, and kind of surprised at the level of especially gastrointestinal side effects that you reported and reported as severe, and I have two questions about that.

First question is how much of that symptomatology is due to the antibiotics? Do we have any way of assessing that? Can we look at any control populations to tell, and secondly, it seems to be a disconnect that they're reporting severe GI side effects, but only three percent at 14 days reported discontinuing antibiotics and nobody has been to an emergency room for their symptoms. That seems unusual.

DR. ROSENSTEIN: I'm sure that it's a methodological problem. I mean we asked them did you have any of the following side effects, and

it's a self report. And one of the answers they could check off is that they had severe nausea, vomiting, abdominal pain or diarrhea, and a quite high proportion said yes to that.

In some of the groups, actually it was a nurse administered questionnaire, and it seems like on the nurse administered questionnaire, the numbers are lower. So it could easily be the methodology, and I suspect that that's similar for other adverse events reporting.

And that's why we went through actually tracking down everybody who had a potentially severe adverse event to make sure that none of them actually had a hospitalization. And I mean it's quite actually satisfying to find out that very few of them have what would be characterized as severe adverse event.

DR. EITZEN: Thank you.

DR. WOODCOCK: Question here?

MR. DUNCAN: Yes, Phil Duncan from Congressman Istook's office. This is probably for Dr. Friedlander. What is the real final cause of

death in the patients? Is it hemorrhage or oxygen deprivation or combination?

DR. FRIEDLANDER: Well, of course, we don't know. I think based upon some of the pathologic studies, I'm not familiar with the details of some of the current cases in terms of the people who were directly handling those cases. But pathologically from looking at the largest collection of data from Sverdlovsk, it looks as if at least the pathologists who examine them feel that a lot of this is due to obstruction in the mediastinum, and interference with pulmonary function.

Large effusions, outflow obstruction, hemorrhage, what's called high pressure hemorrhage in the lung and elsewhere, suggesting extravasation of blood into tissue, atelectasis in the lung, interference with pulmonary function. In addition, again pathologically there are some patients that have vasculitis, and if there's involvement of the brain with hemorrhagic meningitis, then clearly that's an easily explainable cause of death.

So the combination of pulmonary obstruction, edema, interference with pulmonary function and, of course, these people are septic and toxic at the same time.

MR. DUNCAN: And as follow-up, I've been presented with some material that shows that there's been some experiments with hyperbaric oxygen in vitro that have had significant impact on anthrax. There's two studies that were shipped over to me, and also when you have lung conditions like that, I was wondering how much just having more oxygen to them so you didn't have to worry about that part of it might help with the effects of the antibiotics over time?

DR. FRIEDLANDER: I mean clearly that could be a benefit, but it would be something that would have to be evaluated.

DR. WOODCOCK: All right. Thank you. Our panel is out of time.

DR. FAUCI: Good morning. My name is Tony Fauci from NIH. My co-chair is Dixie Snyder from the CDC, and welcome to the next section of the

program entitled Post-Exposure Immunoprophylaxis, which is really getting very close to the issue that we're going to be discussing later on when we get to the general discussions of pros and cons.

Very briefly, before I hand the program over to Dixie to introduce our speakers, we've heard very nicely this morning regarding the assessment of exposure risk as well as the post-exposure chemoprophylaxis and the data on both of

those are really in many respects very clear with some unanswered questions.

The session here on immunoprophylaxis really related somewhat to the data that had been presented a little bit ago this morning, and that

has to do with the real and/or perceived benefit or potential benefit of combining vaccination with continuation of antibiotics and then stopping to determine if you can get an added benefit over just a continuation of antibiotics and observation.

As we've heard very clearly from the very nice presentation that Art just gave, the scientific data in the experiments in that he did,

that extraordinary amount of work that I now realize looking at those data points with you, Art, really tells us, as Art mentioned, that there is no significant difference in that experiment between chemoprophylaxis, in that case, doxy, compared to doxy plus immunization, although as he pointed out very appropriately, there are theoretical considerations, theoretical considerations based on data from that study and others that showed that animals that, for example, were rechallenged were protected if they had vaccine and antibiotics, but not animals that just had antibiotics alone, with the theoretical consideration if there were spores there, that the spores may then germinate and give disease after the antibiotics were discontinued.

So in the lack of solid scientific data experimentally, but with some considerations that are also compounded by the relative doses, as very nicely pointed out by John Eisold and his colleagues, that individuals not only at the Senate but also in the postal facilities might have had, and a differential degree of exposure among

different groups I think also is going to compound, not the problem, but at least the consideration.

We move now to vaccines. I know virtually everybody in this audience is aware of this, but we must point out that when you think about vaccination, there are several categories of vaccinations. There's required vaccinations, vaccinations, for example, during the period of time before the eradication of smallpox that were required, school type vaccinations to get children in school, measles, mumps, rubella, et cetera.

There's recommended vaccinations when you recommend influenza for individuals in a particular group, and then there are vaccinations that are available, neither required nor recommended. Some of those, many of them fall into the case of an experimental category where you're doing a clinical trial, where you have something under an IND. It might be available for someone, but it is neither required nor necessarily recommended, and I think these are some of the issues that are going to come up right now.

So having said that, let's take a look at this vaccine in question, take a look at its efficacy, take a look at its safety record, and let's take a look at some of the IND requirements, and for that I'll hand the program over to Dixie.

DR. SNIDER: Thank you, Tony. Our first presentation, which we'll move right into, is by Phil Brachman. Phil, of course, is a former CDCer and has had personal experience with anthrax vaccine in clinical trial.

DR. BRACHMAN: No slides. At Emery, we're just getting into the computer age so I have not prepared any slides.

[Laughter.]

DR. BRACHMAN: When I entered CDC in 1954, my first assignment was to work on anthrax and to work with Fort Detrick on evaluating the vaccine that George Wright and colleagues had developed at Fort Detrick in the early 1950s.

The vaccine was made with the Volum strain of organism grown in a defined media. It was sterilized. The organisms were filtered away,

filtered out and the protective antigen was precipitated with alum and the vaccine was thus ready for use. They tested its safety in 600 personnel at Fort Detrick, and in 1954, it was my job then to identify an industrial population in the United States in which the vaccine could be field tested in an efficacy trial.

For several years, I in collecting surveillance data was able to identify four goat hair processing mills in the United States that among about 1,300 employees in the combined four mills had on average of 1.3 cases of cutaneous anthrax per 100 employees per year.

In the United States, it's of interest that the greatest number of cases of anthrax that we have seen since the 1950s up to the present time really have been in goat hair mill workers. These mills were located in Pennsylvania and in New Hampshire.

I visited the mills, got permission from management to talk to the employees, and we set up a program, a voluntary program among then the

employees in these four mills. The immunizations extended from 1955 up through 1959.

We had 379 employees in the vaccinated group and 414 in the placebo group. What we did is I went into the mills and separated the employees out into two categories by their length of employment, by age, by the department they worked in, and by their specific job, since it was obviously a higher risk in the areas, the employees who worked with the imported goat hair initially versus those that worked with it in the spinning and weaving departments later on in the processing of hair cloth that was the product of these mills.

We then asked for volunteers, and approximately two-thirds of the employees did volunteer to join the program, one-third refused, and they were therefore not brought into the study. And we then, having split up the employees already, we then proceeded to give those vaccine and give the placebo, which was a tenth of a percent of alum in a five-tenths of a milliliter dose given subcutaneously.

The vaccine was given at starting point, and then at two weeks and then four weeks and six month boosters for three doses and then annual immunizations were given, and I gave each and every one of the doses.

I also examined each of the employees, whether vaccinated or placebo group, at 24 and 48 hours myself, and noted whether they had any reactions or not.

We maintained close surveillance on the employees. The companies were quite cooperative, and any time there was a case or suspect case, they would call, and I would go and visit the company, visit the employee, get cultures, and get blood and make some clinical judgments.

There actually was a decrease in the population under the program because three months after we initially started the immunizations in the factory in New Hampshire, as you probably recall, in 1957 they had an epidemic of nine cases of anthrax, four cutaneous, five inhalational, and subsequent to that epidemic, we took that mill out

of the study and vaccinated all of their employees, not knowing whether our epidemiological studies could indicate that the epidemic was over.

So, therefore, they were taken out of the study. Over the period of time of the study, there were 26 cases of anthrax, five inhalational in the epidemic, and 21 cutaneous cases. The cutaneous cases, 13 of the 21 cases occurred in the group that received the placebo, two occurred in people that were in the placebo group, but did not receive all of the placebo inoculations, one case occurred in a vaccinated employee. She developed cutaneous anthrax five months after receiving the initial series, just before the first booster dose was to be given.

There were two cases that occurred in vaccinated employees, but they had not had the regular schedule, so they're called incomplete, and then there were three cases that occurred in unvaccinated people who did not enter into the study.

23 of the cases occurred in people who

worked in the high risk areas, and three cases occurred in people that worked in the low risk areas. The analysis that we conducted were in person months so that we could include the people who dropped, who did not stay in the entire length of the study, and so we would not lose them to our analysis. 13 cases occurred. 13 cases were expected, and one case occurred, and our vaccine efficacy was 92.5 percent.

Looking at reactions, which is of some interest, I noted by the erythema around the site of inoculation in a deltoid and I also looked at induration and edema, and I came up with various indices that I used to evaluate the reactions, and it turned out that there really was a very minimal number of reactions.

Obviously, when you insert a needle into tissue and inject a substance, you're going to get potentially a little bit of pain, a little firmness, and this was really the maximum, this was the type of reaction we saw in a number of people, which this appeared within one to two days.

Out of the all of the individuals who received the vaccine, of which there were about 350, only 21 had any significant degree of edema, and that would have been edema just around the inoculation site, possibly for one or two or three centimeters.

There were three individuals that had edema that extended from the deltoid down to the forearm, and in fact, one of them had edema down to the wrist. It turned out that that was the president of one of the companies.

This edema, though, disappeared within four to five days. There were no systematic reactions reported. Nobody was hospitalized, and only six working days were lost, mainly by those people that had the more extensive edema. So our conclusions were that this was certainly a safe vaccine. Reactions were minimal and that it certainly was an effective vaccine.

Upon completion of the study, the vaccination programs were made mandatory for the employees in these mills, and they subsequently

have had no more cases, though they are no longer in operation. While they were, there were no more cases of cutaneous anthrax. Thank you.

DR. SNIDER: Thanks, Phil. Our next speaker is Lt. Colonel Phil Pittman, who has had experience with the DoD program.

LT. COL. PITTMAN: Okay. Thank you very much. First of all, I'd like to thank John Grabenstein, my friend John, who prepared these slides when we thought that he was giving this talk, and I was giving another one, so rather than to redo them, we decided to go ahead and use these slides.

This one is to indicate that the U.S. military has performed or is in the process of performing some 17 studies to review the safety of this vaccine. In addition to the U.S., the Canadians have also done a safety study. So over all, there are a number of studies looking at the safety of the anthrax vaccine.

Although I will discuss the local and systemic effects of the vaccine, as a composite of

several of these studies, we will then discuss a couple of studies that are in red in a little more detail, staying within the confines of the time here.

Again, looking at the injection site reactions, and we'll divide the discussion into injection site reactions and those that are systemic. We all know that there are a number of injection site reactions that are caused by essentially all vaccines, and these include redness, itching, soreness at the site of injection, and swelling. For the anthrax vaccine, for AVA, about 30 percent of men and 60 percent of women will report some form of mild local reaction, and these reactions tend to last for a few days.

Both gender do, in fact, have reactions that may occur in the range of one to five inches using AVA, and a few, perhaps, .1 to one in a hundred would have a larger reactions of five inches.

We do occasionally at USAMRIID and in the larger seen reactions that have had swelling to the

elbow and less often swelling to the wrist, as Dr. Brachman had mentioned that he saw with the earlier vaccine.

In addition, there are subcutaneous nodules that are located at the injection site as well. These do not interfere with the activities of vaccinees, and they last for a few weeks and occasionally they may last longer, a month or so, in some individuals.

The vast majority of these occur in females. Females have subcutaneous nodules at the rate of 60 to 80 percent, but once again these do not tend to cause any difficulty with their work and they resolve spontaneously.

With respect to systemic type of reactions, rashes occur in about 16 percent, headache in 14 to 25 percent, joint aches we've seen in 12 to 15 percent, and there are also additional symptoms such as malaise, muscle aches, nausea, chills and fever, that occur at a less frequent rate.

These symptoms all resolved within a few

days. And in fact, most of the erythema and induration that we see resolved within three to five days after injection. Occasionally, there are severe allergic reactions that occur at a rate of around one per 100,000 doses.

I should say that we are in the process of evaluating the long-term effect of this vaccine. We were asked to do this by the U.S. Army Surgeon General, and are in the process now of developing the protocol that will evaluate the long-term effect of the vaccine among laboratory workers at USAMRIID who have been receiving this vaccine since about 1970.

This slide taken from the Defense Medical Surveillance System reviews the rate ratios for specific medical visits and anthrax vaccination. That is the incident hospitalization and outpatient visit rate among anthrax vaccine recipients, divided by the rate among non-recipients of active duty individuals.

The recipients have about 750 person years of experience. Non-recipients almost 3.5 million

person years of experience. We can look at the category of diseases or symptoms, individuals who are vaccinated or unvaccinated, showing the rate per 100,000, and the rate ratios, unadjusted, unadjusted, with 95 percent confidence interval, and the interpretation of the significance of these findings.

If we look at connective tissue diseases, we can see what the reported rates are for vaccinated and unvaccinated, and the unadjusted and adjusted rate ratios with their confidence interval.

And we see that that is not significant. You can go through these for any symptom that you would like to review and look at its significance.

This slide reviews the VAERS reports. As you know, the VAERS system is one developed and is used by the FDA in the general public for the reporting of vaccine adverse events, and in this case, we have a special committee which is the Anthrax Vaccine Expert Committee, which is formed by the U.S. Department of Health and Human

Services.

This committee meets every four to six weeks and reviews VAERS forms that are available at that time. There have been a total of over a half million individuals who have been vaccinated with over two million doses of the anthrax vaccine as of the 24th of September. This number, this column shows the total number of unique VAERS forms, and we say unique because some of these are duplicate. You may have two or three members of a family submitting a VAERS form for its service member who may have had a reaction to the vaccine.

These are counted once for the purposes of this analysis. So the total reactions are here.

The number of reactions that are felt to be certain are probably related to the anthrax vaccine are in this slide.

We can see, just going over a couple of these, that there have been 161 cases of individuals who have lost 24 or more hours of duty time, and of these 161 cases, 89 have been thought to be due to the anthrax vaccine.

And they have lost duty because of injection site reactions, acute allergic reactions, flu-like symptoms, et cetera. There have been 57 hospitalizations total. Among those, ten have felt to be related to the anthrax vaccine.

All ten of these were due to allergic inflammatory reactions at the injection site. These are large red raised reactions that most primary care physicians who are not familiar with the anthrax vaccine might think are cellulitis. So that it be no the safe side, patients are admitted and given antibiotics for the required period of time until the reaction is resolved.

But as you can see, most of the VAERS forms are submitted for, at least of the serious ones, significant ones, for events that are felt not to be due to the anthrax vaccine.

This is another study, but involved a group of flight aviators located at Fort Rucker, Alabama, where the U.S. Army has an Army Aviation Unit. These individuals undergo annual physical examinations by their flight physicians, and these

data are put into a data register and was available for evaluation.

In evaluating over 3,000 such matched pairs of anthrax vaccinated and unvaccinated individuals, we saw no difference in the following list of physical findings and laboratory findings that range from hearing loss to weight loss or gain, changes in interocular pressure, development of proteinuria, glycosuria, hematuria, or diabetes.

So, in closing, the anthrax vaccine does, in fact, cause injection site reactions as expected with an aluminum adjuvanted vaccine that is administered subcutaneously. Currently, this is the only aluminum adjuvanted vaccine that is administered subcutaneously. All other FDA approved aluminum adjuvanted vaccines are administered intramuscularly.

We have seen some acute allergic reactions. Anthrax vaccinated individuals are as healthy and as sick as, if you will, unvaccinated individuals. And the anthrax vaccine has a side effect profile similar to other vaccines. The

safety surveillance of the use of this vaccine is ongoing. Thank you very much.

DR. SNIDER: Thank you. Our final presentation is by Kathy Zoon, who is Director of the Center for Biologics Evaluation Research at FDA.

DR. ZOON: Good morning, and while we're changing computers, I'm just going to go ahead with my presentation so we don't lose time. My name is Kathy Zoon. I'm the Director of the Center for Biologics Evaluation and Research at the FDA, and our center has responsibilities for vaccines, biological therapeutics and blood and blood safety,

I was asked to introduce the process we use by which a new vaccine is developed and some of the regulations that are in place for vaccines. I'd start out to say generally the clinical investigation plan in almost all cases is covered through the investigational new drug application process. And there are three phases that we use for clinical trial development: Phase I in which we look at safety and mutagenicity, and Phase II where

we look at immunogenicity, safety and dose ranging. And finally in Phase III, where we're looking at efficacy, safety and immunogenicity.

Just to remind everyone, while we're embarking in clinical trials in humans with the clinical plan, even before those events happened, we meet generally with sponsors to look at the biological rationale for the development of such a product, any preclinical data including in vitro data and animal testing data in which to develop a rationale for going into man, and finally looking at the product, the characteristics of the products and the manufacturing process used to prepare the product.

Finally, at the end of Phase III and clinical development plan, generally a submission will be made to the agency for review of the data to support the approval of that material. Our work is not done. Actually our work just begins because in Phase IV, we will look at the inspections of the sponsor who is making the product, continued and monitored the safety through

surveillance mechanisms, and continue to get reports on efficacy.

We also do lot release on vaccines. Oftentime there are changes to an application or a different indications, and often those will be submitted as a supplement to the biologics license application.

These are the laws and regulations governing vaccine development. They include the Public Health Service Act, the Food, Drug and Cosmetic Act, the FDA Modernization Act, and a variety of regulations found in the Code of Federal Regulations dealing with biological products, standards, investigational new drug applications, well controlled clinical trials, good manufacturing practices, et cetera.

Our philosophy in the review of vaccines is we very much look at it on a case by case approach, based on rational science, using sound scientific principles, based on preclinical studies, product development and protocol designs.

It's a risk versus benefit assessment. We

clearly engage in identifying and evaluating safety concerns, related to the product and to the population and the clinical trial design.

A certain amount of flexibility can be built based on these parameters. We look at the quality control of the production process to ensure that there is a safe, efficacious and consistent product, and that the facilities are in compliance with FDA regulations.

The anthrax vaccines, right now we have one anthrax vaccine that is currently licensed. That's the BioPort vaccine. This is protected antigen based vaccine. There are a number of potential vaccine products for anthrax that are currently being considered or under development, and these include anything from highly purified recombinant proteins and both single and multiple immunogens, viral or bacterial vector vaccines, DNA vaccines, and live attenuated spore vaccines.

The licensed vaccine, the one that's really under consideration for these studies, is manufactured by BioPort Corporation. As already

mentioned, it is avirulent non-encapsulated strain of volum. The major protective component is PA antigen, protective antigen, and it's complex with aluminum hydroxide as a preservative, benzethonium chloride, brand name Phemoral, and formaldehyde, which is a stabilizer. It's given subcutaneously, zero, two, four weeks, and at six, 12, and 18 months with annual boosters.

Dr. Brachman already outlined the prophylactic efficacy data, so I will not go into it, other than there was 93 percent efficacy rate with the vaccine. Additionally, there was surveillance data that was collected by the CDC in combination subsequent to that study with mill workers as well as laboratory workers.

So this was part of our database. When FDA incorporated the Center for Biologics as it's currently framed, there was an equivalent of a DESI review which is to look at all the biological products regulated by CBER and do a relook at their safety and efficacy.

And then this independent panel found that

this anthrax vaccine was safe and efficacious and should stay on the market.

There has been a fair amount of experience collected for this vaccine under IND 180, which is the CDC IND, and then also a large cohort of information has been collected from various sources, particularly with the respect to DoD since Desert Storm in 1990, where 268,000 doses were administered, and then from 1991 to 2001, where approximately 1.6 million doses were administered.

This represents the vaccine adverse reporting system that Dr. Pittman alluded to. This is updated as of yesterday. Now, I want to point out here that anyone can report a VAERS adverse event. There is no causality required for reporting for VAERS. And, again, the most common event that we see are injection site adverse events, and there seems to be no clear pattern of association between deaths or serious adverse events and the anthrax vaccine.

Just to say that again the AVEC committee that Dr. Pittman alluded to also reflects a similar

finding that there is no pattern of adverse events associated, severe adverse events or deaths associated with the vaccine.

As I mentioned, this is one licensed vaccine that we have. There are limited license lots available within the dating period. Most of those are under the control of DoD. Approximately five million doses are available under IND. Many of these doses, and I will describe them in more, had some manufacturing deviations or had some minor changes in their specifications.

The agency has looked at these doses and feels that in an emergency situation, these doses may be appropriate to use under IND, but they do have some associated deviations.

When the facility was being renovated--the BioPort facility was currently recently renovated--they prepared three consistency lots which once the plant supplement is ready to be approved will be available for distribution after lot release.

Most of the IND products that are

available and all the licensed products are currently under the control of DoD.

There is two exceptions to this. Recently, DoD has agreed to transfer to HHS, and this is in the process of happening, 10,000 doses of FAV 063, which is one of the exhibit lots that has been made within the renovated facilities with the updated procedures. And there's also a lot that has been committed which is an older lot manufactured in 1992 that has approximately 200 doses.

This has also been committed to HHS, although the transfer has not officially occurred. The deviations with this lot include the Phemoral which is the preservative I mentioned is below release specification and has passed recent preservative effectiveness tests as of June in 2000. It also passed container integrity tests in 2000. It's passed its potency test in October of '98, and has also passed the general safety and sterility and other tests in that same time frame.

CBER conducts preapproval inspections

prior to licensure. This inspection is going on as we speak. So thank you very much.

DR. SNIDER: Thank you, Kathy. Don't run away.

DR. FAUCI: Can we have the other presenters please come up to the stage so we can entertain some questions and discussion? We seem to be a little bit off on time but not a lot.

DR. BRACHMAN: I forgot to mention one thing. Could I do that before the questions come?

DR. FAUCI: Sure. Absolutely. A request to make an additional comment by Dr. Brachman. And I think that would be appropriate before we entertain questions.

DR. BRACHMAN: Before I might get a question, when I was giving the results of the number of cases that occurred in the populations in these four mills, I mentioned the cutaneous cases. I forgot to mention the inhalational cases that occurred in the epidemic. I'm sure somebody might bring that up.

Of the five cases of inhalational anthrax

that occurred in one mill that was part of the immunization study, three of those cases occurred in unvaccinated individuals, one of whom actually had started to work one month before he became ill, and two of them occurred in the placebo group.

Now the statistics did not allow us to give statistical validity to preventing inhalational anthrax, but certainly the trend is that the vaccine would prevent against inhalational in humans. Thank you.

DR. FAUCI: Thank you. We'll start off the questions here.

DR. GOLDMAN: Yeah. I'm Lynn Goldman again. My question is for Dr. Zoon actually and has to do with the available supplies of anthrax vaccine. You mentioned that there had been an issue with manufacturing deviations and how those deviations connect to the supplies that are actually available, and what is meant by manufacturing deviations, whether this had any implications in terms of either the efficacy or the potential for side effects from those vaccines?

DR. ZOON: Yes. As I mentioned in my talk, our discussions with DoD have made available to the HHS 10,000 doses of the FAV 063, which is one of their exhibit lots that have been made after the facility has been renovated and new procedures put in place.

Although that 063 meets all the specifications of the anthrax vaccine, it is not licensed yet because the inspection is ongoing and clearly we are looking very carefully at the production and review of that in the facility right now. But barring that no findings on that inspection would impact on that particular lot or the exhibit lots, they would be technically be able to be released for license following lot release by the FDA as licensed material.

So that's that. The 015 is an older lot, as I mentioned. It has some GMP deviations. We had an assessment team put together that included people from the FDA, DoD and others that have looked at the lots, and this particular lot, while the preservative is slightly lower, still has

preservative effectiveness, and so we believe if there were an emergency situation, that this lot could be considered for use only under IND, though it would not ever meet the specifications for licensure so I want to be clear about that.

But there is no reason to expect that the side effects from this lot would be any problematic.

DR. FAUCI: Thank you, Kathy. John.

DR. EISOLD: Yeah, John Eisold, the U.S. Capitol. I think my question I was going to ask has been answered, but I do want to make a clarification and an observation. Somebody came up to me and asked me have I vaccinated anybody, immunized? No. The program never got off the ground so that if that was unclear in my remarks, I just want to clear that up.

The observation is that if the program goes ahead and a certain number of people are immunized, I think we need to look down the line so we're not second-guessed about any relatively. I have no doubt about the efficacy and safety of the

immunization, whatever lot we use. But there will be somebody who will question if we use some lot with more deviations or more questions about it, five or ten years down the line, as you well know, and so that I would just encourage us to take a look at getting the best product if we go in that direction.

DR. FAUCI: Question.

DR. YOUNG: My name is Sammie Young. I'm a retired Air Force Reserve Medical Service Corps officer, and I spent 29 years and two months as investigator and regulatory official with the Food and Drug Administration. She was Kathy when I knew her, when she came on board.

[Laughter.]

DR. YOUNG: So my question is in two parts to Dr. Zoon. The first is I'd like for you to clarify the 1985 efficacy review report on anthrax vaccine which stated that there was not enough data to make a decision on the aerosolized contact.

The order in accordance with the 1962 amendments to the Food, Drug and Cosmetic Act on

efficacy required that a proposal be published and that the order be finalized in order to establish the safety and efficacy provisions for a drug or a biological. That order was never finalized. So we have a vaccine out there that is spoken of as approved, but yet the final order that would make that approval effective has never been published. That's my first comment.

The second one, Section 501(a)(2)(b) of the Food, Drug and Cosmetic Act states amongst others that a drug or biologic that has not been manufactured in accordance with current Good Manufacturing Practices is adulterated. We don't administer adulterated drugs to human beings in the United States, and that hasn't been done as far as I know since, you know, the earlier days of the '40s. So my question is how have you come to the point that you can bypass a federal law and how you can you assure that the people from CDC who are going to get this vaccine that it's not adulterated or misbranded and that it will be safe for them?

I have a little bit, a little more--well,

go ahead.

DR. ZOON: Can I answer that, too? I'll go look into why. I'm not aware of why the order has not been published, but I will look into it.

Secondly, with respect to the vaccine, the material that we're discussing, as I said, 063, is currently an exhibit lot for a renovated facility that is scheduled for inspection, and that has met all the testing requirements as designated by the specifications of the manufacturer and then reviewed by lot release by CBER.

With respect to the FAV 015, which is the lot that is low on Phemoral, I would say that we would never license this product. However, with full disclosure and informed consent on this product and based on a risk assessment as to whether or not this product was necessary, the review of this lot was felt if there was indeed an emergency it could be used under IND with full informed consent.

DR. YOUNG: The material--may I get a clarification? The material that is being used in

the IND is not the material that was manufactured by the current manufacturer?

DR. ZOON: All the materials that are being considered or made available to HHS are made at BioPort. Some of it was made under the conditions of its former--well, under the conditions of its license, but it's not the one with the supplemental changes to the facility and the production procedures.

But this is the same vaccine that was used in the Brachman studies and used in many other states once it was approved.

DR. YOUNG: And looking at the material that has been manufactured by the current license holder, that material was produced during a period when this company was not in compliance with current Good Manufacturing Practices, which by federal law and case law will support that, that that product in quarantine is adulterated.

And as one who spent a lifetime in the Food and Drug Administration in a career, we did not permit the reconditioning of product that had

not been manufactured in accordance with current Good Manufacturing Practices because you can't go back and do something you didn't do in the first place.

So how are we going to deal with the material that is in storage? Now one last comment, it's a recognized scientific premise or whatever that end product testing alone is not sufficient for the release of a drug product.

DR. ZOON: Just two comments on that. The material was actually manufactured in 1992. And at that time, the BioPort was not under an intent to revoke or any of the conditions that we currently have.

However, in saying that, I will agree with you that we have looked at this. These lots would never met the criteria for release for licensure. And the only reason that these would be considered, as I said, was an emergency situation with full informed consent on the nature of the product and what the deviations were, and quite frankly making sure that was transparent so the individual looking

at this could be fully informed.

DR. YOUNG: Well, then a last comment on that then. I have a lot of experience in the investigational drug area, too. Will the informed consent statement say to the people from CDC that your product is legally adulterated?

DR. ZOON: I think it would lay out the manufacturing deviations. It would also lay out where it didn't meet spec.

DR. YOUNG: Thank you.

DR. FAUCI: Kathy, could I just ask you maybe to--because there was a lot of legally adulterated stuff going back and forth, and it confused a lot of people--to perhaps just emphasize the status of the 10,000 dose exhibit lot is an ultimately licensable product; is that correct or not?

DR. ZOON: It is. The only caveat to that that I would say is that the inspection is ongoing.

DR. FAUCI: Right.

DR. ZOON: And the outcome of the inspection could potentially impact on those lots

if significant problems were found. But if there were none, then, yes, these meet all the specifications, and if the inspection reveals that they're made under good GMPs, then they would be licensable.

DR. FAUCI: So they would be in contradistinction to the 200,000, which would only be used in an emergency under an IND?

DR. ZOON: Right.

DR. FAUCI: Just to clarify for the audience. Okay. Next person.

MR. HANDY: Redmond Handy with No Abuse. We're a nonprofit service members health rights organization. Dr. Zoon, I want to thank you for all of your efforts in the past couple or three years in attempting to get the Department of Defense to abide by the regimen on the vaccine protocol, the letters that you wrote suggesting they need to abide by those things.

What I'm concerned about and my question for you concerns the current use and the future use by the Department of Defense with this vaccine. As

you know, all the hearings that have gone on in the past two or three years and the controversies surrounding that really probably started as the FDA approved DoD's use experimentally of medicines and vaccines and drugs during the Gulf War.

And since that time, we have instances where there have been deviations from those protocols and at the beginning of this session, Dr. Henderson mentioned that this post-exposure treatment is indeed experimental. Now in the material that DoD had turned over to Congress during the hearings, they had plans to use this vaccine on a post-exposure basis, which would be experimental.

Of course, the DoD is using this on a mandatory, not an informed consent basis. Based on your efforts to get the DoD to comply with the informed consent regulations concerning the deviations that you knew about then, what does the FDA plan to do about any efforts by the DoD to use this vaccine on a post-exposure experimental basis and how will you enforce the informed consent

requirement for the DoD, or will you allow them to use it on a forced experimental basis as occurred during the Gulf War?

DR. ZOON: The only thing I could tell you, and there are others here from DoD that can possibly supplement, we've discussed with DoD a post-exposure protocol, IND protocol, which has been drafted. In fact, DoD graciously gave that to CDC to allow them to use that as a fundamental way to help them prepare their post-exposure protocol. So I think there is a recognition that these are experimental, that they would need to be under IND by both the military and the civilian sector.

DR. FAUCI: Question.

DR. MARTIN: Yeah, Greg Martin from Bethesda Naval Hospital. Since most of the side effects appear to be local side effects related to subcutaneous vaccination, is there consideration in the CDC IND of using this in an intramuscular versus an IM mode?

DR. SNIDER: Yes.

DR. MARTIN: Could you elaborate at all?

DR. SNIDER: Well, actually Brad should come up and answer that question, but I mean we do have a protocol for a study that we would like to get underway very soon which looks at a different dosing schedule as well as looking at intramuscular as opposed to subcutaneous. Brad. He's right there.

DR. PERKINS: That was well done, Dixie.

DR. FAUCI: Okay. Let's take just a few more questions and then we'll have to take the break. Art.

DR. FRIEDLANDER: Just in reference to that comment, an initial study was done by Dr. Pittman comparing IM versus sub-cu suggesting that an additional study should be done and CDC is doing that.

I want to make a point in reference to Dr. Brachman's presentation. The vaccine that was used in the New Hampshire mill workers was a precursor vaccine to the current licensed vaccine. The current licensed vaccine was felt to be four times more potent than that vaccine, based upon animal

testing.

DR. FAUCI: Thank you, Art. Ivan.

DR. WALKS: My concern is that whatever we do here today will be out in the public domain.

Since I don't understand any emergency use for an anthrax vaccine--we have effective chemoprophylaxis--how would you define an emergency use, and if we don't have any imaginable emergency use, why would we make available a vaccine only for emergency use?

DR. FAUCI: Kathy?

DR. ZOON: I'll try. Originally when the discussion was going on, and this is an evolving issue, and so I think what I would say is we wanted to have something in the stockpile we felt that on a public health assessment, it was warranted to use. And what that line is that defines an emergency I think is not a clear line in the sand.

I think it's based on scientific and public health evaluation and the need to use a vaccine in a particular situation. And the reason I've been so open about the material is because I

think that has an impact on how and what material should be used, when and where and under what conditions.

So I think your point is very valid, and I think looking at the nature of the material, until we have adequate quantities of licensed material, that does play in the risk assessment and which way to proceed.

In terms of the original assessment of a design of a protocol, we will really looking at a scenario where there was a major release of large quantities of spores that one might because of the dosing and framework of this might lend itself to a protocol that might consider vaccination, although the trigger point was not discussed. So I think it was considered that it might be a useful supplement to our armamentarium in case of a bioterrorist event so that we would have this material available.

DR. SNIDER: I think if I could just give a little bit--I agree with Kathy. I think a little more specificity. For example, if we weren't here

today but a few weeks ago, and we started seeing breakthroughs of people on chemoprophylaxis or people coming off started developing in very large numbers anthrax, people who were on long-term chemoprophylaxis, I think as far as we were concerned at CDC, that would be an emergency.

If there were additional attacks that were extensive, let's say, in D.C. or in New York City, so that the city was paralyzed, and we needed to get first responders vaccinated, so we could get people to the hospital for a whole variety of reasons, continued to have police on the street and so forth, those are the kinds of scenarios that we had in mind.

But, again, we really couldn't list them all out. There are too many different possible scenarios.

DR. FAUCI: Final question for this session.

DR. GRABENSTEIN: John Grabenstein, U.S. Army Medical--actually two clarifications for the record. During the Persian Gulf War, there was

indeed, and it's public record, waivers of informed consent for IND medications in the Gulf War, but they did not involve anthrax vaccine. That was a licensed product used in a pre-exposer scenario for pre-exposure prophylaxis.

And the DoD, Department of Defense, is currently abiding by Title 21, Code of Federal Regulations, with respect to the post-exposure use of anthrax vaccine, in which we filed and had the FDA accept a three-dose post-exposure prophylaxis, IND protocol for anthrax vaccine. So it's DoD's intent to fully abide by the law.

DR. FAUCI: Thank you. With that, we'll move on to a 15 minute break before we go to the next session. It's about ten minutes to 12 now. Come back about five after.

[Recess.]

DR. KOPLAN: Welcome back. Dr. Helms, you might as well come on up. If you start talking, maybe folks will start coming in.

DR. HELMS: Dr. Koplan had quipped to a couple of us up here on the podium right after the

close of the last session that he was tired of hearing simply data, he wanted to hear what to do now, and he wanted to hear people saying I think you ought to do this, and I think you ought to do that.

Well, representing a committee like the Advisory Committee on Immunization Practices, I can't speak in terms of I, but I certainly will speak with the committee, which has been active in reviewing this whole area of anthrax, in particular its new form in bioterrorism, and the way this country has had to adapt to deal with it.

It's going to be my task to present to you the ACIP's perspective on this area, and I'm going to do it in the context of ACIP recommendations which have passed through to Dr. Koplan.

In December of 200, in fact, a year ago today, Dr. Koplan, December 15, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention released its recommendations on the use of anthrax vaccine absorbed, AVA.

These recommendations dealt in part with the issue that we're discussing today, which is post-exposure prophylaxis and prevention. I'm not going to bore you with all of the recommendations that were in it in relation to other aspects of anthrax.

Subsequently, Dr. Koplan, after the release of this particular document, has asked the ACIP to consider various questions and concerns which had arisen with regards anthrax and the use of anthrax vaccine and antibiotic prophylaxis over the course of the epidemic since it's occurred in September, and we have reported to him twice on this.

I'd like to focus with you for the remainder of the talk now on issues related to post-exposure prophylaxis, both antibiotics and in terms of vaccine, as we have dealt with the issues at the ACIP.

It would be most helpful to begin here at the beginning, which is with the original recommendations which went out a year ago. The

first recommendation that went forward listed at the top here is that post-exposure antibiotic prophylaxis should be continued for at least 30 days if used alone, and although supporting data are less definitive, longer antibiotic therapy up to 42 to 60 days might be indicated.

Remember this was before the current epidemic. If AVA vaccine is available, this is the second item on the slide, post-exposure antibiotics can be discontinued after three doses of vaccine have been administered, according to the standard schedule of zero, two and four weeks. The caveat there was if AVA vaccine is available.

The third item, although the shortened vaccine regimen, that is the three short regimen, has been effective when used with post-exposure antibiotics in animals, the duration of protection from the shortened vaccination course is not known. Therefore, if humans are subsequently exposed, additional vaccinations might be required.

Further animal research was suggested to determine the optimal number of days of

administration of post-exposure antibiotics and any additional benefits of receiving anthrax vaccine in combination with those antibiotics, and those were the original recommendations.

Moving on now to the subsequent recommendations presented to him in November and December of this year, the first question really was to clarify the routine duration of post-exposure antimicrobial prophylaxis. As you will remember, in the original recommendations, it was expressed as a range of days, 30 to 60 days, and the people in the field were basically asking how many days should it be, and had actually come down themselves on the number 60 days which was appropriate.

We confirmed that in this recommendation and recommended that routine use be for 60 days. This was based, of course, on the studies that you heard today that antimicrobial prophylaxis of 30 days duration while clear-cut in protecting animals did not provide complete protection, that some animals died in those groups.

Because there is little information regarding the duration of post-exposure antimicrobial prophylaxis among exposed persons who are fully vaccinated, ACIP recommended that fully vaccinated persons receive at least a 30 day course of, perhaps up to 60 days, of antibiotic prophylaxis.

Third, post-exposure antibiotic prophylaxis was not recommended for fully vaccinated persons whose potential exposure is limited to biosafety level three laboratories or who wear appropriate personal protective equipment.

Now, in its earliest deliberations in this post-anthrax outbreak era, the ACIP did not initially recommend AVA vaccination in addition to antibiotics for post-exposure prophylaxis. This was based first on the available experimental evidence which you've heard already, suggesting that animals treated with both antibiotics and vaccine show no clear-cut survival over animals treated with antibiotics alone.

And secondly, and perhaps more

practically, the fact that in those early deliberations, the AV vaccine supplies were very limited at the time and not available in large amounts to civilians.

Recently, however, the ACIP has reexamined the issue of post-exposure use of AVA vaccination in the light of several new pieces of relevant information. The first ongoing epidemiologic investigation suggesting that some persons may have been exposed to high doses of B. anthraces, infectious particles in excess of those studied in animal models.

The degree of effectiveness of antimicrobial prophylaxis in such individuals thus may be less predictable than in persons exposed to fewer particles.

Second, in a study of over 9,000 persons, which you've heard today about, these folks receiving antibiotic prophylaxis for suspected or confirmed exposure to B. anthraces, adherence to regimens ranged widely, from only 45 percent in Florida up to about 85 percent I guess in

Washington, D.C.

And so the effectiveness of antimicrobial prophylaxis when adherence is low may also be less predictable.

Third, an increased supply of AVA vaccine has become available for civilian use as you've just heard. The available vaccine comes from two lots, neither of which is currently licensed. Moreover, AVA is not licensed by the FDA for post-exposure prevention of anthrax.

Now, given all these three new items, the ACIP endorses the CDC making anthrax available as an investigational new drug and on IND to exposed persons.

In addition, the ACIP encourages the CDC to obtain serologic testing on a subset of vaccinees in order to determine the immunogenicity of AVA in its post-exposure use.

It was felt that although the observational study proposed under the IND will have some limitations, cons, if you will, it also has some pros. The first is that it may provide

additional protection for persons enrolled in this study. That's not clear, but it may.

It will allow collection of adverse event data among exposed persons in post-exposure settings and combined with ongoing surveillance of the exposed cohorts may provide data to support development of an additional recommendations for prevention of inhalational anthrax in the future.

When occasions like this occur, as devastating as they are, not only is it the duty of the Public Health Service to protect the public, all of us to protect the public, it's also our duty to take advantage of the opportunity to figure out how to handle such an emergency better in the future. Such an IND, the ACIP felt would help in this line.

Last, as you've noted, the ACIP has previously suggested that animal research studies of post-exposure prophylaxis including whether or not there's additional benefit of receiving anthrax vaccine in combination with antibiotics ought to be carried out.

In summary, I presented the perspective of ACIP as reflected in our recommendations to the CDC. The ACIP continues to be involved constructively by Dr. Koplan and the CDC as this anthrax crisis evolves.

DR. KOPLAN: Thank you, Dr. Helms. The next presenter is Dr. Inglesby from Johns Hopkins. Tom.

DR. INGLESBY: Thank you, Dr. Koplan. Dr. Gerberding asked us to come to present the judgments of myself and my colleagues at the Johns Hopkins Center for Civilian Biodefense Strategies regarding the utility of post-exposure vaccination in persons exposed to aerosolized anthrax spores in these attacks.

The factors in our consideration before we give our judgment about this question, the factors that we considered strongly in this judgment are: the clinical characteristics of inhalational anthrax, the evidence for spore latency which we've heard well described earlier this morning, the post-exposure prophylaxis strategies to prevent

delayed germination of spores, the evidence for vaccine efficacy and the vaccine safety profile.

I'll take these in turn. The first problem, as you all well know, is that inhalational anthrax resembles other clinical diseases. So for people standing in emergency departments, this is a very difficult problem. There are no early simple rapid diagnostic tests that can say, can help a nurse or doctor standing in an emergency room say sick or not sick from anthrax.

It's a constellation of lab tests, clinical signs and symptoms that would help people make these judgments which may not at all be clear at the moment of presentation. So this is a big problem in terms of management.

It's a rapidly progressive disease, potentially with high mortality as you all know, and it is unclear from evidence at hand when the illness will become refractory to antibiotic treatment.

So we conclude from this that a post exposure prophylactic strategy should be pursued as

opposed to an expectant strategy of waiting for symptoms to appear in patients.

Just to give you a sense, this is from a number of CDC studies combined, but these are the appearing or presenting symptoms or symptoms in patients who are presenting, which you can see are the same as many illnesses seen in every shift in every emergency department: fever, cough, chest pain, shortness of breath, nausea, vomiting, et cetera, very difficult to distinguish at the beginning of an illness.

The second factor is the evidence for delayed germination of spores. You've already heard this. I won't review it. But essentially there are a number of important studies: the study by Dr. Henderson in 1956, showing the long, the persistence of viable spores; the study reviewed by Glassman in 1966, which shows a fatal case in monkeys after 98 days following exposure; Dr. Friedlander's landmark studies; and the Messelson study in Science which recounts the experience in Sverdlovsk where there was an inhalational case 43

days after exposure.

So our conclusion from this: inhaled spores persist potentially for a long duration in host, in animal hosts, including humans.

Evidence for vaccine efficacy. We've already recounted today from Dr. Brachman himself the evidence for efficacy in his study. We also have heard about the evidence from the Federal Register of 1985: 27 cases of anthrax in the un-immunized occupational workers, zero in the immunized.

The evidence for vaccine efficacy in animals. This is, again, I should back up and say evidence for efficacy in preventive strategy as opposed to the post-exposure strategy. So the evidence in animal models, you've already heard this morning well recounted by Dr. Friedlander and others the animal evidence regarding a post-exposure vaccine strategy. There's also substantial evidence from USAMRIID and elsewhere regarding the efficacy of the vaccine in the preventive or in the post-exposure strategy in

animals.

The vaccine on day zero and two weeks was 100 percent effective. At eight and 38 weeks, against an aerosol challenge in one study, Dr. Ivins and collegues. Dr. Pitt, who is in the audience, and colleagues, in another study showed that vaccination at time zero and four weeks was protective in nine out of nine monkeys, and in a summary of the monkey data published by Dr. Friedlander, this summary showed that in 62 of 65 vaccinated monkeys, all survived subsequent to heavy aerosol challenge. Zero of 18 monkeys survived the same challenge. So there is ample evidence for vaccine efficacy if the vaccine is used in the preventive strategy, as a preventive strategy.

Correlates of immunity, just again to underscore what Dr. Friedlander presented to you in his study, antibiotic treated animals without vaccine showed no serologic rise. Vaccinated animals had a fourfold rise, and survived subsequent aerosol challenge when rechallenged

later.

Actually this is a mistake here. Dr. Ivins--this is actually Dr. Pittman's studies which will be published in the Journal Vaccine in 2002, and those studies show in a number of animal models that the vaccine produces marked rise in serologies in monkeys using a variety of different strategies: at zero and two weeks, zero and four weeks, and zero, two and four weeks. And that's to be published data in the coming months.

We've already heard a lot about safety so I probably won't even recount this, but essentially--this is now dated information--we've seen more recent information by Dr. Zoon today--but even back in 1999, we had quite a bit of information, and we knew there that there were 215 adverse events reported in the department of Defense series with 22 serious events reported, no causal events associated.

The Canadian armed forces studies shows similar side effect profiles although slightly higher, a mild reaction rate of ten percent, and

Dr. Pittman has recounted some of the work that he's now to publish in the Journal Vaccine in 2002, similar, very low profile of adverse events.

So, to summarize the conclusions that we take from these various factors: first of all, we would favor a post-exposure prophylactic strategy over an expectant strategy, waiting for patients to present with symptoms, because of the protium manifestations of this disease and the possibility that it could be missed in an emergency department.

The second conclusion is that inhaled spores may persist for a long time in the human host, and certainly that is evidence in the animal host.

The third conclusion is that a 30 day antibiotic course was insufficient for a number of animals in terms of complete protection, but an antibiotic and vaccine course for a similarly small number of animals was 100 percent effective in nine out of nine animals. The vaccine is protective against aerosol challenge if given ahead of time, and the vaccine has an acceptable safety profile.

So, our recommendation when asked if we would support giving vaccine to those who have been exposed to aerosol spores is yes, anthrax vaccine should be recommended for those persons whom investigating health authorities who have the most available information to determine risk or exposure determine to have been exposed to anthrax spores, and we would concur entirely with the IND strategy that's been proposed.

Thank you.

DR. KOPLAN: Next is a perspective from the local health department, Dr. Seigel.

DR. SIEGEL: Thank you, Dr. Koplan. I couldn't start without thanking Dr. Koplan and the CDC and all of our partners as we've gone through the anthrax event here in Washington, D.C. for a level of cooperation inclusiveness that bodes well for our ability to work in the future, and we're very, very appreciative of CDC for putting this event on today.

I think from the perspective of Dr. Walks and myself and Dr. Benjamin, I would just frame it

as really two simple questions: should we offer vaccine to those individuals from whom we are responsible for advising, and then can we logistically support such an operation?

The second question is pretty easy, I think, because the answer is yes, we can logistically support this. We have shown that taking care of some 17,000 people with prophylactic antibiotics, bringing them back for a second full course, which represented some 3,500 people in the D.C. Brentwood experience is possible.

And we routinely give flu vaccine to large numbers of people, both through the Department of Health, here, Maryland and Virginia, as does the U.S. Postal Service, and yesterday I had conversations with some of the medical people from the Postal Service, and they feel that in the event a decision were made to offer anthrax vaccine, that assuming adequate support from either U.S. Public Health Service personnel or through contract nurses, hopefully paid for by Dr. Koplan, et al.--

[Laughter.]

DR. SIEGEL: --the possibility of doing that would be relatively simple. So the answer to can we do it logistically is certainly yes. Should we is far more complex as we've heard today.

A couple of issues just to briefly mention. We, as I said, put about 3,500 people, 3,400 people on 60 day therapy, and our information, anecdotal, not complete, not fully validated, is that about half of those individuals are probably non-adherent, and of those, some 50 percent perhaps not taking their course of antibiotics, none of those individuals have become ill.

So individuals taking antibiotics are looking at the non-ill people saying why should I continue and nobody is getting sick, and therefore why do I need anything else? So the practical business of getting people to enroll in a vaccine availability study is going to be a challenge.

It's even more challenging when you think of the fact that this is an experimental vaccine that, as will be reported in the Washington Post

and other of the many media today has some issues attached to it, is going to be an additional challenge.

The availability, if we were to decide on using the quote "new vaccine," the best vaccine, the best batch of some 10,000 doses representing availability for about maybe 3,000 plus people when there are 10,000 people on 60 days of therapy, will again present some interesting questions about who gets what.

If offered on Capitol Hill to the 70 or 700 people, certainly it should be offered to Brentwood. We would certainly say that that would be a fair thing to say, and we certainly don't want disparity between one group of individuals and another group of individuals.

Whether we in the public health arena make that recommendation is still going to be at issue. As I spoke to USPS people yesterday, they said even if you guys decide to make this recommendation, we will take it under advisement and independently make a decision about whether we will recommend in

consultation with union representatives and others whether we will make the recommendation to our workers to participate in such a program.

So there certainly will be lots of questions that we will have to address. We need to be very careful, I think, when we are dealing with widely diverse populations as Dr. Walks has already mentioned that we frame this in a way that doesn't have connotations of past government offerings of experimental programs to individuals from minority groups.

So these are some of the issues that we would be challenged with, and I will just have to say for myself personally, as a physician, having been around for awhile now, that I am personally, and this isn't speaking for Dr. Walks or Dr. Benjamin or anybody else, I am personally unconvinced today that I would recommend to an individual patient that was on antibiotics, knowing that there is probably not great risk of those individuals getting inhalation anthrax, I probably would have a great deal of difficulty recommending

to an individual patient that they take the vaccine at this point.

Thank you very much.

DR. KOPLAN: Thank you, Dr. Siegel. And finally the last comments in this section from a state health department perspective, we've got Dr. Georges Benjamin from the state of Maryland.

DR. BENJAMIN: Good morning. Let me just say from that from a state health department perspective, there's really usually four areas of focus that we try to address when we look at these kinds of issues.

One is look at the science. Two is look at the mechanics of what we have to do. Three in terms of what resources we have to muster together to do this. And fourth are the communication challenges. We've really taken most of the science, but from the state health perspective, clearly we always want to know is there anyone at all at risk? And there's some evidence to suggest that that's true, and we need to be concerned about that.

The second question is can we clearly identify what that risk group is? I think we certainly have a construct to do that.

Do I have the tools to do an effective additional intervention? We have the antibiotic intervention. Do we have the tools and we're basically talking about vaccine here. And, of course, is it safe, effective and approved? And that's a debate that, of course, that we're going through right now.

Also, what happens if we don't do it? In other words, what happens if we do nothing? You know the first do-no-harm scenario, and can we effectively manage that if something happened, and we did nothing? In other words, can we get our arms around all those people that could be sick, and if it's a little event, probably so. If it's a big event, it may be a much tougher issue to deal with.

At the state health and also at the local health level, dealing with the mechanics of identifying, making sure we know who those patients

are, because that was truly a challenge for us on the antibiotic side. We need to make sure that if we go forward with this that we truly know which patients are in the study, and everybody in the region has got to know that, and all the various regions involved, making sure that we have clarity about patient education, informed consent. Very quick training of staff, the IM versus sub-cu debates have got to be resolved very, very quickly.

Liability issues need to be addressed very quickly. Long-term follow-up, particularly adverse reactions. Surveillance systems in place to make sure we're not missing anybody so that we've kind of defined who that high risk group is, but suppose that high risk group tends to be bigger, we want to make sure we have a system in place to identify those sentinel cases.

Most states have an IND process, an IRB process as well. And we may have to link this process at the state level for the IRB processes if state health workers are going to be involved. And there is a whole range of associated lab tests, and

obviously the protocols involved with that.

The resource issue obviously reminding everyone if we do this now, we are still in the height of doing our flu vaccination programs, and so we're obviously going to have to marshal additional resources in terms of people to actually make that happen.

And then the tremendous communication challenge that we're going to have with this. I think it's very important that we truly understand the message that we want to communicate, truly understand how to get that message to those that we believe are at highest risk, those that we believe are at no risk, and explain to them why they're not at risk. Elected officials, the other part of the public health and medical communities, and the media.

And then there is a small cadre of people out there who for one reason or another have requested the vaccine that have not yet gotten it such as public health lab workers, in particular, and there may be some other groups like first

responders that we're going to need to have to tailor that message to them as well.

This is obviously going to be a very difficult decision and a very difficult challenge, and obviously the states are willing to work with us to come to the right answer.

DR. KOPLAN: Georges, stay up here. We'll get the group up and have some discussion. Folks who made it through their conclusions, if you'd come up and you may have to expand or defend them. Can I just kick off the discussion asking you each, those of you who would make vaccines available, would you accompany the provision of those vaccine with continued antibiotic use through the course of the first three doses of the vaccine? Tom, you recommended making vaccines available.

DR. INGLESBY: Yeah. I think that is. It's an unfortunate situation that we're, you know, at the point of ending 60 days and having to talk about this, but I think it is inconsistent to advise a group that they need a vaccine because they're at continued risk of delayed germination of

spores and to not provide antibiotics. So I think we would concomitantly advise continuation of antibiotics until the vaccines had been administered. At least 30 days additional antibiotics.

DR. BENJAMIN: I'd agree with that as well, too.

DR. KOPLAN: Brad had a construct for levels of risk that he put up earlier. You've all, most of you have said make vaccines available for those at greater risk. Would the construct as presented make sense to you or would you have alterations on that as it was presented?

DR. SIEGEL: I think a threat assessment and a risk assessment is a really good thing, not only for this but for when we put out all of these threat analyses that come out of the federal government, period.

But one thing I didn't say was one reason to offer vaccine to the postal workers is that there is a continued threat of anthrax coming through the mail, and so that a positive reason for

being vaccinated would be for future, for pre-exposure prophylaxis of those first-line workers as well.

DR. HELMS: I would agree with that. I would think that particularly with the vaccine being relatively scarce, anything that could be done in a long run to identify and focus on a group of individuals at highest risk of recurrence would make a big difference.

MR. ASHER: I'm Mike Asher, HHS. Perhaps a semantic or a terminology issue. We used the words "investigational, experimental, licensed," and unless I have this wrong, let me see if I can state it correctly. It's a licensed product, it's not an experimental vaccine. The issue of whether investigation, the work with this vaccine would be considered investigation, is related to the fact that people would want to get information. So you might want to do this under IND to study some other variants or to get data on immune responses and other things, rather than just give it.

So it is, however, possible under law to I

think just give it. But I think everyone would agree that if you're going to do this, you would like to get the information, but there is no constraint on the use of this product from the standpoint of it being experimental. If that's wrong, let me know, Tom.

DR. KOPLAN: Dr. Zoon.

MR. ASHER: Is this experimental or licensed?

DR. KOPLAN: Kathy, you can just yell out the--

DR. ZOON: It's licensed for pre-exposure. It's not licensed for post-exposure. That would have to be a separate data, animal data and more--

MR. ASHER: Right, but that's different.

DR. ZOON: --as a supplemented indication on the license. Vaccine product in its formulations--but how it's used for different indications has to be separately considered.

DR. KOPLAN: Right. So wouldn't this be an off-label use of an already approved product?

MR. ASHER: To some extent, but I was

concerned that the comment was made that the newspaper is going to report this is an experimental vaccine. It's an experimental use or investigational use of a licensed vaccine. That's a big difference, because it means it's passed all the hurdles for licensing, which makes it a very acceptable vaccine.

And I want to follow up a little bit on Georges' comment, because I think that's an important point. We do a lot of recommending of other vaccines such as rabies where the risk is very, very low. And the reason we do that is the alternative is unacceptable, and unless I'm wrong, I think we have given out many, many doses of rabies vaccine for exposure to raccoons, and has there ever been a case of human rabies from raccoon virus?

Do you want to not recommend that and have the first case occur, and I think there's your point, George? I totally agree. The alternative is unacceptable.

DR. BENJAMIN: Yes.

DR. KOPLAN: Dr. Fauci.

DR. FAUCI: Jeff, I'd like to ask a question of Larry and Dr. Benjamin and others. You made the very important point that if it comes to the conclusion and the decision to make the vaccine available under the circumstance that we're talking about, namely post-exposure prophylaxis, that there has to be equality among the different groups because you have diverse groups is an absolutely critical issue.

You yourself volunteered the information that for you you're not so sure, and I totally respect that opinion, that you would be recommending that to the people that would come to you, given what you know now about the data that have been presented.

In addition to having equality among different groups that are very diverse, there has to be also the at least approaching equality of the availability of people to go to someone and say, well, what do you think? Now the people on the Hill have Dr. Eisold. Do you feel that the people

that you're responsible for under a situation where a vaccine would be made available, that they would have the opportunity to go to a physician, yourself or even a private physician, and say this is what I hear.

I hear that it's going to be given under, as Michael said, not experimental, but under an IND situation. These are the pros. These are the cons. This is an informed consent. Can somebody help me make a decision? Are they going to be able to have that availability to them to make a decision? Because the decision is going to have to be theirs. It's not going to be mandated. It might not even be recommended. The decision is going to be theirs. How do you feel about the cohort of people that you and that Dr. Benjamin and others are responsible for, and our colleagues in Florida and in New York also? Is there going to be relative equality of that availability?

DR. SIEGEL: Well, Tony, you know another echo from your and my long involvement with HIV because so many of these same kinds of questions

have come up over the years. My feeling is that part of the reason for the non-adherence in the Brentwood cohort was the fact that we had a single contact or two contacts with very little direct physician follow-up, whereas I think John had much more ability to have from his staff interaction with the Daschle group, and therefore more questions, more availability of medical input and perhaps better adherence as a result of that.

There's no question that there are discrepancies in availability of medical personnel who are trusted by different populations and are available in order to make those very points. So I think it's an additional challenge. I don't think it's insurmountable, but I do think that we would have to very carefully design the ability of the appropriate kind of people to interact with the individuals we're responsible for to make sure they had all the information, and truly were giving informed consent.

DR. BENJAMIN: The short answer is everybody should have the same access if we choose

to do it.

DR. FAUCI: But since it's going to be an informed consent, someone is going to have to explain to people what the risks and benefits are.

DR. BENJAMIN: Yes.

DR. SIEGEL: Yes.

DR. MITCHELL: I'm Clifford Mitchell from Johns Hopkins, Occupational and Environmental Health. A question on risk stratification, which is both from the point of view I guess of the administering party from a population point of view and also from an individual who is going to have to make a decision about this.

How would you stratify risk between somebody with moderate exposure but possible risk factors, particularly immune compromise of some kind, and someone with higher exposure with no other risk factors, a relatively healthy person?

DR. SIEGEL: And how do you find out that information when you're talking to people because the business of disclosing immune incompetence in a medical setting has a whole other set of issues

attached to it.

DR. INGLESBY: I would just add that I think that there is little data as it is, but there's far too little data to be able to make those judgments about whether a healthy person, you know, what the chances of disease are in a healthy person as compared to a variety of possibly immuno-suppressed states, and it seems to me just reviewing the 11 cases with inhalational anthrax and the ones that have died, a number of them have been apparently quite healthy.

So I'm not sure we can make any kind of cut between the prior disease status or comorbidity. And I'm not even sure that we can make scientific cuts at heavy versus moderate exposure. I don't know how we do that. I think, you know, Dr. Perkins provided the most logical construct yet I've heard in terms of risk stratification, but in the end his conclusion was that he wasn't certain that that should be the way that we do that, and maybe we have to treat everybody that we think was exposed to spores, and

that's the unfortunate position that we're in. And I think I agree with that.

DR. SIEGEL: And just to remake the point that was made earlier, that the heavy spore growth on the Daschle group was because those individuals were swabbed pretty quickly right after the event.

In Brentwood, perhaps with the same level of exposure, all 3,100 negative swabs were negative, but that was many days later.

DR. INGLESBY: Right, and just to add to that, that one of the cases in Brentwood who died had a negative nasal swab. So, you know, the operating characteristics of the nasal swab I don't think we should use as a cut for who gets whatever we decide is the right strategy.

DR. SIEGEL: And therefore any extrapolation of the dose exposure from that information.

DR. HELMS: In a practical sense, given antibiotics, one doesn't need a question in the first 24 hours what to do. But subsequently the use of the vaccine becomes the issue, and what is

arguing to me for is that these individuals become long-term involved with the system that's working this problem up, which means that the issues of whether they're immuno-compromised, perhaps HIV patients who don't want to talk about it, would be something that would have to come up in the right context and that the groups involved in caring for these folks have got to be sensitive to it.

PARTICIPANT: This is really a follow-up question to a couple of things that have already been addressed, Dr. Fauci's comment and a question about informed consent, and the characterization of an acceptable licensed vaccine made just previously by another gentleman.

But I want to ask the question in regards to some specific statistics. I guess I would address this to is it Dr. Inglesby.

DR. INGLESBY: Yes.

PARTICIPANT: You recommend the vaccine based on safety and efficacy conclusions. I notice that there was a study in Vaccine in this year, Vaccine magazine this year that Pittman wrote about

systemic reaction rates being 3.6 percent.

Our concern throughout the time that this has been an issue with the military has been that the people who have to take this vaccine don't necessarily view this as an acceptable vaccine, even though it is certainly licensed, and the reason is is that once you peel back the onion and start looking at some studies, and I'm curious to know what you have done with this information, because I'm sure you're well aware of the Trippler study showing--that was reported in the GAO report in April 1999 before Congress--reaction, systemic reaction rates being 48 percent, in which case the product label says the vaccine should be discontinued.

The obvious question is if you're going to have half the people taking the vaccine and getting this kind of reaction rate and shouldn't continue the series, then what's the point in giving the vaccine? That statistic was substantiated by Fort Bragg study showing 44 percent systemic level reaction rates, the Surgeon General of the Army

wrote attorney Mark Zade, saying that the reaction rate, systemic level reaction rate is somewhere between five and 35 percent.

These figures are as high as a quarter of a million times higher than the product label which says that the systemic level reaction rate is .2 percent.

So my question is when you give informed consent, you give people the information on the vaccine, is this kind of data going to be available for them to make judgments about the risk that they're taking compared to the studies that you showed on the slides of, you know, 3.6 percent that was published in Vaccine?

DR. INGLESBY: I think if possible, I would like to incorporate the smartest people in the room who have that data at hand. Maybe Dr. Pittman or Grabenstein or Dr. Zoon. I can't speak to each of those individual studies that you have that you have that you've enumerated here.

PARTICIPANT: I'll start with the 48 percent systemic reaction rate. We showed on the

slide the systemic reaction rates that Dr. Pittman showed if you sum up the numerals of the headache plus the muscle ache plus the fever plus the chills, plus the nausea, you can derive a numeral of 48 percent. That is mathematically it's correct, but it is taking it out of context of what the information provides.

What I consider the most reliable evidence for the physical outcome of the act of vaccination comes from a series of 2,800 service members vaccinated just south of the DMZ in Korea where if there was a 0.5 percent, a half percent, sick call rate among those people, if 48 percent of them, you know, if the numeral is 48 percent, we're going to see more than a half percent sick call visit rate.

So I forget how all this started, but effectively this vaccine has a safety profile like that of all other vaccines.

DR. KOPLAN: Ed.

DR. EITZEN: Yes. I wanted to start out by making a comment about the nasal swab, you know, we're talking about the congressional staff for

having a lot of positives and not many at Brentwood. We do have some limited animal data that would suggest that after 48 hours that the nasal swab will not be positive even when animals have had large doses aerosolized at them.

So that could be a possible factor, but also I know in this event that we've seen over the last couple of months, we've also seen people with positive nasal swabs days or even weeks out after the supposed exposure. So it doesn't necessarily hold, but a negative nasal swab later might be interpreted as possibly positive if it had been taken earlier. That's one comment.

The other comment I wanted to make was in regard to, you know, exposure risk stratification and risk stratification in general. The study that really worries me is that Canadian envelope study that was mentioned in one of the presentations that alluded to several hundred or even thousand LD50s of organisms possible in the immediate area of opening an envelope of a fine powder dry powder.

It worries me to think about residual

spores in that context, and again I don't have any data with which to say that other than just a concern that if the exposure level is so high, then is it possible even at 60 days that there would be enough residual spores to go on and cause disease?

DR. INGLESBY: Is it just spores in the environment or in the human?

DR. EITZEN: No, no. In the person exposed. And so I guess if I were, if I had a patient in front of me, and I'm a treating doctor knowing that, I'm not--I think I would have a hard time not recommending vaccination for three doses before antibiotics are discontinued.

DR. SIEGEL: Well, my understanding is there is no evidence in the post-exposure period in individuals treated with antibiotics for an appropriate period of time, there's any evidence that there's any breakthrough or inhalational or cutaneous anthrax in individuals treated in the absence of a second exposure.

DR. EITZEN: But we don't have any data? All we have is animal data.

DR. SIEGEL: Well, we have a whole bunch of people who are two months out now who haven't been on antibiotics who were exposed.

DR. EITZEN: But we don't know the level of exposure is what I'm saying.

DR. SIEGEL: Well, back to your earlier point. The fact that the Brentwood people had, you know, again, it makes the point that the nasal swabbing technique along with the other epidemiologic sampling is simply just that, epidemiologic. It isn't diagnostic. It doesn't in any way help us determine quantitative exposure.

So you know if somebody is standing at that machine, at machine 17 or whatever, where the Daschle letter got pounded, and got the big plume, which we know happened there, a whole bunch of people got exposed. None of those people got sick. Some are not taking antibiotics.

DR. EITZEN: Okay. I think valid point, but my point about the nasal swab was a separate point. I agree with you that that's just an epidemiologic tool and should not be used to assess

exposure risk. But I think that Canadian study was really worrisome.

DR. KOPLAN: There are four people standing. Please make your questions brief.

PARTICIPANT: I'm a reporter with the Washington Post and I'm asking this question now rather than afterwards because it has to deal with multiple people and it has to do with the number of people who might need vaccination and the amount of doses that were available. To follow up with Dr. Siegel said, if all 10,000 people currently getting antibiotics are given the vaccination, and each of them needs three doses, that would require 30,000 doses, and Dr. Zoon said that there were currently 10,000 doses in the licensable category.

And the remainder would have to come only in terms if there was an emergency. And secondly, if we don't include all 10,000 and you include only the high risk group, I was looking at one of the slides of Dr. Nancy Rosenstein, I copied it down rather quickly, it seems like the group that would be called high risk is still over 5,500 which would

still require more than 10,000 doses.

DR. ZOON: Thank you. I'd just like to make one clarification. At this point, there are more doses in FAV 063 than 10,000 doses. But that's the first basically amount DoD said that they would provide to HHS at this time. So I think--just a clarification. That's not the total number of doses in FAV 063, that there are additional doses available.

DR. SIEGEL: How many are there all together?

DR. ZOON: Excuse me?

DR. SIEGEL: What's the total number that there are in that batch?

DR. ZOON: I believe in that particular lot, it's around 165,000.

DR. KOPLAN: Let's move along. If you'll save, you three, you'll be first up in the next round of questions, but let's get this summary and then see where we are at that point. Julie.

DR. GERBERDING: Thank you. I have the challenge of trying to summarize some very

complicated information into a format that hopefully will succinctly do what risk communications are supposed to do, and that is to say that we know, say what we think we know, and say what we don't know.

So I'm going to try to do that, but I thought it would be worthwhile to start by just reminding us why we are here. We're really here today in the words of Dr. Walks to accomplish two things. One is to assess our options for preventing illness among persons who have been exposed, and secondly, to promote public trust in public health decision-making. By putting all the cards out on the table in front of our colleagues in HHS, the DoD, the stakeholders and the affected sites, the health departments and the press, we hope that we'll be able to get input and ultimately lead to the best possible situation under the current circumstances.

In terms of risk assessment, which was the first panel on this program, I think there are some things that we do know. We do know that efficient

B. anthraces aerosolation can occur, certainly with some of the powders that have been through the mail system in the last several months.

We also know that the exposure dose probably varies depending on how close you are to the source when it's released and how long you are in the period of release.

We know that despite our capacity to think about populations, we cannot accurately identify individual exposure, and we cannot accurately quantify individual risk.

So probably one of the key questions that we really can't use in making our decisions is what are the characteristics that really indicate higher risk? Dr. Perkins has put out some stratification criteria that probably make common sense, but we acknowledge that we don't really have the data to support this.

We have pieces of information, observations, and these investigations are all ongoing so we're still pulling this information together and trying to make the most sense out of

it as we can. But keep in mind the word "ongoing," because we're learning as we go.

We also believe there are some characteristics that might indicate a lower risk.

For example, no known direct exposure to B. anthraces powders or environments that have only focal contamination, but admittedly we have never defined what "focal" is, what "diffuse" is, what "widespread" is, what "heavy" is, what "trace" is, or any of the other pseudo-quantitative terms that we've been using to define exposure to risk.

From observation, we can say so far that people who are in groups with no inhalation disease and/or who have delayed antimicrobial treatment but no disease or with low adherence to antimicrobial therapy appear to be at low risk but time will tell whether or not that ultimately proves to be the case.

And there are some other questions that I think are very important in the context of risk assessment that have been brought up by several of the speakers here. One is what is the relationship

between exposure dose and incubation period? We have talked about the unusual incubation period being relatively short.

We know from the Sverdlovsk experience that it can be as long as 58 days if a plume is released, but we don't know whether or not people who've sustained lower dose exposures might have longer incubation periods, and that's a very critical piece of information in helping us assess the risk in a population because if there is a longer incubation period, then more time of observation has to occur before we can draw any conclusions.

How can environmental contamination be accurately quantified and used to assess exposure risk? CDC in conjunction with federal agencies from other parts of the government have been meeting frantically almost over the last couple of weeks to try to improve our risk assessment and risk quantification from environmental measurements, and while we can say that certain forms of environmental sampling such as wipe

sampling or vacuum sampling are more sensitive at detecting environmental contamination, we're a long way from being able to conduct a quantitative environmental risk assessment.

And the last question that was brought up earlier and importantly, which I think we will be able to provide some information soon, is does the serologic test data contribute anything to our understanding of risk assessment among the people who have phlebotomy. So far we're not finding anything particularly helpful here, but I think the data are still coming and Brad may be able to address specific questions related to that particular topic during the next question and answer period.

Now, moving on to the second part of the panel's today, the chemoprophylaxis panels, what do we know or think we know here, well, reassuringly, we know that among the persons who have been offered antimicrobial prophylaxis and taken at least some of it, we have no cases of inhalation anthrax. That is an extremely reassuring piece of

information, and I think that's one we should keep in mind as we deliberate all subsequent decisions.

And we also recognize that adherence is very variable and for some people it's very low.

There may be a correlation between individuals' risk perception and their ability to adhere to a regimen and, in fact, it seems that that correlates to some extent with our assessment of risk, but it's an imperfect correlation, and achieving 100

percent adherence, particularly among those at high risk or what we believe to be high risk of exposure is a very, very difficult challenge.

I can't think of any program at CDC where we've worked harder or tried more to promote

adherence among a very large group of people in a very short time frame, and yet we acknowledge that even at 30 days we are not at the levels that we would like to achieve.

We also know that antimicrobial adverse

events requiring hospitalization and emergency visits appear to be rare. We have not observed any at ten to 14 days and none so far have been

identified in the evaluations ongoing at the 30 day time point, but the long-term consequences of adverse treatment remain to be evaluated.

We all have some concerns about ciprofloxacin in particular where there may be reports of tendon rupture, neuro-psychiatric problems or other longer-term manifestations. So evaluation of both short-term and long-term antimicrobial safety and efficacy/effectiveness is going to be essential to really understand what is the impact of this treatment on individuals.

A key question in all of this has been repeated many times, both from the podium and from the microphones on the floor: do spores persist after antimicrobial therapy, and if they do persist, do they present a risk of germination in inhalation anthrax?

Now, we know that in non-human primates, spores can persist, and at least my interpretation of the data was that the initial dose or the exposure dose as well as the duration of time since exposure are factors that affect the number of

spores that might find on necropsy.

So far, in humans, we don't have any data even remotely approaching this. We have no cases of inhalation anthrax among the persons who have completed therapy and we have no cases among those not adhering, but it's far too premature to draw conclusions about whether ultimately any of these people will have spores that germinate.

Now, moving on the vaccine component of the presentations, what do we know or what do we think we know? I think we believe the vaccine is effective, though probably not 100 percent, very typical for all vaccines. This particular vaccine has some short-term side effects. Most of them appear to be local and self-limited. Serious reactions are rare, but there's a great deal of controversy about the data that are out there, and I think as many of the panelists have suggested, full disclosure and review of all of that data is a very necessary component of decision-making here.

And we all I think can agree that long-term evaluation of the impact of this vaccine in

any population is important and is ongoing and the data are not complete at this point in time.

The available vaccine is investigational for post-exposure intervention and informed consent is required. One of the available vaccine lots contains less preservative than required for licensure and again the controversies about the various lots and what's the appropriate lot to use is something that I think would necessarily be an important consideration in our deliberations.

And finally, and again importantly, our nation's vaccine supply is limited, and we have to make very careful decisions about how it's deployed.

One of the key questions here obviously is does adding vaccination plus 30 days of treatment decrease the risk of inhalation disease beyond that associated with the antimicrobial treatment alone? So for those who have actually completed the 60 days, is there any benefit or among those who actually were supposed to complete the 60 days, but couldn't adhere to the regimen, is immunization at

this time an important protective strategy?

We have delineated at the beginning, Dr. Henderson outlined for you three options that are the basis for the decisions that we will be facing in the next several days. First is to continue with the strategy of treating preventatively with 60 days of antibiotics and then stopping the therapy, encouraging people to continue with close medical monitoring.

And we have an option of extending the duration of treatment for another 30 days to try to make sure that any residual germinating spores are affected. And then, finally, to continue antimicrobial therapy for as long as people have taken it up to now and then add vaccine with the 30 days of treatment while the antibodies are being developed, so that would for some people end up to be 90 days of treatment total plus the immunization of three doses.

All of these options, whichever option is appropriate or options are appropriate, there are several factors that we will have to keep in mind.

Antimicrobial adherence support is necessary no matter what choice. Side effect management is going to be a very important aspect of any of these decisions.

Careful, short and long-term monitoring is absolutely essential. We will be learning as we go regardless of what options we have at our disposal, and finally empathy and equity for all of those affected by the decision must be the primary principle that dictates our decision.

These were the words that John Eisold used at the beginning of the meeting, and I think this is a perfect way to summarize our deliberations today. We are listening and we are learning.

Thank you.

DR. HENDERSON: We have time for additional questions and discussion. We thank you very much, Julie. I think that really summarized things beautifully. I think we want to conclude pretty much on time, so if you can keep your questions brief and answers the same. Yes.

MR. FARRANTO: My name is Al Farranto.

I'm with the National Association of Letter Carriers, and I was listening to the people who have gotten the vaccine, they talk about side effects and those kinds of things. My comment to the CDC people that are here, I just want you to understand that postal workers are not military people. The military people are relatively young and in good health.

Postal workers average middle age; they have all kinds of various things that they live with from diabetes to whatever you want to think of they have. To put them on a vaccine, who knows what types of side effects, what could happen to those people. Relatively now they're doing well with the current medication that they're on. Many of them decided not to take it because of side effects. And I'm not going to take up a lot of time with that. I'll have my opportunities to speak how I feel about it at the various places I deal with the Postal Service.

But I think we need to really think about this vaccine. There's a public perception about

vaccine. If we start putting postal workers on vaccine in a preventive way because of the threat of anthrax, that now puts the public confidence in the mail, there's a consideration there.

So there are a lot of things to think about other than just the medical theories and the dialogue I heard here today. There's a big picture here--public confidence, the people who work in the Postal Service, what could happen to them, and the types of things that have happened in the past. The CDC recommendations in the beginning, where we were trying to get people on the medication, they were told they didn't need it.

And now we're looking at, well, maybe they should be vaccinated? So we've come a long way in three months, but I just wanted to get my comments out here to you. We need to have a lot more dialogue and consideration, and we need to really, really think this out.

DR. HENDERSON: Thank you very much. Lynn.

DR. GOLDMAN: Yes. I' Lynn Goldman from

Johns Hopkins University and a couple of brief comments. I think that the last panel was very wonderful, and it was really great to hear the perspectives from Maryland and D.C. on this.

And I think there are some very critical issues about this if there is a decision to move forward in terms of the people who are going to be on the receiving end. And one has to do with simply how the assessment of the risk is done.

I think that what we've heard is that the weakest link in the chain really is our knowledge about exposures among those who did not become infected, and that there will need to--and if you do decide to go forward, there will need to be criteria that are established in terms of who would be determined to be at highest risk for anthrax and therefore requiring a vaccine and I would urge that you continue this process of making decisions in the open, sharing information and particularly sharing the information with the people who will be impacted, the workers and the unions, in that.

The other issue which is also kind of an

equity issue has to do with, again, if you decide to proceed, the issue of access to the medical care and monitoring that will be needed and the fact that I think that the model that's been used, which has been based on a public health model that's used for flu vaccine and other vaccines and is very good in that context, I think for this context that you might want to be creative and think about some different models that might also--and use the management of the workplaces, the unions, the workers themselves, not simply rely on public health clinics.

And I would hope that there might be a way to bring in more resources. Dr. Walks and Dr. Benjamin both mentioned the resources issue, but there do need to be the adequate resources to provide that kind of access to the medical oversight that might be needed.

DR. HENDERSON: Thank you. To the other side.

DR. CHASE: Two quick questions. One, is there any possibility of considering adding this

vaccine to those already covered by the I believe it's called the National Vaccine Act or National Vaccination Act? I'm guessing the odds of that are not real high.

However, the second question is could there nevertheless be produced a VIS, a Vaccination Information Sheet, that is standardized which would I think serve--or an equivalent to that--which would serve several useful purposes, sending a single message in communicating with the vaccinees between those who are administering and communicating with them and ultimately fully promoting trust as was suggested earlier?

But I'd like to put those questions out now. If they can't be answered now, I'm hoping that the responsible parties will take them into consideration in the week ahead.

DR. HENDERSON: I think to the first question I'm quite sure we can say there is no possibility of incorporating that into the vaccine compensation trust fund for a whole lot of complicated reasons, but could not be done.

For the second, I think your suggestion is good, and I think we just have to--we'll have to look at the strategy. If we were to put the vaccine out, it would have--we'd have to undertake a number of special initiatives here.

Phil.

DR. RUSSELL: Phil Russell from Health and Human Services. A small technical point, but I think it's important in considering the risk of delayed germination of spores. And that is most of the, if not all of the, experiments that we've seen were done with wet aerosols and these were spores derived from either fresh wet cultures or frozen, wet frozen cultures.

The risk we're dealing with here is a lyophilized dry powder, and if that has any effect on the time to germination, it probably prolongs it, and it may be a significant factor, and that would increase the level of risk from the dry powder.

DR. HENDERSON: Thank you.

DR. KAWAMOTO: Melody Kawamoto. I'm from

CDC/NIOSH, the part that's concerned about workers' health. I have a concern and a question. My first is the concern about trying to use traditional risk assessment methods or qualitative or quantitative for a low risk disease. My feeling is that using epi data for decisions, especially when, you know, based on people who aren't taking antibiotics and the cohort that had colleagues/coworkers with inhalational anthrax, I feel that because it's such a low risk disease, we cannot really take this information or accept it with great confidence.

So I'm not sure that using that kind of thinking is really going to be helpful, especially if, you know, when we say the alternative is not acceptable. I think it's a point that should be considered.

And then for the three options that were given, I think there is a group that has been left out, which would be option four. For those who weren't able to tolerate antibiotics and who had a credible risk of exposure, I think that maybe they should be considered for the vaccine because they

don't really have any other option.

DR. HENDERSON: Thank you. Jeff, do you have any comment?

DR. KOPLAN: No.

DR. HENDERSON: One last comment.

DR. WALKS: Ivan Walks again. I really want to start by thanking the Centers for Disease Control, Dr. Koplan, Dr. Henderson, for holding this sort of a forum. It's refreshing to have this sort of discussion take place in public where people can see that we are learning.

One of the challenges we had here in the District was that a lot of the comments made early on after the Daschle letter was opened sounded like typical doctor comments. They were given with a lot of confidence and we really knew what was going on, and I think that Dr. Gerberling did a tremendous job in saying a couple of times what we don't know, what we don't know, what we don't know.

This admitting in public that sort of the brightest and the best, and I'm just visiting with you guys, don't know a lot is a tremendous, I

think, refreshing thing for the public to hear.

But I think what we can do is to use this opportunity to partner with folks like the folks here from Hopkins, maybe some folks from the American Public Health Association, to help them help us craft a message that goes out to not just the public we're talking about, but all of the docs and the nurses out in the public.

We have a tremendous opportunity and obligation, I think, to teach the folks who really touch the people on a day to day basis, and that whole education piece is one we have to do.

And my last comment, and I will be brief with this, is that in talking with pharmaceutical companies in the past about how they do the drug testing on their way to FDA approval, there is not a diverse population of physicians that tends to interact with that group, and so you don't get diverse patient populations as part of the studies and so you wind up with things like Haldol doesn't work as well in African American men without side effects as the profile tends to look on the label.

Those kinds of things I think we can avoid maybe if this is the beginning of a different kind of way that we talk to each other, talk to the public, and then include those educators so that we can reach a diverse population of providers and then a diverse public population. We can really change the entire paradigm of how the public views medical information coming out of the experts.

So thank you.

DR. HENDERSON: Thank you very much. I think to me this has been an extremely useful discussion, and I think all of you who have attended and have participated are to be thanked for this because I think there are a variety of points of view here, and it's quite clear as we are illustrating again and again, that there's a lot we don't know.

I think there is a feeling on the part of some, I'm sure, of why don't you know? Where has medical science been in the last 25 years? And the fact is I think we had Art Friedlander almost alone. There were very few people working on

anthrax at all once we closed down our weapons program, and here was this lonely man. Suddenly people have found this disease, and indeed there has been very little financial support, and it's a very peculiar disease, as you've heard.

It's a very strange disease with these spores germinating after a great delay and giving us a paradigm such as I can't--I just don't identify in the rest of infectious diseases. So it's given us something very new to look at that has been very puzzling.

A certain amount of work has been done with monkeys and I was glad that Art put up his indication of just had difficult it was to do a group of studies with monkeys. It is expensive, it is time consuming, it is expensive in manpower. And at this point in time, monkeys are in extremely short supply, and that's posing yet more problems. So that it has not been an easy subject to address, and I think the fact we don't have more knowledge is we can be thankful, because if we had more knowledge, we would have had many more human cases

to have acquired that knowledge, and that we would just as soon not have.

I think we can say the experience so far has indicated that the antibiotics as we've used them have been extremely effective. Certainly this has been quite remarkable and we've not apparently --we'll knock on wood--we're not there yet, but we have not had any failures of individuals put on antibiotics, but then, of course, we have not had any other cases either of a greatly delayed onset.

As you may know, we have now or will soon have enough antibiotics to treat as many as 12 million people for 60 days.

In fact, we can deal with populations now, we feel, as large as 20 or 25 million if we had to with the antibiotics that we have. And this, I think, should be reassuring, certainly to dealings in a responsive mode to an attack should it occur.

Distributing that vaccine will be an enormous problem. The antibiotic would be an enormous problem, and this is something that we're going to have to be working on in the months and

years ahead.

I think a vaccine which would be what we call a second generation vaccine would be a great advantage, and we're certainly, at this time, this is very high priority in government to move ahead and try to develop a recombinant vaccine which would have ever fewer reactions than this, and would be much easily standardized so that we would have a consistent good product.

One can't make any promises as to how soon that will be available, but it is really on a fast track at this point with Dr. Phil Russell working on this, and Tony Fauci from NIH. Kathy Zoon and the CDC group and making a very strong group with our friends from USAMRIID who are doing a lot of work as well.

So it's across government operation. I think we could agree that there's enough evidence out there and things we don't know which suggests that there is something we need to be a little more careful at looking at beyond 60 days. I think that would be a reasonable conclusion to reach. The

very much larger dose that certainly some people have gotten is very different than we had anticipated in the first place. The aerosolization from the envelopes from this Canadian study were a great surprise to them and certainly a surprise to us as we saw that data.

And yet we've had no cases that go beyond 60. I mean there are no human cases. It's inferential data based on a very few monkeys, something of what we know about spores, but still we don't have any human cases that have gone out to that time.

And so it's a little difficult to know what the risk is. It's more of a sense that there might be a problem there, and the question what do we do about it? Certainly, I think there are three perfectly logical channels to follow, one being that those who choose to take notion, we have identified many of the people who have been in an areas where a lot of powder or spores have been present who we would think might be at somewhat higher risk if it is there.

And for them to be in touch with their physician and certainly to identify themselves quickly if they come down with the disease and say I think I have been exposed to anthrax and therefore ask that special concern be given to getting antibiotics maybe earlier than you would otherwise.

So I think there is a perfectly reasonable option here that would be very good. And the failures we've seen have been failures in individuals who did not get early treatment. I think those that have gotten early treatment have done quite well.

And I think we're looking at case fatality rates which are certainly well below those which we've quoted in the literature.

The second option are antibiotics and here we have again I think it's been quite successful. And yet antibiotics taken over a period of time, as we've heard, are very unpleasant and the further one goes, I think the more likely one is to get into trouble with the antibiotics. So that's a

negative side of it. On the other hand, this has seemed to work perfectly well.

And we've discussed the question of a vaccine and should vaccine be made available purely to those who would like it on purely a voluntary basis, and to say we have the vaccine, it does have some adverse reactions, you've heard there are adverse reactions involved here. Is it going to be that much better? Is it worth your while to tow for 30 more days on an antibiotic and then to take the three doses of vaccine? I think adults dislike shots more than kids do, to tell you the truth, and I think there's going to be some adverse feeling about having three inoculations, and this is a vaccine, which as you've heard, it has regularly some systemic reactions and pain in the arm and so forth.

It's not exactly the most pleasant vaccine to take, but it is proven to be effective. So that if the vaccine were to be offered and, as I indicated at the beginning, we will be consulting and advising the Secretary on this, and coming,

hopefully having a--well, we expect to have a decision on that very early in the week, that it would then be made available to individuals with an indication that this is to be done as an investigational treatment.

At that point, there will be need to explain to all concerned about the drug, I mean about the vaccine, and there would certainly have to be a systematic follow-up of all those who have received it.

So these are the three approaches that are here. As I say, I think the one thing that we would all could concur in is the feeling that there is a concern beyond 60 days, maybe out to 90 days, and now how much concern I think is very hard for any of us to measure, and I think that's where we are.

So I think with those few words, I'd propose that we conclude the meeting. I'd ask before concluding whether Jeff would like to have a few words or, Tony, would you? Kathy? All right. We then I think can stand adjourned, and I thank

you all very much for your participation.

[Whereupon, at 1:30 p.m., the meeting was adjourned.]