

Transcript for program “**CDC Responds: Update on Options for Preventive Treatment for Persons at Risk for Inhalational Anthrax,**” broadcast Friday, December 21, 2001, 12:00 noon-1:30 pm (EST) from the Centers for Disease Control and Prevention, Atlanta.

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*Lisa Rayam:*

Hello, I’m Lisa Rayam. Welcome to this program, “Update on Options for Preventive Treatment for Persons at Risk for Inhalational Anthrax.” This broadcast will present to you, our audience, an update on prophylactic treatment options for persons who were exposed to anthrax spores. CDC is committed to providing updated information --- with programs such as this --- that deal with important clinical and public health issues.

The objectives of today’s program will enable you to

- understand the rationale for three treatment options,
- describe the recommended protocol, IND, consent issues, and efficacy of the anthrax vaccine and
- discuss prophylactic antibiotic efficacy and safety issues.

Now before we continue, here are important contact numbers you will need if you have trouble receiving the program during our broadcast. For technical assistance in the United States, please call 800-728-8232. The international technical assistance number is 404-63-1289.

If you would like to ask our panel questions during this broadcast, if you are in the United States, for voice calls, the phone number is 800-793-8598. To fax us, the number is 800-553-6323. We also have a TTY number for the deaf and hard of hearing. That number is 800-815-8152. If you are viewing from outside the U.S., for voice calls, the number is 404-639-0180. To fax us, the number is 404-639-0181. And the TTY number is 404-639-0182.

And now, remember, the phone numbers will only be answered during the broadcast. Please don’t try to use them after the program. But if you do have additional questions after the broadcast today, fax them to 800-553-6323, if you’re in the U.S., or 404-63-0181 for our international viewers.

Now, I would like to introduce you to Dr. James Hughes, Director for the National Center for Infectious Diseases here at CDC in Atlanta who would like to begin our program with a few words concerning bioterrorism and the risk of inhalational anthrax. Dr. Hughes, welcome.

*Dr. Hughes:*

Thank you, Lisa. Hello. I’m Dr. Jim Hughes, Director of the National Center for Infectious Diseases at CDC. Thank you for joining us today for this next program in the clinical education series, “CDC Responds.”

Since early October, CDC and many other partners have been responding to an unprecedented bioterrorism attack resulting from the dissemination of *Bacillus anthracis* through the US postal system. 22 persons with anthrax have been identified; 11 people have developed inhalational anthrax, and 5 have died as a result. Many more people have been exposed to anthrax spores, putting them at risk for development of inhalational disease. Persons known or suspected of

having exposure to airborne anthrax spores have been prescribed a regimen of 60 days of antibiotics --- we believe that many infections have been prevented as a result of this prompt action. However, we are concerned that the risk of infection for persons who were exposed to high doses of spores may extend beyond 60 days. As you will hear, only limited data are available to assess the magnitude of this risk.

Unfortunately, there is little recent clinical experience with this disease in the United States, and we continue to learn about the illness. In today's broadcast, you will hear what we know and what we don't know about this risk. A panel of experts from CDC will provide an update of the three options for at-risk people who are completing their 60 days of prophylaxis.

We also want to remind our viewers that until the perpetrators are caught, another bioterrorism attack could occur. Therefore, health-care providers, laboratorians, and public health officials must remain vigilant for cases of anthrax. On behalf of CDC, thank you very much for joining us for today's program.

It's now my pleasure to introduce Dr. Julie Gerberding who will act as the clinical moderator --- as well as a panelist --- for today's program.

*Dr. Gerberding:*

Thank you. Welcome to this episode of "CDC Responds" as we explore the options for optimizing the prevention of post exposure anthrax. I'd like you to introduce you to the various members of the panel today.

First Dr. Bradley Perkins, the chief of the Special Pathogens Branch at CDC and a senior anthrax scientist. We also have Dr. Jai Lingappa, an epidemiologist and another anthrax expert. And finally we have Dr. Nancy Rosenstein, a medical epidemiologist, who is especially familiar with the consequences of chemoprophylaxis following anthrax exposures.

This program is directed towards clinicians. We hope it will help you get the information you need to address options with patients and make the best possible decision in this time where we don't have enough scientific information to be more directive. So I'd like to start by asking Dr. Perkins to give us the background data which will to help provide the context for making decisions about treatment.

*Dr. Perkins:*

Thanks very much, Julie. On Tuesday of this week, a decision was announced to provide additional options for persons exposed to *Bacillus anthracis* spores. Those options include maintaining the earlier recommendation of 60 days of antibiotics with medical monitoring.

The first new additional option is to obtain and take 40 days of additional antibiotic treatment with medical monitoring. And the second additional option is to take 40 days of antibiotic plus three doses of the anthrax vaccine over four weeks with medical monitoring.

Prior to the recognition of the first case of inhalational anthrax in early October in Florida, the Advisory Committee on Immunization Practices - the ACIP - had already made recommendations

on the use of antibiotics and anthrax vaccine in settings of post exposure prophylaxis. These recommendations were published on December 15<sup>th</sup>, 2000, in the *MMWR* [CDC's weekly publication, *Morbidity and Mortality Weekly Report*]

At that time, they recommended post-exposure prophylaxis following aerosol exposure to *B. anthracis* spores. They suggested that antibiotics for at least 30 days be used; that is, antibiotics be used for at least 30 days when used alone and that longer therapy, based on data available may be indicated. They suggested a range for that therapy of 42 to 60 days. They also suggested that if anthrax vaccine was available, antibiotics could be discontinued after three doses of vaccine at zero, two, and four weeks.

Following the October 3<sup>rd</sup> recognition of inhalational anthrax in Florida, subsequent investigations were initiated in New York City on the 12<sup>th</sup> of October, in Washington, D.C. on the 15<sup>th</sup>, and Trenton, New Jersey on the 17<sup>th</sup>, and finally - and most recently - Oxford, Connecticut on the 20<sup>th</sup> of November. During this time, a number of public health decisions, actions and options were explored regarding post exposure prophylaxis. As soon as the case of inhalational anthrax was recognized in Florida, CDC filed an investigational new drug application with the FDA to use anthrax vaccine as an adjunct in post-exposure prophylaxis. Following the recognition of the risk associated with the American Media Incorporated (AMI) building in Florida, we decided to use 60 days of antibiotic therapy as the principal treatment for post exposure prophylaxis.

At that time we reconvened the Advisory Committee on Immunization Practices and they endorsed the routine use of 60 days of antibiotics as the primary treatment for post exposure prophylaxis. We simultaneously began negotiations with the Department of Defense, who at this time was the sole owner of anthrax vaccine in the United States, and obtained approximately 217,000 doses of anthrax vaccine to use as we saw fit as part of public health response to this epidemic. We reconvened the ACIP and they encouraged the provision of this anthrax vaccine under the investigational new drug (IND) application to be given to exposed persons in the context of this investigation.

During the course of this investigation, we confirmed 22 cases of anthrax, 11 Inhalation and 11 cutaneous cases. This graphic shows the number of cases over time and also shows when the identified envelopes contaminated with *Bacillus anthracis* spores entered the mail system at the Hamilton, New Jersey postal facility. You can see two peaks or two increases in the number of cases across all sites following the introduction of those envelopes into the mail system.

Now, I think it's important at this point to emphasize what Dr. Hughes said - that this is an unprecedented biologic attack - and although this epidemic curve looks like many epidemic curves associated with biological phenomenon, and had to learn during this investigation about risk to individuals associated with this criminal activity. As a result of this investigation, we recommended that approximately 10,000 individuals take 60 days of antibiotic therapy for prevention of inhalational anthrax. These courses of therapy were initiated between October 8<sup>th</sup> and - most recently in Connecticut - November 25<sup>th</sup>. We were primarily targeting persons with occupational exposures, media outlets, postal workers, and congressional staffers that had been exposed during the bioterrorism attack.

I'm going to review some of the technical basis for these newly recommended options. It starts awhile back, and I think this quote captures it very well. In 1947, when Dr. Barnes recognized that persistence of spores in the tissues after their germination was a critical aspect to the pathogenesis of anthrax infection.

There are two key non-human primate studies that I'd like to briefly review. One published by Henderson, et al., in 1956, and the other published more recently by Dr. Art Freidlander within the Department of Defense in 1993. I've noted there on the graphic that each of these were challenge experiments using Rhesus monkeys. These non-human primates received aerosol challenges of between 4 and 8 lethal doses; 50% doses with one LD50 representing approximately 50,000 spores. This is important as we consider some later data that I will discuss.

These data show survival curves, with the survival time in days. You can see the survival of controls that received no antibiotics and were challenged with aerosol spores. All of them died over the course of eight days. Survival could be improved by treatment with antibiotics after exposure to aerosolized anthrax spores. The first treatment group received five days of penicillin, and all that really did is shift the survival curve to the right. All of the animals eventually died, but they died over a longer period of time. He also did experiments giving animals ten days of treatment and 20 days of treatment. You can see on the survival curves that there is some improvement in overall survival by lengthening the duration of antibiotic therapy following aerosol challenge with *Bacillus anthracis* spores. However, even in animals that received 20 days of penicillin therapy, survival was less than 50%.

This is also an important experiment done by Henderson, et al. This shows the potential benefit of the addition of vaccination to antibiotic therapy. On the survival curve labeled "A" at the far left, you can see, again, all ten animals included in this group died within five days after aerosol challenge. On the survival curve labeled "C", this is again similar to the early graphic where animals received 10 days of antibiotics, and the survival curve is shifted to the right, but all ten animals died before 20 days. However, if you look at the flat lines at the top of the graphic, you see that all animals that received vaccine prior to exposure, as well as animals that received a combination of 10 days of antibiotics plus vaccination, survived for the duration of study follow-up, suggesting the possible benefits of vaccine in addition to antibiotic therapy.

This is an important slide, and what we have done here is to model the *Bacillus anthracis* spore clearance data from the 1956 paper by Henderson. On this graphic you see on the y-axis the percent of original spore retention, and on the x-axis you see the days after exposure going out to 100 days. The dark line is a logistic regression fit. The data in the Henderson paper, and the dash lines are 95% confidence intervals around that line. What this suggests is that over a period of 60 days, you get an approximately two-log reduction in the amount of *Bacillus anthracis* spores in the lung. So, for most low or intermediate levels of spore exposure, 60 days of antibiotics alone may be sufficient to clear *Bacillus anthracis* spores from the lung, and diminish or eliminate the risk of inhalational anthrax disease following the cessation of antibiotic therapy. However, for higher dose exposures, 60 days of antibiotics alone may not be enough to completely eliminate the risk of inhalational anthrax.

This is another set of survival curves from the more recent paper by Dr. Art Freidlander. This is consistent with the earlier data, but Dr. Freidlander used rhesus monkeys and gave them 30 days of antibiotics rather than the five, ten and twenty days given by Dr. Henderson. You see the two curves below the legend box. One is the control curve. All but one of the animals died over the first ten days. It's also interesting to note that animals that received vaccine alone following exposure also died at the same rate as the controls. However, when the animals that had received 30 days of antibiotics alone, after challenge they all did very well during the 30 days of antibiotics; there were not no deaths, but there were few deaths: One to two per each group in all of the groups - except the group that received the combination of doxycycline and vaccination. However, it's important to note that in this study, there was no statistical difference between 30 days of antibiotics alone and 30 days of antibiotics with vaccination.

This graphic shows the Senate-bound letters that have been identified to date. The letter on the top addressed to senator Daschle was actually opened in Senator Daschle's suite and a number of people were exposed. The letter addressed to Senator Leahy was actually not delivered and was identified subsequently after the Senator Daschle letter had been identified. The quality of the powder contained in these letters gave us some important information about the extent of aerosol risk that persons may have experienced along the chain of transit of these envelopes, as well as in Senator Daschle's office where one envelope was opened.

These [prophylaxis] options are especially relevant in the context of a recent study by the Defence Research Establishment Suffield, Canada. This work was conducted between February and April of 2001, this year. They did this research in response to the numerous hoax events that we have experienced for the last several years regarding persons claiming to have sent *Bacillus anthracis* in letters. To try to estimate the risk of threat letters that may actually contain *Bacillus anthracis* spores. They obtained weapons-grade *Bacillus globigii* spores. These spores are quite identical to *Bacillus anthracis* spores but pose no health risk. They used them to simulate a potential release of *Bacillus anthracis* spores; they did this in an 18-foot by 10-foot by 10 foot chamber simulating an office-sized room for release. They sat a technician at table. They put 0.1 gram and 1 gram in envelopes of the reagent. And they had the technician open these envelopes. Then using extensive sophisticated aerosol sampling techniques, they were able to estimate the amount of contamination that occurred in the room. Based on these data, they estimated that over a 10-minute period following the opening of these envelopes, an estimated 480 to 3,000 LD-50s could be the potential aerosol exposure. This is much higher than the aerosol exposures that were delivered in the non-human primates on which our chemoprophylaxis recommendations are based.

In conclusion, among persons with heavy exposures to *Bacillus anthracis* spores, 60 days of antibiotics alone may not eliminate risk of inhalational anthrax. Additional antibiotics or antibiotics and vaccine may provide benefit to persons who remain at risk for inhalational anthrax after 60 days of antibiotics alone. Thanks very much.

*Dr. Gerberding:*

Thank you, Brad. That was excellent summary. I think it helps us understand why we are here. That is, we can't be sure that the people who have gotten the highest exposure to anthrax are really not going to get inhalational disease after their antibiotic treatment.

Now, let me turn next to Dr. Jai Lingappa who will tell us about the program that's available for anthrax vaccination, how the program works, and what we need to know about getting patients enrolled if that is the appropriate decision.

*Dr. Lingappa:*

Thank you, Dr. Gerberding.

The objective of the anthrax vaccine and antibiotics availability program is to make antibiotics and vaccine available to those people who have had a high dose exposure to *B. anthracis* spores.

Persons who have been exposed to high doses of anthrax spores and were directed to take 60 days of antibiotic prophylaxis are eligible to enter the program. There are no specific exclusion criteria for eligibility.

As Dr. Perkins has gone through, there are three options that are available for the persons who are eligible for this program. The first option is to continue with the original recommendation of 60 days of antibiotic therapy and continue onwards with medical monitoring.

The first additional option available to people who decide to enroll, and participate in the Program, are to continue with 40 additional days of treatment alone, and follow on with medical monitoring.

The second additional option that's available to participants is to continue the 40 additional days of antibiotic treatment along with three doses of anthrax vaccine given over a course of four weeks, and follow on with medical monitoring.

As a part of this program, the anthrax vaccine would be delivered in a three-dose schedule with the first dose given at start in the program and second dose given two weeks. After that, a third dose would be given at four weeks into the Program.

Now, for all adults who are enrolled in the program, the vaccine would be given via subcutaneous route, since this is the route that's actually licensed for pre-exposure vaccine. For that small number of individuals - children and older adolescents where the vaccine does not have a licensed route - we'll use an intramuscular route in this program since there is some limited data that there may be lower rates of local side effects through an intramuscular route.

In terms of the risks involved for patients who decide to become participants in this program, risks from antibiotics are primarily hypersensitivity reactions. In addition, there are reactions of photosensitivity, primarily associated with ciprofloxacin and doxycycline, and tendonitis associated with ciprofloxacin. Although not contraindications, tetracycline and doxycycline have been associated with dental staining in children under seven years of age, as well as prenatal use of the antibiotic. Ciprofloxacin has an unproven association with bone and joint formation problems during use during pregnancy.

In terms of the risks associated with the use of the vaccine, there have been a variety of studies looking at the use of the vaccine, again in a pre-exposure setting. In those studies, local reactions, including soreness, redness, itching and swelling have been noted with increased rate of reactions

among women. In addition, many people will have a lump at the site of the injection, and that usually lasts a few weeks and goes away on its own.

Systemic reactions have been noted, including rashes, headaches, malaise, muscle aches and fever. These usually resolve in a few days. There are rare reactions such as severe allergic reactions that occur in less than one per 100,000 doses. In addition some reactions such as Guillian Barre syndrome have been reported as connected with this vaccine. However, no causal association has been made with these more rare reactions and the anthrax vaccine.

The benefits for joining the program are based on the fact that we do not know that there what the risk of disease is among people who have been exposed to anthrax spores and who have taken 60 days of antibiotics. However, if there is a risk among these people, then 40 days of additional antibiotics or 40 days of additional antibiotics and the vaccine may be of benefit in reducing that risk of disease.

Now, the antibiotics used in this program are considered investigational --- for two reasons. One, no antibiotic that's been recommended is approved for use beyond 60 days of prophylaxis for inhalational anthrax. In addition, one of the drugs that's being used in this program, amoxicillin is not approved for use as prophylaxis against inhalational anthrax.

In addition, the anthrax vaccine used in this program is also considered investigational --- for three reasons. First, the vaccine is not approved for post exposure prophylaxis. Second, the vaccine is not approved for a three-dose regimen. And third, the lot of vaccine to be used in the program is currently not approved for commercial use. So, in discussing this with patients who are considering enrollment of this program, the consent document includes focus on three issues:

- 1- there is no data to predict if vaccination or vaccination plus antibiotics will be of benefit when used after exposure.
- 2- the vaccine is not approved for this particular post-exposure use, and
- 3- the lots of the vaccine that are used within this program is not licensed by the FDA.

Thank you. I'll stop there.

*Dr. Gerberding:*

Thank you very much. I think we have heard something about the rationale for considering options, and a description of the program that we are offering to those persons who are exposed. Now I'd like to hear from Dr. Rosenstein a little bit more about the chemoprophylaxis, because the options do include more days of antibiotics. I think it's important to know what the experience has been with the antibiotics and what have we learned so far. Are they safe and can people really take them?

*Dr. Rosenstein:*

I will talk about the use of antibiotics for post exposure chemoprophylaxis. Approximately 10,000 people were offered 60 days of post exposure prophylaxis. The first group from Florida started antibiotics around October 8<sup>th</sup>, and the last group from Connecticut began their antibiotics around November 25<sup>th</sup>. Most of the people who are on antibiotics are associated with one of six sites, and

principally these are occupational groups; most people are either employees at AMI in Florida, postal workers, or congressional staffers.

Today I'll discuss the denominators and demographics from the current individuals on post-exposure prophylaxis, the adherence promotion activities, and early data on monitoring events associated with antibiotics. This graphic gives you a breakdown of the number of people offered and taking antibiotics by site. I've also tried to provide - in the third column - individuals who may fit into categories that we're calling "those potentially at higher risk." And where possible, I'll try to provide data for people in whom antibiotics were recommended and groups that may be at higher risk for development of inhalational anthrax.

This graphic gives you an overall breakdown of the demographics by site. Approximately half to two-thirds of the individuals are male. Very few of the women have been pregnant. The racial breakdowns do vary by site. Overall, most individuals are in the 18 to 64-year-old age groups but there are somewhere between 1 and 5% of people who are less than 18 years of age, with the highest proportion of people less than 18 in Florida. These are primarily visitors to the AMI building. In addition, there is somewhere between 0 and 5% of people who are over 65 years of age.

Our activities to promote adherence have evolved as we learned to best promote adherence during this difficult and stressful situation. This slide lists of the things that we have done in some or all of the sites. There has been extensive distribution of educational material. There have been telephone calls to individuals who did not return for refill medications. Small group meetings have occurred in all of the sites. And there have been health fairs where we have a variety of individuals with different expertise; for example, with expertise in antibiotic side effects who can counsel people regarding the risk and environmental contamination. There has been counseling done in collaboration with the state and local health departments.

We're doing a number of things to try to monitor adherence. Some of the data is based on counting the number of individuals who returned to get antibiotic refills. We are doing cross-sectional evaluation at seven to 14 days, and again at 30 days. These are standardized questionnaires that are self, nurse or telephone administered. Participation in the surveys has varied by site between 50 and 100%.

I'm going to give you some of the early data results but please recognize that data collection and analysis are ongoing. This graphic shows the number of individuals who are reporting taking antibiotics by site. As you compare the data at 10 to 14 days versus 30 days, you can see that the adherence falls during the course of this. In Florida at 30 days, only 45% of the individuals reported taking antibiotics. However, adherence among the higher risk group potentially - of people who are employees at the Ami building - is actually 70%. In Capitol Hill, there is 88% adherence at 30 days, but as far as we can tell, all of the Daschle workers for whom Information is available are still taking their antibiotics. In New York City, adherence at 30 days is 40%, and this is even among the potentially higher Risk group of people working on certain floors of postal facility.

Well, that data was really the number of people who we think are taking antibiotics. But as we look deeper into that, we get this data. I'm looking specifically at two cohorts, the New Jersey and

Washington, D.C., postal workers. In the people in this cross-sectional survey, 88% overall reported taking antibiotics. But if you ask for more details - for example, did they take the antibiotics yesterday? Or are they taking their antibiotics every day? - you can see that the numbers are actually lower. We also know that self-report actually overestimates adherence by as much as 20%.

This graphic compares adherence by antibiotics with ciprofloxacin and doxycycline at 30 days. You can see that adherence is similar between the two antibiotics.

I'll next turn to talk about adverse events. We have two concurrent systems to monitor adverse events. One is an ongoing passive surveillance system and on top of that, we have the surveillance at 7 to 14 and 30 day evaluations. We do screening with a questionnaire, and further events are evaluated during interviews with patients and health care providers and medical chart reviews. The adverse events are being categorized by FDA criteria. This is data from self-reported adverse events at 10 to 14 days. As you can see, at 10 to 14 days the majority of people were actually taking ciprofloxacin. Severe nausea, vomiting, diarrhea and abdominal pain was the most common adverse event reported. Somewhere between 2 and 5% of individuals reported serious adverse events that would require follow-up, but as far as we can tell, none of the Individuals were hospitalized because of their adverse events. Therefore, none of the adverse events would be categorized as severe based on FDA criteria. I don't want to in any way minimize the impact of these adverse events. But adverse events don't seem to be the main reason for people to discontinue the antibiotics. Only 3% of people at 10 days reported discontinuing the antibiotics on the basis of adverse events.

I'll next turn to show you the data at 30-day evaluations. At 30 days more now taking doxycycline with fewer taking ciprofloxacin. The most notable finding is that the overall adverse events increased across the board. Gastrointestinal events seemed more common. People did report the adverse events and as we re-looked into them; we have found none of these adverse events have required hospitalization. And we have not yet identified any people in the cohorts who would have a severe adverse event as categorized by FDA criteria. In addition, less than 10% of people overall report missing doses or discontinuing the antibiotics because of the side effects.

We're not done yet and there's more still going on in this area. We're planning towards the end of therapy or 60 day program evaluation. At this point, we will evaluate the entire program including adherence and adverse events. Adherence promotion activities and evaluation continues, and we continue to do surveillance for anthrax and adverse events associated with the post-exposure among all exposed groups.

*Dr. Gerberding:*

Thank you. That was an excellent summary of the work so far. We are coming to the conclusion of our written comments. I'm going to have the job here of putting together the graphics that you have seen and the clinical experience that we have had in a context that maybe clinicians will be able to use to make decisions.

If I can have my first graphic please, I think one of the major things that we should keep in mind in all of this discussion is this fact: To date, no cases inhalation anthrax have occurred among the

10,000 people for whom antibiotics have been recommended or offered, and we continue to monitor the affected sites up and down the east coast. So, while we are looking at additional options for safety, I think it's important to begin with the awareness that that we are not talking about a known hazard. We are talking about something that is theoretical for these people.

One of the key questions that we have still remains. Do spores persist after antimicrobial therapy and is there a continued risk of *Bacillus anthracis* disease? Does adding to the current therapy further decrease the risk of inhalation disease among those who have completed all 60 days or among those who have not actually been able to complete their full 60-day treatment regimen?

The options that we have been discussing include these three approaches:

- The first is the initial recommendation that we made several weeks ago, and that is to continue antimicrobial therapy and stop, and then go into a monitoring program with their clinicians or clinicians in the CDC surveillance program.
- A new option is to add an additional 40 days of antibiotics to the 60 days so that people would be treated for up to 100 days with antibiotic therapy.
- The second new option is to also add 40 extra days of antibiotics, plus three doses of vaccine administered over three weeks.

What we're really facing here as clinicians is how do we take all of the information we have heard about populations of people being treated or exposed in various contexts, and use that data to make rational decisions for individual patients?

That really involves balancing what we can say about the benefits of this treatment with what we can say about the treatment risks. We have to do this in a time where we acknowledge that we have far too few data to really develop firm conclusions. But when we're thinking about an individual patient, certainly we want to look at that patient's risk of inhalation anthrax. We want to take what we can say about the efficacy of either vaccine or antibiotics, and also assess that patient's capacity to adhere to either the antibiotic regimen or the monitoring program required for the immunization. That has to be balanced against what we can say about the safety of any of these options. In addition, there must be consideration of what impact the treatment might have on the individual's capacity to work. And in some sense we need to be respectful of the impact that the decisions will have on the supply of antibiotics or vaccine, as well as impact on the antimicrobial resistance.

What can we say about exposure risks that might help us assess the risk in an individual patient? First of all, we have learned that sometimes transient aerosolization does occur and it can be highly persistent. We know that very quickly after a letter containing anthrax spores is open, the spores can be found virtually throughout the entire environment in concentrations far in excess of what we believe to be the lethal dose 50. We also know that exposure dose varies with the distance from the source of the aerosolization and the duration of time that the individual was present in the airborne environment. Unfortunately, we have these perspectives that can help quantify the decision, but not accurately. We still are left with not having a precise measure of individual exposure risk or individual risk of inhalation anthrax.

Here are some tips that might be helpful in trying to bring this down to the level of an individual patient. It's obviously important to take a history of that person's exposure. Was the individual in

an environment where they had direct contact with the powder known to contain *B. anthracis* spores? Was the person in an area where such an envelope was opened?

Were they in a work environment where we know there was widespread environmental contamination? Many of the postal facilities where we have been able to do extensive environmental evaluation have demonstrated widespread contamination throughout the facility which suggests the potential for airborne exposure in that environment.

Finally, is the person working in a place where someone has already acquired inhalation anthrax? Certainly, that would be a sign that there was a hazard in that work setting. Additional things about the history that might suggest higher risk include working in an area where *B. anthracis*-containing envelope was processed using mechanical postal equipment. The postal service is working with CDC to provide specificity around the types of equipment where this can occur and will make available to us the list of the names of the machines that you can use as a tool when you are eliciting a history from a patient.

Some of the questions to ask concern their involvement with mechanical mail cancellation machinery, mail sorting equipment and other machinery in postal facilities where envelopes are pinched or agitated. It's also possible that some workers who have handled anthrax-containing envelopes were involved in sorting through the mail using procedures that would involve manual manipulation. This may also pose a risk, particularly if the envelope was not intact.

Another key component of the history for assessing the need for optional therapies include the individual's capacity to adhere to antibiotics. Dr. Rosenstein provided us a great perspective on this. Some patients can clearly take 60 days of antibiotics, but others are finding it very difficult. Some stop before they have had completed all 60 days, and others may take the antibiotics for 60 days, but are missing doses. These individuals may not have the level of protection that we would like, so their risk may be greater and additional therapy may be appropriate.

There are also some things that we believe may indicate lower risk. Again, looking at the exposure history, if a person has no known direct exposure to powder, has never been in an environment where there's widespread contamination, or has only been in environment where there's no known contamination or only focal contamination, they're probably at low risk for inhalational disease. The short duration of time in the contaminated environment is relevant. If they are a member of a group with --- no inhalation disease, a group that has had their antibiotic therapy delayed from the time that a known letter went through the facility, but there was still no inhalation disease, or a group for whom it is known that low adherence with antimicrobials was present but there was no presence of the disease --- these are markers of unlikely exposure, but none of these things can be taken to completely rule that out.

Now just to summarize some of the facts that patients need to think about when we're talking about additional days of antibiotics. As I said before, -- antibiotics recommended for 60 days of treatment seems to have so far protected the 10,000 people in this group. We know, however, that adherence was not perfect, and highly variable. There seems to be a tendency for adherence to correlate with an individual's perceived risk. We also recognize all of the difficulties in achieving 100% adherence despite aggressive adherence programs. When addressing an individual patient, asking

them questions about how difficult it was for them to take antibiotics, what might be done that would make it easier, and how the clinician and the patient could work together to achieve better adherence is really a very important aspect of the decision process.

There are additional facts about chemoprophylaxis that have a bearing on the program, and that includes the safety of the chemoprophylaxis. We are relieved that we have not seen serious complications from the treatment. But the data are relatively early and we want to be sure that we put this in the context of what we know about all drugs --- that occasionally serious side effects do occur and we certainly can't guarantee that we're not going to see serious adverse effects, particularly if we extend treatment to 100 days. Obviously monitoring the short and long term safety and effectiveness is essential.

Now, to summarize some of the facts about vaccine that are germane to this decision. It's important to keep in mind that the experience so far is limited to vaccination of healthy military personnel. In that population, we know that pre-exposure vaccine is effective although perhaps not 100%. We recognize that this vaccine has short-term side effects. Most of these appear to be local and self-limited. Serious reactions have been rare and there's been fairly aggressive monitoring for serious reactions. But the vaccine is relatively new, and the long term safety evaluation is still incomplete.

The use of all available vaccine of this program is investigational and patients will need to provide informed consent. The available vaccine lot is not licensed, but it is expected to be licensed soon. The nation's vaccine supply is limited, so as we face treatment decisions, in the larger context here, we have to keep in mind that what we have today may be something that we also need tomorrow, and balancing supply and demand is also a key perspective.

Again, the three options that we are considering are

- to conclude the 60 days of antibiotics that were Initially recommended,
- to add extra days of antibiotics for a total of 100 days of treatment,
- or to provide vaccine plus 40 additional days of antibiotic prophylaxis.

All of these options will require antimicrobial adherence support if we are to get maximum benefit of treatment. We need to be alert to side effect management. If we help patients recognize the symptoms of the antibiotics or the vaccine, they will be inclined to manage them and be effective in taking their medications. The short term monitoring are requirements of the program and we need to be alert to any untoward effects.

We at CDC and elsewhere are acknowledging that we have a lot to learn about the value of the therapies and we are still learning as we go. We are extremely intent on maintaining empathy and equity for all affected by the decisions. We're sorry that we can't provide more definitive treatment information, but we will certainly do our best to make all new information available as we get it and to continue to provide our input into the decisions that clinicians and workers are facing.

So, let me turn, now, to the next segment of our program where we will be bringing up questions. I'd first like to thank the panel for their input. This has been incredibly important subject matter.

And for the viewers, the phone lines are now open for your questions and comments. Once again here are the numbers to call...

Dr. Perkins, can you tell us about the sites where individual risk may be the highest?

*Dr. Perkins:*

I think we can look at the total experience we have gained during the investigation, and make some qualitative comments about stratification of risk across the various affected populations. I think the criteria that you presented are useful in that regard. For example, among postal workers at the Hamilton facility in Trenton, New Jersey and the Brentwood facility in Washington, D.C., we know that an envelope contaminated with *Bacillus anthracis* spores passed through each facility, and we know there was occurrence of anthrax cases in both places. Those persons, particularly those persons that worked in the proximity of the automated sorting machinery that you described, or manually handled potentially contaminated envelopes --- they may have had a higher risk of exposure than others. Similarly, where we understand the circumstances of exposure very well in the Senator Daschle suite, where we know the characteristics of the powder, we know the people who were in that room, for how long they were in the room, and the extent of their aerosol risk. I think that allows us to suggest that they may have been at risk for heavier exposures that require prolonged antibiotic therapy, or antibiotics in addition to vaccination.

*Dr. Gerberding:*

Thank you. Dr. Rosenstein, what can we do to promote better adherence? All of the options require taking antibiotics. What really can be done to help make it easier for people to finish their course?

*Dr. Rosenstein:*

Based on the focus groups and the small group discussions, it's very clear that individuals need good advice and counseling to help them take their antibiotics. So, for example, the opportunity to discuss with the clinician the need for antibiotics and to have help with the monitoring and managing of the side effects could do a lot to promote adherence among the people at risk for disease.

*Dr. Gerberding:*

Dr. Hughes, if this happens again --- and you always make the point that this is not over until the perpetrators are caught --- will we use vaccine the next time around?

*Dr. Hughes:*

In view of what we have learned over the past two-and-a-half months and in consideration of the data that you have heard presented by the co-panelists, I believe we would recommend that vaccine and antibiotics be used together for prophylaxis following a potential exposure to inhalational anthrax.

*Dr. Gerberding:*

We acknowledged that what we're dealing with here is post-exposure vaccination, and we have little data to promote the efficacy in this context. I'd like the facts. What do we know about the efficacy for pre-exposure immunization?

*Dr. Lingappa:*

The efficacy has been mostly assessed within animals. There is a study in human beings that was done in the 1950s when the principal exposure was occupational exposure to anthrax was in mill workers. In that situation the vaccine was found to have a 90% high effectiveness. As Dr. Perkins described, the animal studies have indicated that the effectiveness in pre-exposure settings is quite high.

*Dr. Gerberding:*

Brad, do you want to add anything to that?

*Dr. Perkins:*

Yes. Let me expand on the comments because I think its important for everyone to recognize that the pre-exposure vaccination regimen for anthrax vaccine is different than the one we're recommending in the current circumstances. Pre-exposure vaccination with anthrax vaccine consists of six injections delivered over an 18-month period, followed by annual boosters. That's the regimen that was tested in the 1950s in a very nicely controlled, double-blind, placebo randomized trial that indicated that the vaccine was 93% efficacious for prevention of a combination of inhalational anthrax as well as cutaneous. There are no similar data looking at the efficacy of the anthrax vaccine when used in humans in the three-dose regimen that we're recommending for post-exposure prophylaxis. The data that exist are immunogenicity data in humans. There appears to be a good immune response to the vaccine at zero, two, and four weeks that would be likely to protect people through a long period as a result of exposure to *Bacillus anthracis* spores. We do not think that this regimen is appropriate for long term pre-exposure protection against anthrax though.

*Dr. Gerberding:*

Brad, that leads me to a follow-up question there. If people take this vaccine after exposure, will they have long-term protection? Will they be protected if there is an exposure in their future?

*Dr. Perkins:*

No. People need to understand, Julie, that this regimen of vaccination is only indicated for post exposure protection of an event they have already been part of. And they need to understand that we do not have any data that would suggest that this would be an appropriate regimen for long-term protection for subsequent events.

*Dr. Gerberding*

We have a question from Martin in New York. How will vaccine be distributed? Will it continue to be distributed at public health sites or through private doctors? Can you help us?

*Dr. Lingappa:*

Yes. Because this is being done under an investigational program, the vaccine can only be distributed through special sites. Currently, those are being set up. The Capitol Hill workers received vaccine within Capitol Hill. And we're in the process of setting up sites where other persons who might be considered or consider themselves at risk for a high exposure could obtain the vaccine.

*Dr. Gerberding:*

Thank you. We have a number of questions here about the logistics of accessing vaccine. Sarah in Washington, D.C., asks, "if you are in the Hart building, but one floor below the zone where we have evidence of environmental contamination, and you didn't take antibiotics for 60 days, what should you do?" Brad, do have you an answer for her?

*Dr. Perkins:*

You know, as everyone knows, there were groups of people on the East Coast that were recommended to take 60 days of antibiotics. We felt that those persons that we recommended 60 days of antibiotics for were at risk for inhalational disease. However, if you were recommended to receive 60 days of antibiotics and did not take them for the entire 60 days, you basically have demonstrated that you were not at risk of inhalational disease because we think that any cases of inhalational disease would have occurred within that time frame.

*Dr. Gerberding:*

Can private doctors get this vaccine?

*Dr. Perkins:*

No, Julie. That's a good question. It's important to note that because of the regulatory requirements for delivery of this vaccine under the Investigational New Drug application, the vaccine is not going to be available to private clinicians. However, we urge and hope that exposed persons will take advantage of discussing the treatment options with their private physician, and then presenting to the clinics --- as Dr. Lingappa described --- to avail themselves of additional antibiotics and vaccine.

*Dr. Gerberding:*

We have a related question from a doctor in Pennsylvania who is inquiring about patients who were in D.C. and needed that, but have probably gone home for the holidays. How can they get the vaccine?

*Dr. Perkins:*

I think it's important to reassure everyone that the CDC is working with the state and local health departments to develop a plan that will get vaccines to people as quickly as feasible. This is not an emergency, but it's something we are working on urgently to try to insure that people who need treatment can get it --- as quickly as they have the information and the capacity to make an informed decision. So, the best thing for individuals to do who are in an area outside of the affected area --- if they have a patient who is concerned or may need a vaccine --- is to give us a call at CDC at the numbers that we presented earlier or call the CDC Operations Center at 770-488-7100. We will help get that connection made.

*Dr. Gerberding:*

We also have a question from Ron in Illinois. He asks that we repeat the information about amoxicillin and adherence. Do you want to take that, Dr. Rosenstein?

*Dr. Rosenstein:*

Sure. Amoxicillin was primarily recommended for children. As that data showed, less than 3% overall of the people who were recommended for 60 days of antibiotics were children. So far we only have limited data on amoxicillin and we have not gotten severe side effects associated with amoxicillin.

*Dr. Gerberding:*

We have another question about vaccines. Many people have heard about the relationship or alleged relationship between the vaccine when used in the military and a variety of complications, including Gulf War syndrome. You can tell us what we know and what we don't know about that, Dr. Lingappa?

*Dr. Lingappa:*

Yes. As we mentioned, there has been there's been a lot of data or a lot of discussion about this. There are several reports of things like Guillain Barre syndrome, Gulf war illness, chronic fatigue has been brought to the attention of the reporting system. It's important to note, though, that to date, the current data indicate that individuals who receive the vaccine are at no higher risk statistically for all of these reported syndromes in comparison to individuals who did not receive the vaccine. So, at this point, we do not have any data that causally links the vaccine to these syndromes.

*Dr. Gerberding:*

While we're on the subject of vaccine side effects, let me ask you more about the subcutaneous nodules. What do they look like and how troublesome are they for people?

*Dr. Lingappa:*

They vary. But generally the subcutaneous nodules --- where you actually feel a lump or knot under your skin at the site where the injection occurred --- can be associated with some degree of pain initially. But often they are not painful. Subsequently, they can last in duration as long as a month or even longer. But again, as I said, they generally will go away with time. We have not found any long-term problems associated with those [subcutaneous nodules].

*Dr. Gerberding:*

Thank you. Pat in Washington, D.C., asks, "Do you recommend that Brentwood Postal service employees take the vaccine. If so, why. And if not, why not?"

I'll start the answer to that question. I think what we have been struggling with all along here is trying to take what we know about groups of people and make recommendations for individuals. The data just simply are not there for us to do that in the way that CDC likes to do when we're asked to make important public health recommendations. But what we can say is that our understanding of the exposure circumstances in Brentwood suggest that it is in the same exposure category as the Daschle office. There is widespread contamination in both of these facilities, and we would be looking at similar decision processes for workers in both sites.

For an individual worker in Brentwood, I think we would want to make sure they understood that we consider them to be in an environment where there was a high degree of exposure. And then go

on to assess the other aspects of the decision process --- such as how are you doing with antibiotics? How difficult has it been for you to take them? And how do you really feel about vaccines? Can you tolerate three shots? --- You know, all of the practical aspects of it. If a person was motivated to take the antibiotics and could put up with the shots, we would probably recommend that the individual receive the vaccine. Do you want to add anything to that, Brad?

*Dr. Perkins:*

No. I agree. I think that the Brentwood postal workers need to consider the options for further reduction of risk for elimination of inhalational anthrax disease potential.

*Dr. Gerberding:*

I think that's one of the environments where we are concerned that the treatment may not have eliminated all of the spores, and these additional options could be helpful there.

We also have a question from Julie in Maryland. How is this detailed information going to be distributed to the primary care doctors who will be sitting with their patients as they try to struggle with these decisions. Jim, do you want to give us your perspectives on what else CDC can do to get the word out?

*Dr. Hughes:*

Let me begin with a response to that and ask others to contribute as well. We will be putting this information in *Morbidity and Mortality Weekly Report (MMWR)*. We will use the CDC web site. We will work with professional societies to look at ways that this information can be rapidly delivered to clinicians. We're also distributing the information through the CDC Health Alert Network and Epi-X systems that we have in place to reach public health workers. It's going to require a multifaceted approach to get the word out to clinicians who have an important role to play in counseling individuals.

*Dr. Gerberding:*

Thank you. We have a couple more important questions about vaccine safety. One is a question about specific contraindications to vaccine. I know you said there were no exclusion criteria in the program, but are there any contraindications that would mean someone should not be vaccinated?

*Dr. Lingappa:*

Well, again, I think what's been emphasized several times now is that there's the data for pre-exposure vaccine and then less data for the post exposure use. The data for pre-exposure use indicates that pregnant women are not a group that would be considered for post exposure vaccination. The fact that that vaccine would not be considered for pregnant has to be balanced against the particular risks of disease for the individuals. So in a post exposure setting, it's not a specific contraindication, but the risks and benefits have to be balanced on an individual basis.

*Dr. Gerberding:*

For people who really don't want to be in the program, what options are available? Do we have anything else we can offer them? Brad?

*Dr. Perkins:*

Well, what we'd like to see is that everyone who has been exposed to *Bacillus anthracis* spores --- and were recommended for 60 days of antibiotics --- be very carefully medically monitored. That means we'd like for them to have established relationships with health care providers so if they become ill, they have rapid access to health care providers who can recognize that they may be at risk for inhalational anthrax, and take appropriate early and aggressive steps to potentially thwart disease or treat symptoms early on.

*Dr. Gerberding:*

This is from David in Atlanta. Is the vaccine we are proposing to give to workers as safe as the vaccine that we have given to soldiers?

*Dr. Perkins:*

Every indication about this Lot that we're using would suggest the answer to that question is yes. This vaccine has been produced in recently renovated facilities at the vaccine manufacturer. It has passed all of the FDA regulatory requirements regarding safety and effectiveness. Those standards have actually been recently revised and are quite stringent, so the FDA and we feel quite comfortable with the use of this particular product in the context of this program.

*Dr. Gerberding:*

Thank you. Now, if someone is taking this vaccine and they are at risk for inhalational anthrax, or they're taking vaccine and antibiotics because they have an underlying risk --- and they start developing symptoms, how are they going to know if it's the vaccine, the antibiotic, or they're sick with anthrax? How can they tell the situations apart?

*Dr. Lingappa:*

That's a great question. There is going to be overlap in terms of some of the symptoms. But within the program itself, individuals should keep in close touch with the site coordinators as well as their own personal physicians. We will be assessing within the program how people are responding to the entire constellation of antibiotics, vaccine and their particular disease risk. Through the course of, initially, a six-week period where they report symptom specifically to the site coordinator, and then over a 24-month period where we actually get in touch with them if they have specific symptoms, they also need to keep in touch with their physicians.

*Dr. Gerberding:*

Let me just add to that that if there are particular findings that emerge from that ongoing follow-up, we'll be right back with all of you discussing those findings just like we are right now to give everybody a heads up.

Brad, another related question: how long do we really need to follow people, particularly under this investigational protocol?

*Dr. Perkins:*

We would like to follow people for two years. There will be intensive follow-up for the first six weeks after entry into the program, and ongoing at six-month intervals for a year, and then at a final interval of 24 months after entry into the program.

*Dr. Gerberding:*

Dr. Hughes, can you help us clarify the distinction between an investigational drug and an experiment?

*Dr. Hughes:*

Yes. Let me try to do that. This is very important. The antibiotics that we're talking about using here are obviously licensed antibiotics, but they are under this IND [investigational new drug application] because they're being used in a way for which they are not labeled. Similarly, in terms of the vaccine, as you have heard from Dr. Perkins, this particular lot of vaccine is felt to be fully licensable, and that it will be soon licensed. It is, however, being used in this instance in a way for which previously licensed lots have not been approved. But this is not an experimental vaccine. Thinking of AVA overall, this is a licensed vaccine.

*Dr. Gerberding:*

Thank you. If individuals choose not to receive the vaccine and they choose not to take antibiotics, what do they need to do to monitor their health status?

*Dr. Lingappa:*

They need to keep aware. For example, in situations where they have fevers, flu-like symptoms and so forth, they need to keep in close touch with their personal physicians, because that's whose going to be best equipped to respond to evaluating those symptoms.

*Dr. Gerberding:*

Should they go to the emergency room every time they have a fever? Especially during flu season, and so forth, this is going to be a real concern and an issue. And a simple situation where you have a fever would not in and of itself warrant that every single time. But it's something where they should keep in touch about the spectrum or the severity of the complex, and what types of other symptoms they're feeling, and keep in touch with their physician about what they should do. We recognize this is a confusing situation for patients and we hope the information we are providing will help their clinicians help them.

I'm just wondering, Brad, how long do people have before they have to decide? When does the door shut on the options for the people who have already taken their 60 days [of antibiotics]?

*Dr. Perkins:*

At present, there is no established back end for participation in this program. However, I would suggest that people consult their private physician or whoever they would like to talk to in making this decision, and making it as rapidly as they can make it. Because if you feel like you may be at increased risk, we would like to get these additional preventive measures on board and in place as soon as possible to protect your health.

*Dr. Gerberding:*

Along those same lines, if people chose any of these options, what's the longest they have to wait before they know for sure they don't have anthrax and are never going to get it from the exposures that they have recently sustained? When are they really out of the woods altogether?

*Dr. Perkins:*

I would think that based on available data, that once you get out beyond 100 days from the time of exposure --- which isn't always well known for all of the groups affected by this attack --- but once you're beyond 100 days, I think you can have an increasing amount of comfort. I don't think the risk is there --- I can't guarantee that it's zero at that point, but it's vastly diminished. You know, as you go on from there, I think you can live with an increasing certainty that you're not going to develop this extremely serious disease.

*Dr. Gerberding:*

I now have a question from Betty in South Dakota, who is interested in if the bacteria mutates, will the vaccine and the antibiotics still work?

*Dr. Perkins:*

We followed, you know, a number of characteristics of *Bacillus anthracis* involved in this attack, and it does not appear to be changing in regard to its antimicrobial susceptibility, nor in the effectiveness of the vaccine to prevent disease caused by this strain. At this point, I don't think that's a major concern. Additionally, among the spectrum of bacteria that exist, *Bacillus anthracis* is incredibly stable and one of the bacteria you would not expect to change very often in terms of its genetic characteristics.

*Dr. Gerberding:*

I guess I have one more question. Jim, given that we're in this changing environment and that new information is becoming available daily, what's the best place for people to get the most updated information and where should we refer them for today's latest on anthrax and protection?

*Dr. Hughes:*

I would refer people to the CDC web site, and urge them to consult that on a regular basis. We will be providing new information as we receive it that way. You can access that web site at [www.cdc.gov](http://www.cdc.gov). We would urge you to access it frequently. In addition, we call your attention to the weekly CDC publication, the *Morbidity and Mortality Weekly Report*.

*Dr. Gerberding:*

With that I would like to thank all of our expert panelists: Dr. Hughes, Dr. Perkins, Dr. Rosenstein and Dr. Lingappa. Thank you for joining us for this video. I would like to remind you that if you need to contact us about urgent situations or important information, the correct telephone number is 770-488-7100. Again that's 770-488-7100, a line set up for clinicians and health officials seeking additional information about specific patient issues. Thank you very much for your attention. We look forward to joining you again on CDC Responds.

*Lisa Rayam:*

All right. Thank you. I would like to thank the entire expert panel for sharing experiences and ideas with us today. I'm sure you have answered a lot of questions the audience may have been wondering about. I would also like to thank you, our audience, for joining us for this program, Update on Options for Preventive Treatment for Persons at Risk for Inhalational Anthrax, which was part of CDC Responds, the series that addresses important clinical and public health issues.

As we mentioned earlier in the program, if you have additional questions, fax them to 800-553-6324. Your questions will be answered by CDC over the coming weeks and will be posted on the web side at [www.bt.CDC.gov](http://www.bt.CDC.gov).

If you missed part of this program or would like to see any past programs in the CDC responds series, you can view them any time - day or night - by accessing the web archives on the internet at [Www.sph.unc.edu/about/webcast](http://Www.sph.unc.edu/about/webcast).

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We would appreciate your feedback on this program. So please let us know if you feel we have achieved the goal to supply you with the latest information available, and if we gave you a better understanding of the treatment options for prevention of inhalation anthrax for persons exposed to airborne anthrax spores. Simply visit [www.trainingfinder](http://www.trainingfinder.org), that's one word --.org. New, use the keyword search to find the title of this or any Program in the CDC responds Series that you want to review. Click on submit a review. It's below the title and follows the instructions. Your review will help us meet your needs.

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