DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE MEETING

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THURSDAY,
MAY 17, 2007

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The Committee convened at 9:00 a.m. in the Grand Ballroom of the Hilton Hotel, Washington, D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland.

COMMITTEE MEMBERS PRESENT:

RUTH A. KARRON, M.D., Chair
MONICA M. FARLEY, M.D.
PHILIP S. LaRUSSA, M.D.
STEVEN SELF, Ph.D.
BONNIE WORD, M.D.
JOHN MODLIN, M.D.
SETH HERTHERINGTON, M.D. (Non-Voting Industry Representative)
LISA JACKSON, M.D., M.P.H.
JACK STAPLETON, M.D.
HASSAN AZIZ, Ph.D. (Temporary Voting Member)
LIMONE COLLINS, M.D. (Non-Voting Temporary Member)
BRUCE GELLIN, M.D., M.P.H. (Non-Voting

Temporary Member)
BARRY MASSIE, M.D. (Temporary Voting Member)
PAMELA McINNES, D.D.S., M.Sc. (Temporary Voting Member)
MICHAEL NELSON, M.D. (Non-Voting Temporary Member)
GERALD PARKER, D.V.M., Ph.D., M.S. (Non-Voting Temporary Member)
COL. JAMES SCHULTZ (Ret.) (Temporary Voting Member)
JOHN TEERLINK, M.D. (Temporary Voting Member)
MELINDA WHARTON, M.D., M.P.H. (Non-Voting Temporary Member)

EXECUTIVE SECRETARY PRESENT:

CHRISTINE WALSH, R.N.

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(9:05 a.m.)

CHAIR KARRON: Good morning, everyone.

CALL TO ORDER

CHAIR KARRON: I'd like to ask everybody to please take their seats. We are going to call this meeting to order. This is the second day of the May VRBPAC meeting.

Christine Walsh is our executive secretary, and she has some announcements.

ADMINISTRATIVE ANNOUNCEMENTS

MS. WALSH: Good morning. I'm Christine Walsh, the executive secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee.

I would like to welcome all of you to this meeting of the advisory committee.

Today's session will consist of presentations that are open to the public. I would like to request that everyone please check your cellphones and pagers to make sure

they are off or in a silent mode.

I would also like to request that any media inquiries be directed to Ms. Karen Riley from the FDA Office of Public Affairs. Karen is right there. Thank you, Karen.

I would now to like to read into public record the conflict of interest statement for today's meeting.

This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on May 16th and will be part of the public record for the Vaccines and Related Biological Products advisory committee meeting on May 17th, 2007.

This announcement addresses conflict of interest for Topic 3 related to the discussion and recommendation of the safety and effectiveness of ACAM2000, live vacciniar virus, smallpox vaccine, percutaneous scarification, manufactured by Acambis, Inc.

In accordance with 18 USC Sections

208 (b)(3), waivers have been granted to Dr. Lisa Jackson, Dr. Jack Stapleton, and Dr. John Terling. Dr. Bruce John, Dr. Michael Nelson, Dr. Lemone Collins, Dr. Gerald Parker, and Dr. Melinda Wharton are participating in today's meeting as a nonvoting member, which there is a change if you look at the roster. Dr. Melinda Wharton is listed as a voting member; she will now be a nonvoting member.

Dr. Seth Hetherington is serving as the industry representative, acting on behalf of all related industry, and is employed by Icagen, Inc.

In addition Dr. Hetherington's spouse is employed by GlaxoSmithKline.

Industry representatives are not special government employees, and do not vote. In addition there may be regulated industry and other outside organization speakers making presentations. These speakers may have financial interest associated with their employer and with other regulated firms.

The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

These individuals were not screened by the FDA for conflicts of interest.

With regard to FDA speakers, guest speakers for Topic 3, the Agency has determined that the following information provided is essential.

The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments. Dr. Gerald Parker is employed as the deputy assistant secretary for preparedness and response, Department of Health and Human Services.

Lieutenant Colonel Stephen Ford is deputy director, scientific affairs, military vaccine agency, Office of the Surgeon General.

This conflict of interest statement will be available for review at the

registration table.

We would like to remind members and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or an imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that you might have with any firms, its products and if known its direct competitors.

Dr. Karron, I turn the meeting back over to you.

CHAIR KARRON: Thank you very much, Christine.

I'd like to welcome everyone, and ask all the committee members to introduce themselves. And we'll start with Dr. Farley.

DR. FARLEY: Monica Farley from

Emory University, infectious disease.

DR. McINNES: Pamela McInnes, National Institute of Dental and Cranio-Facial Research, NIH.

DR. PARKER: Jerry Parker, HHS.

DR. WORD: Bonnie Word, Baylor College of Medicine.

DR. JACKSON: Lisa Jackson, Group Health Center for Health Studies.

DR. TEERLINK: John Teerlink, University of California, San Francisco, and San Francisco VA Medical Center, and cardiologist.

DR. SELF: Steve Self, Hutchinson Cancer Research Center in Seattle.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention.

DR. HETHERINGTON: Seth Hetherington, Iogen, Research Triangle Park, North Carolina.

DR. LaRUSSA: Phil LaRussa, pediatric and infectious diseases, Columbia

University.

COL. SCHULTZ: James Schultz, agent representative.

DR. GELLIN: Bruce Gellin, HHS.

DR. MASSIE: Barry Massie, University of California, and also, San Francisco VA, and also a cardiologist.

DR. AZIZ: Hassan Aziz, professional medical technology, Armstrong Atlantic University.

DR. STAPLETON: Jack Stapleton, infectious diseases, University of Iowa and Iowa City VA.

DR. MODLIN: John Modlin from Dartmouth Medical School.

DR. COLLINS: Limone Collins from the Vaccine Health Care Centers Network and Walter Reed Regional Center.

DR. NELSON: Mike Nelson, Walter Reed Army Medical Center.

DR. BAYLOR: Norman Baylor, Food & Drug Administration, Center for Biological

Evaluation and Research.

DR. MERCHLINSKY: Mike Merchlinsky, division of bioproducts, CBER.

DR. ROSENTHAL: Steve Rosenthal, division of vaccines, CBER.

CHAIR KARRON: Thank you, everyone.

Our first speaker is Dr. Merchlinsky.

INTRODUCTION/BACKGROUND

DR. MERCHLINSKY: First of all, I'd like to thank everyone for coming today to help the Agency in its evaluation of ACAM2000, the new smallpox vaccine.

After my brief introduction Dr. Parker will give a talk with regard to the departmental and government requirements, and the anticipated use of the vaccine.

Following his talk Colonel Ford will give a talk on the experience the DOD has had with its vaccination campaign using Dryvax, which is the progenitor of ACAM2000.

The sponsor will give five talks

with regard to their evaluation of the product. And after a break Dr. Steve Rosenthal from CBER will give our take on the product.

ACAM2000 small pox vaccine is a live vaccinia virus smallpox vaccine prepared from infected Vero cells.

It is a clonal isolate of Dryvax, a New York City Board of Health vaccine used in the campaign to eradicate small pox.

Dryvax was used directly against smallpox, and has been shown to have great efficacy against the disease itself.

Dryvax is presently the only licensed vaccine against smallpox in the United States that has been licensed by the FDA. And Dryvax is the vaccine which is presently being used by the DOD and used to vaccinate health care workers and laboratory workers against smallpox.

ACAM2000 is purified after infection of Vero cells by cell disruption

bulk filtration and tangential flow filtration. The viral stock is diluted to the proper concentration and lyophilized. The lyophilized powder is reconstituted with a packet of diluent. After reconstitution each vial has 100 doses of vaccine containing between 2-1/2 to 7-1/2 X 10 to the 5^{th} plaque forming units of vaccinia virus.

The intent was to make this like Dryvax. The diluent, the vial, the doses, the main method of administration, are all identical to that used for Dryvax. And as I indicated Dryvax has historically been shown to be extremely effective against smallpox.

ACAM2000 is proposed for the prevention of smallpox in persons determined to be at high risk for smallpox infection. It is not going to be used for routine vaccination at this time.

Now in making a new smallpox vaccine, we took advantage of the advances in modern molecular biology and manufacturing.

So the last time that Dryvax was manufactured was over 25 years ago, and there are only limited doses of Dryvax remaining.

And by using this there are certain advantages to make a self culture smallpox vaccine, including the use of well characterized viral seeds; the fact that if you start with a well characterized viral seed and a well characterized cell bank, you can get reproducible product manufacturing.

This product has a high level of purity, and there is a high level of adventitious agent testing, and many of these tests were not in existence 25 years ago.

Now our evaluation of ACAM2000, we used a series of Phase III clinical trials to demonstrate non-inferiority to Dryvax. In this case, as I indicated earlier, what we are looking for is a vaccine that behaves like Dryvax, because Dryvax has a historical demonstration of efficacy in smallpox.

And the trials were both in

vaccinia naive, which was trial No. H-400-009, and in those previously vaccinated with Dryvax, which would be H-400-012.

Now the questions we would like the committee to address, first one is, are the efficacy data sufficient to support the use of ACAM2000 in situations where it is determined that there is a high risk of exposure to smallpox virus?

Second question: Are the safety data sufficient to support the use of ACAM2000 in situations where it is determined that there is a high risk of exposure to smallpox virus?

And third, please discuss benefits versus risks of ACAM2000 for use in the high risk situations.

In addition, what we would like the committee to discuss is, does the committee agree that the risk minimization action plan, the RiskMAP for ACAM2000 composed of the following components is needed: one, vaccinee

education; health care provider education; expedited reporting of certain serious adverse events; phase four studies to better define the safety profile, long term outcomes, and risk factors for myocarditis; and evaluation of the RiskMAP.

And finally this is the actual discussion point, discuss methods to increase the sensitivity of case ascertainment of myocarditis and long term follow up and methods to evaluate the effectiveness of this RiskMAP which we presented today.

I'd like to thank you for your attention. And Dr. Parker I think is next to talk.

CHAIR KARRON: Thank you, Dr. Merchlinsky.

DHHS' SMALLPOX PROGRAM

DR. PARKER: Well, thank you very much. It's indeed my honor to be here with you today to give you at least a brief overview of some of the department's all

hazards preparedness plans, and then specifically focus on some of the activities we have in regards to smallpox preparedness plans.

And just a brief introduction about my office. Because it's a new office just created by legislation in December in the Assistant Secretary for Preparedness and Response.

We have responsibilities for really coordinating an enterprise wide phenomenon from R&D to actual delivery of medical products to the patient. And so it's a job of integrating the entire federal, state, local, private sector and individual activities in all hazard preparedness, and then also implementing some of the actual procurement advanced development programs in medical countermeasures.

But today we are focused on smallpox vaccine. I will give a brief overview of the requirement for smallpox

vaccines, and we have actually just heard some of that, and so I will be very brief on some of that, description of ACAM2000.

And I'll spend a little bit more time on the utilization policy, and amplify that a little bit, that we've recently refreshed that policy through a working group in the department.

And then just to highlight some of the preparedness planning activities that we're doing at all levels including the federal level, what CDC is doing, and the states.

First of all, in fact I just learned this fact this week, and I'm sure many of you are very aware of this. But if you're not, this week actually marks the 211th anniversary, May 14th, 1796, of the inoculation of James Phipps, a young boy, with cowpox by Sir Edward Jenner. This boy was larger challenged twice with virutous materials and lived.

Well, certainly the eradication of smallpox from the human population is one of the greatest public health triumphs of the 20th century. The last documented case of naturally occurring smallpox in the general population occurred in 1977 in Somalia, and because of this successful eradication of the virus, general and domestic and international vaccination against smallpox has not been practiced in over 25 years, and research into the development of new vaccinees had languished until recently.

Domestic vaccination program was halted in the mid-1970s, and half of the population has no immunity, and the other half has only limited immunity.

It was around the mid-`90s that really culminated in 1999 that there became a much more acute awareness about the potential threat of a biological attack using smallpox. And it was 1999 was really the focal point when the public health community realized that

more needed to be done to prepare for that - for the potential of a smallpox attack.

And also there was a lot of discussion at the time, and although antivirals, with a limited supply of smallpox Dryvax vaccine at the time, it was agreed that the only - that the best defense that the U.S. government and the U.S. would have was to have a modern, safe and effective vaccine.

That led to a consensus going forward, pre-9/11, in the 1999 time frame, that developed a requirement for a new smallpox vaccine. And even before 9/11 that requirement was set for 40 million doses. But then post-9/11 the requirement for vaccine stockpile increased to 300 million doses, or essentially enough vaccine for the entire population.

We've already really heard the summary of the ACAM2000, but the initial contract for the ACAM2000 was let by CDC in 2000 again for the 40 million doses. In 2001

the requirement of that contract was upped to 250 million doses.

There are other vaccines in the strategic national stockpile. They include Wetvax, 85 million doses. And then a limited supply of the licensed Dryvax vaccine.

And of course we've heard of some of the characteristics already of the ACAM vaccine candidate. But just to repeat that, it's from the New York City Board of Health strain of vaccinia, derived from Dryvax, and it's using modern manufacturing capabilities to include growth and barrel cells. It's a clonal isolate derived from Dryvax and is well characterized, free of adventitious agents. And it elicits immune response analogous to the current Dryvax licensed vaccine.

Now I'll spend a little bit more time on the utilization of the vaccine under different scenarios. And I think this chart if you walk through all the components of this matrix really gets at a way to balance risk

and benefits of the use of the vaccines of what will be demanded by the public if there is an outbreak of smallpox.

I mentioned that we recently had in the department an effort, a working group that was pulled together led by Dr. D.A. Henderson in the 2005-2006 time frame to relook and refresh our utilization policy for the utilization of the vaccine. And that work concluded in 2006, and really this table is the conclusion and culmination of that work.

And it stratifies the use of the vaccine really into four components: first is pre-event; second is if there is an outbreak outside the United States; third, if there is an outbreak within the United States; and subdivided them within the United States are low risk and high risk.

And so that allows us an opportunity also if there is an opportunity in the United States to really then tailor and focus where vaccine would be needed and would

be used even in the United States in the face of an outbreak.

And so you see from laboratorians who are working with various pox viruses today, that recommendation, and laboratorians are receiving immunization.

And of course that is today now in a pre-event setting.

Health care workers, as you know a few years ago health care workers began to get immunized. The vaccine was made available. And today there are 39,000-plus health care workers who have received the Dryvax vaccine.

And in a pre-event mode that vaccine remains available to the health care workers.

If there is an outbreak outside the United States, in anticipation that there is a probability that we would then see an outbreak in the United States, the committee recommends that in fact health care workers who may be at a potentially higher risk of exposure if in

fact the virus enters the United States, then that recommendation would be up to more than available but recommended for those who would really be on the front line in the health care community.

And then of course if there is an outbreak in the United States, in a low risk area or high risk area, health care workers, there would be a recommendation.

But for first responders - and that's first responders as defined more like the fire, police, emergency management type personnel - there is not - the committee felt that the vaccine would be made available throughout that except for when - if there is an outbreak in the United States only in the high risk area, where there is high potential for exposure to those individuals.

And all the way down to community wide vaccination is, only make it available in low risk areas if there is an outbreak in the United States. But it would only be

recommended in those high risk areas where there is active disease.

And so I think you can see from this table that the working group actually was able to come to a very logical place in recommending the use of the vaccine, only when there is a high potential for actual exposure to the virus.

And I think this really allows us then to really tailor and balance the risk benefit in the use of the vaccine knowing its efficacy and safety profile, and then only when there is high risk of exposure.

Now some of the preparedness activities that we were doing to make sure that we do have vaccine in the stockpile, but at the end of the day for that vaccine to be useful it's got to be delivered to patients.

So were doing a lot within the department, and encouraging our partners at the state level, the local level, private sector, to also be a part of preparedness.

And our preparedness has gone much more than individual agents like smallpox or anthrax, but much more to all hazard preparedness to include pandemic influenza.

And so we are doing quite a bit in that all-hazards preparedness approach to make sure we can deliver what kind of countermeasures are needed to the patient.

But in regards to our smallpox preparedness we've had several significant national level exercises to really help us identify what our capabilities are, what are our gaps, what are our vulnerabilities, and where do we need to put additional resources.

And then just in 2006 we had a cabinet level table top exercise that focused on small pox preparedness. And so you can see that this is getting attention at the highest level, smallpox preparedness, but all hazards preparedness as well.

Within our office, we are actually developing very detailed what I call play

books. But it really prescribes what we need to do at the federal level with all our federal partners, particularly in the medical and public health domain, and that would be the Department of Defense, Veterans Affairs, Department of Homeland Security, and other components.

And so that we have prescribed actions that we need to take, but also, know how we need to make audibles and adjust to the situation.

We also in our medical countermeasures group, now BARDDA, we are also looking at next generation vaccines as well, antivirals for smallpox, and a number of potential threats.

At the Centers for Disease Control they have also focused in on all hazards preparedness, and that is encompassing smallpox preparedness. But they are working very closely with the state health officers and local health community to improve their

preparedness and the ability to deliver vaccine effectively if the need were to arise.

This includes our state grant programs, preparedness programs that the states have - there's been $8 billion invested in these preparedness programs since the inception in the 2002 time frame. Today over 90 percent of the states have an approved smallpox preparedness plan, so I think that is an indication of a lot of progress we have been able to make at the various levels in our preparedness activities.

Adverse event monitoring is included in this preparedness plan. And the adverse event monitoring is happening today and will happen through the drug services program and to the VAERS at the CDC.

And of course the strategic national stockpile where we do now have sufficient vaccine to include the ACAM, 192 million doses of the ACAM2000 vaccine. We have sufficient vaccine available for the

entire population if that need were to arise.

And I also want to note that my boss, the ASPR, the assistant secretary, has been traveling quite a bit, visiting with the local health officials. And there is a lot of indication of a lot of great progress at the state level in all hazards preparedness, which is very encouraging for all of us.

Training for smallpox vaccination is a critical element in our preparedness planning, and CDC has done I think a tremendous effort in establishing training programs and making sure that response teams would be able to administer the vaccine if needed.

They developed a lot of training material that I think is readily accessible through websites, videos, CDs, and other manners, and these 39,000 health care workers that had been immunized, some of those constitute smallpox response teams at the state and local level. And some of those

members then have also been received training in the how-to immunize with the smallpox vaccine.

So in summary, ACAM2000 is a new product derived from the New York City Board of Health strain. It is a strain that has been proven to be effective in controlling smallpox outbreaks in the past. There are sufficient quantities in the strategic national stockpile of the smallpox vaccines today.

The U.S. government, the CDC, is working closely with ACAM to maintain a domestic warm base capacity of the ACAM2000. Those - that is currently - continues in negotiation. My office and the CDC are working closely with all levels of state, local and private sector to improve our smallpox preparedness and vaccination planning efforts.

Pre-event vaccination plan will not change. You will hear more from DOD following

me. Laboratorians continue to be - receive vaccinia immunization who are in research endeavors with pox viruses. Host event plans are predicated on containment of disease by revaccination, followed by carefully controlled surveillance plans, i.e. the high risk areas, low risk areas.

Reporting the vaccine adverse events will be through the VAERS program, and monitoring the vaccinees will be by states and documentation will be provided to vaccinees.

And I think I will conclude there. But I do want to, also, before I conclude, I also want to say a special thanks to everybody who has really been working in this enterprise, whether it be CDC, whether it be the NIH, whether it be our colleagues in the private sector, whether it be our colleagues at the state and local level, this has truly been, over the last six or seven years, truly an enterprise effort to get us to the state of preparedness that are at today.

So I just want to say a special thanks to everybody that has been a part of this enterprise effort.

Thank you very much.

CHAIR KARRON: Thank you, Dr. Parker.

Are there questions for Dr. Parker?

Actually, I have one, which is, can you tell us what the current stockpile of Dryvax is?

DR. PARKER: I don't have those exact numbers, but it's around 15 million. But a part of that is licensed, and a part of that is not licensed. I'll get that exact number for you.

CHAIR KARRON: Thank you. Dr. Modlin.

DR. PARKER: But I think it's a good question. I think I mentioned several times, there are only limited quantities of Dryvax, and a component of that is not licensed.

DR. MODLIN: Dr. Parker, John Modlin

of Dartmouth right here. What can you tell us about the ongoing assessment of risk from smallpox?

And I ask the question because I like many other people -

DR. PARKER: The risk of a smallpox attack?

DR. MODLIN: Exactly - participated in the whole extent of policy issues and so on from five to six to seven years ago, particularly around the ACIP, and the discussions that went on there, and one of the biggest things that we struggled with, normally when we make policy around vaccines of course as everybody knows we weigh benefit and risk.

And the inability to characterize and quantify potential benefit here with a known risk, and now we have a vaccine that is recognized as probably a little riskier than we recognized even at that time, it turns out to be a critical issue.

And I would think that this would be one of the most important things that the federal government would be focusing on so long as we continuing to immunize large numbers of service personnel.

DR. PARKER: Well, the threat - the potential threat is real. Can I quantify the probability that we are ever going to be attacked by an adversary using smallpox? No, I cannot.

But I think that threat remains real. The consequences of an attack however are grave. I believe with that, and utilization policy that we have - are coming to, that the vaccine would be reserved for those who have a high risk of exposure I think accounts for that.

Now part of the other question is, is the DOD - and there is a special I think need and requirement there, and members of our Armed Forces who are deploying to potentially high threat areas where we know we are dealing

with adversaries who may be thinking about using unconventional means, and that our deployment - and DOD will speak much more to this than I will - but there is a need to make sure that our forces are not degraded in that environment.

So the threat remains real in my mind, and many of us within the U.S. government circle - but again I cannot give you the probability of that.

DR. MODLIN: I guess my question really is, do we know anything more about the threat now than we did five years ago?

DR. PARKER: I think our conclusion and our thinking about the threat five years ago is the same today, and it really comes down, as I used to talk about the threat, and what I really studied more on the threat side as opposed to the countermeasure side, it really came down to, there is some probability that we may see smallpox in the future. Therefore we must be prepared.

To not be prepared, if you had my job, I can tell you that I don't want to be in a position where we don't have a vaccine when we could have.

CHAIR KARRON: Dr. Self.

DR. SELF: Yes, on your slide four, the utilization matrix, could you give a rough sense of the size of the top three populations, the lab workers, the health care workers, and the first responders where in a pre-event the vaccine would either be recommended or be made available?

DR. PARKER: Let's see. I don't know if somebody from CDC may help me out here on the laboratorians and how many are being immunized today.

DR. WHARTON: Melinda Wharton, CDC. My understanding is that about 600 laboratorians have been vaccinated within the last year. These are primarily people who are working with ortho pox viruses in the laboratory setting. And they are deemed at

high risk of exposure for that reason. It has nothing to do with the release of weapon smallpox.

DR. SELF: I couldn't quite hear. But then the health care workers and first responders?

DR. PARKER: Well, the health care workers, actually, when we originally began to look at health care workers, I believe it was anticipated there may be upwards of 400,000 or so health care workers that might be in that population, but only 39,000 have come forward to request immunization.

Some of that, the request for the vaccine did fall off when there was an increased incidence of myocarditis. Whether that is a cause and effect relationship, I don't know. But that's when the demand seemed to diminish. And so the population reported by the states may be in that range. The first responders, we're actually working through some of that in our pandemic influenza

preparedness activities, and defining those populations. I'll get those numbers, so that we can kind of gauge those with what we are doing in pandemic influenza preparedness planning. But we are having to make some very, very tough decisions with pandemic influenza, because there is relatively little vaccine. So you have to make some hard choices. And who would be able to receive the vaccine, and not only first responders, but the maintenance of critical infrastructure.

And one of the - one of the - I guess if we were experiencing a smallpox attack, at least today we don't have to make those hard choices. Because we at least have vaccine available that right now could be used under an IND in emergency use. But I can get those numbers to you from how we looked at that with pandemic influenza that really categorizes not only first responders, broadly defined first responders beyond the health care community, but then also looking at what

are some of the critical infrastructure.

And that may not apply as much in smallpox, because we can really look at where the outbreak is occurring, and focus the need for vaccine in the area of an outbreak, and not necessarily need to - it's different from pan flu in that case.

CHAIR KARRON: Dr. LaRussa.

DR. LaRUSSA: So two questions.

One, I tend to think of this as a combination of routine use in laboratory workers and the military, and then held in storage if needed for an emergency.

So I guess the first question is, what is the plan for integrating this with the available suplies of Dryvax? Are you going to use the Dryvax first and then use this for routine use only if you don't have any left over?

And I guess the second question is, I guess in a national emergency all bets would be off. What is the reason for bringing the

vaccine to the committee now and asking for the approval of the committee?

DR. PARKER: Well, first, of course we have been - there has been considerable thinking about which vaccine would be used. Because there is Dryvax, Wetvax, and ACAM2000.

And today we will use a licensed vaccine first. It is perhaps premature for me to really comment. I don't want to presuppose a decision here on ACAM2000, so it's really premature I think to conclude what would be different in the future. But certainly we want to use a licensed vaccine first, and that's the policy now.

But that would have to be changed as we move forward. But I don't want to presuppose anything.

DR. LaRUSSA: So I guess the question is, at the current usage rate, how long will Dryvax last?

DR. PARKER: Well, depending on the Department of Defense - maybe some of these

answers, what we might want to do is a tag team after DOD presents, because it depends on the DOD use.

But it's also going to depend on the continued potency and viability of Dryvax. So it's not just utilization in the utilization policies for the laboratorians or DOD or any future health care worker that wants to volunteer to get it, but it's also the viability of the current product.

So it's complex.

DR. LaRUSSA: You don't want to hazard a guess?

DR. PARKER: Well, I need to get what DOD -- the numbers that they are going to be using. But there are 15 million doses of Dryvax. Does somebody remember the number of doses that are still licensed from CDC? What's a component of that? So you can see it's not going to be long, depending on DOD's needs, and continued loss of potency, it's limited. What that time is, it's not long.

But we can do the math I think after we hear what DOD is going to say. Then you can project something on potency.

Our goal is we need to have safe and effective medical countermeasures, and we need to use licensed products, is our goal.

And this product is at its point in the developmental life cycle that it needs to be considered.

CHAIR KARRON: Dr. Massie.

DR. MASSIE: Two questions.

One is, in this plan for preparedness is it envisioned that these groups would be exposed on a voluntary basis to the vaccine or mandatory if there were an outbreak?

DR. PARKER: Well, I mean at the end of the day for civilian population I think it really will come - it's voluntary. They need to request that they get the immunization. And I think in face of a high risk exposure many would volunteer to receive a vaccine.

DR. MASSIE: The other question, and I don't know if we know, and I don't know if you are the right person to answer, but obviously the concern, and the reason why we're all here is, the high case fatality rate in morbidity mortality related disease.

But do we have any idea what those figures would be in this type of situation, in a developed population? Smallpox hasn't really affected people with good health care and modern anti-infectious treatments available.

Do we have any idea of whether that 30 percent figure is what would really be a realistic expectation in a situation like this?

DR. PARKER: Well, I think we have to look back on what are the historical mortality rates depending on the strain of virus that we might see in the future.

We have to factor that half the population has no immunity, and half the

population has some but probably little or waning immunity. And so we have a very vulnerable population.

But it's not only mortality; it's the morbidity associated with the disease that also has to be factored in. So it's morbidity and mortality. And it's also part of the strategy to help contain the spread of an outbreak so we can keep - assuming that there is a smallpox outbreak, that we have fewer of those high risk areas rather than more of those high risk areas, so less of the American population would be affected.

DR. MASSIE: I understand the strategy and the rationale. It's just that 30 percent figure I thought probably represents a fair amount of super-infection and other complications that might be dealt with differently than were they outbreaks that occurred within the last 50 years such as they have been, and perhaps now the case fatality rate would be lower though not trivial

obviously.

DR. PARKER: Well, it wouldn't be trivial, and I don't think the morbidity associated with the disease would be trivial either. And you have to take into consideration both morbidity and mortality, and again, what strain of virus we may be exposed to.

So it's hard to say whether it's going to be 30 percent. But we need to prepare though for the worse. Hopefully it's not that. But I think we don't want to underestimate the morbidity associated with the disease as well and must take that into consideration.

CHAIR KARRON: Other questions?

Thank you very much , Dr. Parker.

DR. PARKER: Thank you.

CHAIR KARRON: Our next speaker is Colonel Ford from the DOD.

DOD PRESENTATION

LT. COL. FORD: Thank you for the

invitation to come represent DOD and our smallpox vaccination program.

I chose this as our introductory slide to hopefully provide some context for everybody in the room. I'd like to introduce you first to this website, which is an information repository for all the data and all the clinical information related to our smallpox vaccination program, but also introduce you to the people that I work for, which are the war fighters there in the upper right-hand corner.

And make no mistake: it's our non-negotiable contract with our service members, with their families and the American people, which leads our program and weighs heavily on us and the responsibility in delivering a quality immunization program that's founded in science and one that is delivered according to quality standards for immunization delivery and medical care.

In December of 2002, the president

directed smallpox immunization of our armed forces. On December 16th, 2002, the Department of Defense initiated our vaccination program primarily of forces deploying to higher risk areas, emergency, essential civilians and contractor personnel performing mission essential functions; and again, assigned usually to the U.S. Central Command area of responsibility or career.

I want to provide the distinction that this is a mandatory program within the Department of Defense. And because it's a mandatory program obviously we have to weigh the risk of immunization and the threat posed by smallpox against an obviously low threshold for accepting adverse events in a pre-event exposure scenario.

To date we've screened over 1.3 million service members for contraindicating conditions, and exempted 110,000. And we've actually immunized over 1.2 million troops.

To familiarize you with our

program, our program is based on the principles of providing education through multimedia communication channels, and we provide educational resources to leaders, to health care workers, and to vaccinees and their family members.

A robust screening program using a standardized form to identify ACIP recognized contraindicating conditions; an adverse event monitoring system, again, using multiple surveillance systems, standard case definitions, a national pregnancy registry, and provide long term follow up care through our vaccine health care center network.

And all to ensure that immunizations are delivered by quality standards, and that quality standards are adhered to before - during the actual immunization process, and in after care if an adverse event occurs.

To familiarize you a little bit with the process of how a service member is

immunized, health care workers and actual immunizers have education that they receive through multiple mediums, and that the immunizers actually have their technique validated.

When but when a service member comes to an immunization clinic and is eligible for smallpox vaccination, they receive an education tri-fold in addition to watching a video that provides them information about the threat; the vaccine; expected adverse events; and what to do in the event of an adverse event occurs.

And this is an example of our smallpox tri-fold which each service member receives.

And what's important is that much of the information that is contained in this tri-fold is what would be contained in a medication safety guide. And if you'll see in the middle of the tri-fold, there is actually a cutout area which has important contact

information for individuals both related to who to contact if you have questions about policy or who to contact in the event you have an adverse event, and where to go if you experience an adverse event, and how to seek care.

On the reverse side, which you can't see, is an area which reinforces vaccination site care, recommendations as well as good hand hygiene and other recommendations for protecting household contacts.

And again this is all augmented through PowerPoint slides and other training aides and materials.

Not focusing solely on the service member, we also have educational information that we provide to protect household contacts. And again it emphasizes and reinforces recommendations for protecting household contacts.

In fact we even have educational materials for families that have pets, because

we know pets are important members of everybody's family, and how to protect them in the household.

So after they receive their educational materials and watch the video and receive their briefing, they complete this medical note for contraindications.

And you can see it's a screening form where by answering the questions contraindicating conditions are determined. And then through a triage system, based on their responses to these questions, they would see a health care provider, and a determination would be made by the health care provider whether to exempt them from the immunization, or whether to immunize.

This is an example of a clinic flyer that's in our immunization clinics that makes everyone aware of the national pregnancy registry. And to date there are 392 women that have been enrolled in the registry; and the data analysis that is available from the

registry shows no increases in pregnancy losses or birth defects in those currently registered.

An important component of our program is obviously the monitoring and surveillance of adverse events. Our joint regulation - and when we say joint, that means all services, Army, Navy, Air Force, and Marines - are governed by this requirement that reporting of adverse events is required in any situation where an adverse event results in hospitalization, a life-threatening event, time lost from duty for more than 24 hours, which is more than one duty shift, any event related to suspected contamination of the vaccine, or any event warranting permanent medical attention.

That said, what has been the results of our monitoring activities since 2002 through May of 2007?

Again, we have screened over 1.3 million troops for contraindicating conditions

and vaccinated over 1.2 million. We believe the exemption process is working well. There have been no cases of eczema vaccinatum among service members. There has been one unfortunate case of a contact transmission to a child with a contraindicating condition. No cases of progressive vaccinia. The number of VIG treatments are more rare than expected - the number is at six.

We believe our education is working well as evidenced by the rates of auto-inoculation and contact transfers, although we emphasize in all our materials and in all our outreach to our facilities that we can't let our guard down despite these numbers at home.

In other case evaluations of other serious adverse events there has been four cases of encephalitis, and of course, the unexpected number of myopericarditis cases currently at 140, although not an unanticipated adverse event.

Fortunately most of the vaccinia-

associated myopericarditis patients experience complete resolution of their myopericarditis symptoms and objective findings by six months.

There have been two deaths in the post-vaccination period, and one that is currently under review, which perhaps does have myocarditis as a contributing factor.

However I would strongly everybody in the room not to misinterpret this information. And the reason being is that for only one of the cases is there actually a causality assessment that has been completed. And it was conducted by an expert independent panel of civilian experts. And based on some confounding factors related to receipt of multi-immunizations and a lupus-like illness that occurred, the causality was deemed only possibly associated with receipt of the vaccine.

The second case is currently being evaluated, and is again confounded by a parvo virus B-19 infection, which also causes

myopericarditis.

And the third case is under just initial evaluation, and I can't provide any information for that.

We use standard case definitions. And DOD was important in developing the case definitions for myocarditis and myopericarditis, and in our multidisciplinary review of these cases which occurs monthly we determine, confirm probable or suspect cases based on a combination of those subjective and objective findings in assigning causality.

Other monitoring activities include cohort studies that contrast unvaccinated and vaccinated personnel. The defense medical surveillance system is an important tool for us. It's a large linked database analogous to the vaccine safety data link project. And it includes the information listed there for you. And most importantly the information is tied to serial serum specimens which may be useful in doing serum studies after an event.

There are some unpublished manuscripts that are under review, one of which is a paper that describes the lack of an association of ischemia or chest pain after smallpox vaccination. And another important resource to us as a transition to an electronic medical record in the Department of Defense, it's the Armed Forces Health Longitudinal Technology Application, often called the AHLTA which is being phased in which will assist us in monitoring adverse events through the electronic medical record and the encounter system.

We have a commitment to scientific communication. Our program is transparent, and DOD has been sharing its experience since the program's inception back in 2002 with our interagency partners.

We were again involved in the first case definitions development for generalized vaccinia and myocarditis, and we participate in multiple working groups to include CDC,

ACIP and the Defense Health Board, which is formerly the AFEB. And a small list of scientific publications are listed there for you.

Talking about quality care, when an adverse event occurs DOD has the vaccine health care center network, which is an expert clinical consultation group that is available 24/7. They have a call center. It's a toll-free number, and a secure consultative email system to provide support to service members and their families, and to other health care providers, both within the military and in our civilian counterparts, when they have a service member that presents perhaps with a vaccine-associated adverse event.

They are advocates for our patients. This is an example of one of the treatment guidelines, and the algorithm for myopericarditis which resulted from activities begun at the vaccine health care center, and what we use in determining or doing our

causality assessments. And again it's based on case reviews and expert consensus opinions.

Some examples of some research that the VHC has done and which contributes to our understanding of the monitoring process is the knowledge, attitudes and believe study which they published. And this was to assess the knowledge, attitudes and belief within the military health care system regarding the identification and reporting of adverse events. And it was a survey with a high response rate. And 54 percent of the study respondents said that they were at least somewhat familiar with the VAERS system, and 48 percent of those that responded said they've identified an adverse event; and about 45 percent reported that adverse event through VAERS, which is actually higher than what you would see from the general population.

And they all - the preferred method of reporting to VAERS was using the web-based system.

And to reinforce the importance of documenting adverse events through VAERS are each of the surgeon generals has developed policy statements encouraging our health care providers to use the VAERS system.

Another example of some research that has been resulted from hypothesis generation through our monitoring programs is this immunogenetic study that is being conducted in collaboration with Dr. Wilson at University of Washington and CDC and Kaiser, in trying to determine risk factors for myopericardial injury or inflammation, since we know that it appears that primary vaccinees, male, young people, Caucasian, seem to be at highest risk. So perhaps there is a genetic link, and that study is ongoing.

And I'd like to acknowledge the contributions of these other individuals in preparing these slides.

CHAIR KARRON: Thank you. Are there questions for Colonel Ford? Dr. Modlin.

DR. MODLIN: I wonder if you can tell us more about the sequellae of myopericarditis. You did mention that most had recovered and that there were two or three deaths that were possibly related.

But we know that there are both short term and long term complications of myopericarditis including dilated cardiomyopathy which can be obviously a very serious life threatening condition. And I'd be curious if that and other complications have been noted, and if so, in how many of these 140.

LT. COL. FORD: Yes, I'm actually going to defer to Dr. Nelson for a discussion of this, and I have some slides. DR. NELSON: I anticipated this question, so I'm going to help out Colonel Ford. Thank you for putting that slide set up.

What I'm presenting today is some data that was presented at the most recent American Academy of Allergy, Asthma and

Immunology meeting in February. So it is only published in abstract form. And there are several limitations, as I go through some of these descriptions.

So the take home conclusion is that these individuals do quite well. And most of them as stated in Colonel Ford's original presentation have resolution of their symptoms usually well before six months, but certainly by six months.

But I did want to give you some of the data, what we have within our registry, and present to you some of the difficulties that are encountered in conducting such a registry in the setting of the Department of Defense surveillance system.

So what you have here on the left are findings at various time points. In acute presentation, everybody of course was symptomatic. Anybody with data would follow up between one and six months. We had 72 of our cohort of 123. We're in the midst of

recategorizing and reacquiring and reanalyzing the data for the full 146. So this originally originates for the first 123.

We have data for some individuals with follow up visits from six to 18 months, and only a limited number beyond 18 months.

I too would love to have a Kaplan-Meyer curve for each of these data points. But in fact it is impossible to do so due to the way in which this data is reported.

So to show you where these data points came from, what the Vaccine Health Care Center does is very expertly go out and find these individuals who have experienced these events, and they have to contact individual providers.

It would be nice if they were all captured within the Department of Defense health care system. But in fact with these acute emergent presentations, the majority of them or many of them are actually seen in private clinics and hospitals throughout the

world.

So what we have is an individual evaluation which then must be combed and somehow coalesced into some formidable data set. And this is what is presented before you.

So in this particular study we went back and looked at essentially medical records for acute presentations and follow up visits, conducted in a nonstandardized manner. The criteria we used were any symptom within the CDC case definition, essentially chest pain. Any other new persistent symptom that developed along the line of Dr. Modlin's question, that yes, if you have myopericarditis, somewhere down the line you may develop some late sequellae. While in fact we had none that developed any persistent new sequellae beyond the six month time point.

We also wanted to find any new symptoms that affected the quality of life at these later time points as well. And I was

not able to identify any in this particular cohort.

Of symptoms that were presented both acutely and during the follow up visits, fatigue and chest pain were indeed the most commonly reported. And this is consistent with prior studies.

Late chest pain, you'll see, and that is depicted as the red line on the left side in the lower corner, is not zero beyond six months. So I would - everybody resolves by six months, so why are there percentages above zero for these later time points?

And the answer is that these individuals responded to surveys or reported to their clinical providers some transient twinge of chest discomfort, chest pain, that was judged for the most part to be atypical for periocarditis or myocarditis. Nonetheless in transparency we had to report that as a positive symptom. So that's why that symptom is not zero.

So despite percentages in the 30 percent range for chest pain and fatigue and other things, none of these were judged to be directly attributable to the initial myopericarditis event.

As we move over to the right-hand side of this slide we look at the objective finding. There was no persistence of clinically relevant findings; nonpersistent EKG changes are the reason why we're not at zero percent beyond six months as well.

These include ST changes, T-wave changes, that came and went, or were sometimes persistent or present during the initial presentation. They were judged to be normal variants by our interpreters.

Again, this is another factor in analyzing these particular data. There were multiple interpreters of these EKGs. So we were not able to get the original data for all the subjects within the registry. At some point we were still attempting to accumulate

all that data and to reanalyze it in a systematic fashion where we may be able to clean up the data set a little bit better.

But what you have before you today is the low pass filter if you will, any reported symptoms, any vague abnormality that you might see on an EKG, and anything that you migh8t see in a prospective clinical study that evaluates vaccine candidates where, under normal circumstances, individuals may sustain transient EKG changes, or transient twinges of atypical chest pain.

So we think this is a relevant subset. But again, late sequellae, such as dilated cardiomyopathy, et cetera, we did not observe on a significant basis in this data set.

So the take home conclusion, if we can go to the next slide, are that most vaccinia associated myopericarditis outcome patients experience complete resolution of their myopericarditis symptoms and objective

findings by six months.

Up to 30 percent may have nonspecific symptoms, especially chest pain and fatigue, and/or EKG findings that are atypical greater than six months after onset.

Avoidance of activities that increase cardiovascular risk should be undertaken for at least six months by these patients.

And the other take home would be, it's very difficult to do surveillance of these individuals. So as we go to look at implementing risk map programs for future vaccine programs, we have to understand the context that these service members are being vaccinated in the context of other vaccines and usually right before deployment where it is difficult to do the prospective clinical follow up that we would all around this table desire.

CHAIR KARRON: Thank you.

Dr. Teerlink, did you have

something directly related to that?

And then Dr. Jackson.

DR. TEERLINK: Thanks very much for presenting that. I did notice that there was still about a 10 percent - so go back - you know which one - persistence of ecocardiographic abnormalities. And given that echos probably weren't obtained in all these people, this is exactly the kind of thing we're interested in. Because 18 months is where there might be this development of the dilated cardiomyopathy, the development of actually relatively subtle changes in ventricular volumes and structure.

So what were those 10 - and I may be off, maybe it's eight or five, I can't tell - but some persistent echocardiographic abnormalities. What were the nature of those.

DR. NELSON: I didn't go into detail of those, and I actually don't have the original data. Some of them were mild hypokinetic effects, but not really

persistent, so at later time points they would disappear. So for example, just because it's at 10 percent, it's not those same individuals. Some would experience a borderline ejection fraction on one followup visit but not another.

The percentages you see here are not the percentages of the total cohort at that time point. It's the percentage of individuals who we had echodata for, as an example. And I can tell you that the N for echos at time points of six to 18 months or greater than 18 months was less than 10 for the entire cohort. So that percentage you are seeing is, I think one or two individuals may have had an ejection fraction in the lower 40s, upper 30s, but later resolved. It was asymptomatic at the time.

DR. NELSON: So another way to look at that is, 10 to 20 percent of the patients who had an echo had persistent - or had abnormal findings at 18 months. And those

findings were hypokinesis or of a finding that was exactly the kind of thing that would be potentially a concern.

DR. TEERLINK: I wouldn't say concern, because these individuals were asymptomatic. And the individual I believe who had that borderline abnormality was functional at work without restrictions.

DR. NELSON: And so to clarify for me, as a heart failure specialist, recognizing that heart failure is a progressive disease that progresses over time, and usually that it is - in fact patients start out being asymptomatic, with tremendous decreases in their heart function. And then later one, 10 - 20 years, develop the actual heart failure syndrome. That is actually my concern.

DR. TEERLINK: I certainly appreciate that, absolutely. I understand that concern. And we have concern for all of our members within the registry. We think, and I believe the data shows it, that for

patients who have myocarditis and develop cardiomyopathies down the stream, these individuals often develop it well beyond 18 months, at the onset of their late clinical sequellae, which is why this cohort is being followed so closely, and it's anticipated it will be followed for quite some time to come.

Thank you very much for your comments.

CHAIR KARRON: Dr. Jackson?

DR. JACKSON: I have two questions, maybe for Dr. Nelson or a colleague.

So your rate of 140 per 1.2 million doses is about 12 per 100,000. And is that with Dryvax? What vaccines were they receiving?

LT. COL. FORD: Yes, all Dryvax.

DR. JACKSON: All Dryvax, okay. And the time point of exposure is not on entry into the Armed Services, but rather when deployment is imminent; is that correct?

LT. COL. FORD: That's correct.

It's an operational requirement based on area of assignment or whether you have a special mission role or biodefense mission.

DR. JACKSON: So in general following the vaccination, what proportion of vaccinees are still with the armed services say one year or two years later? Do you have any idea?

LT. COL. FORD: I do not have that data for you. I don't have the exact number, but the deployments are generally for a year. So almost all of them are in for the first year, and most of them you know unless they are near their elected termination of service or near a retirement date, the reenlistment rates are very high, so the numbers are very high.

DR. JACKSON: So in general you would expect to be able to follow these people through military channels for an extended period of time?

LT. COL. FORD: Yes.

DR. MASSIE: I guess the same question is, I mean since this is such an important thing to know, and this is the only way we're going to find out, having identified a case, I can't understand why there isn't a plan for serial echos being done on these people rather than an informal registry trying to capture information, might possibly acquire it from multiple sources.

Clearly when we get to risk management, that will be something. But these are people in the military, or in some way recent servicemen, and why can't we just fly them to a place and get an echo, in a systematic way viewed by a Corps lab.

And the second question of course will be, well, how do you interpret it when you get 20 - 30 percent of people who aren't quite normal? So I think a plan for a control group is going to have to be important to.

CHAIR KARRON: Dr. Farley.

DR. FARLEY: I was struck by the

same thing, that a standardized follow up would be very desirable.

I have a couple of questions. One is, so we've established that they would be immunized near the time of deployment. I'm curious whether there is some that window of time, whether they are freed up from duties, or whether they are in a strenuous training period of time while they are being immunized in the time when they are caring for the wound, or the vaccination site.

And if they do manifest any signs of myopericarditis, are they still deployed? I almost got the sense that they were deployed. Are there any changes that occur?

And then the final question is, if they refuse the vaccine what are the consequences to them? If they don't have one of the screening criteria for exemption?

LT. COL. FORD: I can answer probably the first and the last one. I can let Dr. Nelson answer the second question.

Service members can be immunized anywhere up to 60 days before deployment. And there is a great deal of training that takes place, predeployment training that is mandatory before they enter the central command area of responsibilities.

So I mean what they do is strenuous on a daily basis. So yes, they are perhaps engaged in strenuous activities. And of course there is physical training that is required in most units. So the answer to your first question is yes, it's part of our job.

And in answering the third question, which now I -

DR. FARLEY: Well, if they refuse.

LT. COL. FORD: Oh, it's a commander's program. And certainly the commander is responsible for determining what is going to happen. The service member is counseled, and obviously, tries to -- encouraged to take immunization. And of course it's up to the commander's discretion

what the punishment will be if they refuse.

DR. NELSON: So to address your question, if you will allow me to rephrase, I believe that was deployment of those who develop symptoms of myopericarditis. And in fact we do not deploy those individuals.

What we haven't highlighted for you this morning is that the Vaccine Health Care Center has developed a management algorithm for all of these individuals, for those who present with symptoms suspicious or even remotely possible for myopericarditis. Included in that is a litany of studies including imaging as well as enzymes, et cetera, and periodic followup just as you alluded to, at several time points, and well beyond six months, et cetera, so we don't allow these individuals to fall off the face of the earth if you will.

Individuals who are recognized with acute presentation of myopericarditis are certainly not deployed.

CHAIR KARRON: Dr. Modlin.

DR. MODLIN: If you want to create viral myocarditis in the laboratory, the way you do that is, you give a mouse coxsackie virus, and then you force them to exercise. And it raises - of course the cases of myocarditis that have been observed have been observed within a few weeks after immunization right at the time that you would expect peak viral replication to be occurring, which would at least suggest that you have a similar mechanism of pathogenesis, which is direct involvement in mycardium with the virus.

I guess it raises the question of whether or not one couldn't do the experiment, an actual experiment, if actually asking a vaccinee not to exercise vigorously for the first two weeks or first three weeks after vaccination to see if that would in anyway modify the risk.

And it sounds to me like you might have a high enough number of cases that that

would be not an unreasonable experiment to do.

DR. NELSON: I certainly agree that that is a possibility and a good suggestion. I can tell you that there appears to be no pattern amongst those who are vaccinated and sent to a rigorous training center before their deployment, and seeing an inordinate number of cases from those individuals who we know are under heavy exertion, compared to individuals who we are now encouraging to get vaccinated three and four and even 60 days - three and four weeks or eight weeks before their actual deployment; where their level of activity is certainly much less than right before or during their initial deployment.

We have not seen that. I think Colonel Ford can echo that comment as well.

LT. COL. FORD: Again, we temper the requirement to deliver the immunization in a time interval where if a service member is going to develop myopericarditis, that they would develop the myopericarditis here in the

state versus in the theater of operations where now they are deployed and their team is relying on them to perform a function, and they are no longer available and actually have become a casualty and have to be evacuated and an individual replacement found to make up the team.

So we highly encourage earlier versus abrupt immunization at the time they are getting on an airplane to go to the theater of operations.

DR. NELSON: And it's often difficult to meet that time line, because they don't get notified until right before. But if we can increase that number as we are certainly trying to do we could do the studies that you are alluding to. So I think that is a very good direction that we need to move in.

The longer team followup with the serial echos and serial formal cardiac evaluations has been an issue. And it's certainly been on the table, and we've been

conducting it on those we continue to have access to.

As you might imagine individual service members who at the conclusion of their deployments - so no, with acute myopericarditis are we deploying them, but once they are cleared by cardiology several months later, after a period of rest and resolution of any objective and symptomatic findings, some of those individuals are in fact deployed and do quite well.

But as they return back from their deployments, or decide to get out because of their acute event, or sent out because of their acute event, we do in fact lose control of them, and are not able to formally demand that they come in for their cardiac studies. And in fact there are issues with regards to us being able to evaluate civilians within our health care system.

We partnered with representatives of the CDC and the University of Washington in

this clinical study that Dr. Ford alluded to, and we hope to recapture that lost population to help do some of these follow up studies, and we hope to expand those efforts in the near future.

DR. TEERLINK: I mean certainly as a VA clinician I would be more than willing to help personally with this. But in addition it is hopefully made clear to these individuals that it is in their best interests, because this is a service connected issue.

DR. NELSON: Absolutely.

DR. TEERLINK: And certainly I know I'm not alone among VA's physicians in saying that this is part of our responsibility to take care of those who served, and provide the information that is required to help those who are serving.

So I think there certainly are channels to maybe not mandate, but certainly increase and get a relatively high capture rate. Certainly among my patients there is a

very high interest in continuing the clinical research and helping in these ways. So I hope and encourage you to continue to pursue these avenues.

CHAIR KARRON: Dr. McInnes.

DR. McINNES: Certainly the number of cases that you have at the moment, and hopefully will lend themselves to sort of doing a genome wide association study, but what are the plans looking at linkage studies using genomic technology?

DR. NELSON: So they are doing the genome wide scan as you saw some of the - well, not the actual data from it. It's been presented I believe by Chris Wilson in a meeting earlier. They have identified some candidate genes in very preliminary work that we don't need to go into details today about.

Some of the linkage analysis I believe are planned as the follow up studies once the real signal for the candidate genes are evaluated. And I agree that perhaps a

more wide approach to doing linkage studies could be appreciated. And I believe as a follow on study, though not in the current plan, will be added on to Dr. Wilson's study in collaboration with the Vaccine Health Care Center. Excellent point.

CHAIR KARRON: Thank you.

We do need to move on to the next section. But I would just like to ask you a couple of questions, Colonel Ford. One is just a very practical one. If a service member has medical exemptions, does that mean that person is not forward deployed? What happens?

LT. COL. FORD: No, just a screening, contraindication, and a medical exemption does not make the service member nondeployable.

CHAIR KARRON: So they then would be deployed without vaccination.

LT. COL. FORD: Correct. And those people are obviously identifiable from our

immunization tracking system. And the commanders know who those individuals are because they get monthly reports on individual medical readiness.

CHAIR KARRON: And can you give us some sense of how many - I know that you said I believe 1.2 million doses total. But on a yearly basis is that number increasing, decreasing, staying the same on a yearly basis?

LT. COL. FORD: I can't give you a specific number because it would identify numbers of operational forces that are moving in and out of the theater. I can only tell you that as our number of primary immunizations goes up, and they return to the theater, not requiring a second immunization, our requirements would go down.

CHAIR KARRON: And then just - obviously you can't give us much information about this - but in terms I think analogous to the question that Dr. Modlin asked for the

civilian sector, risk assessment, is that done on an ongoing basis? Is it done for each theater separately?

LT. COL. FORD: I can tell you that, again, as Dr. Parker alluded to, it's the consensus opinion of the intelligence community that smallpox is a real threat, a clear and present danger to our operational forces. And I can tell you that as new intelligence is gathered and made available, all our force health protection immunization programs undergo thorough review by the civilian leadership of the Department of Defense.

CHAIR KARRON: Okay, thank you.

At this point we'll move on to the Accambis presentation, and I believe Dr. Wonnacott will begin.

ACAMBIS, INC. PRESENTATION

DR. WONNACOTT: Good morning. My name is David Wonnacott, and I'm pleased to be with you to provide a few introductory

remarks, and to briefly set the stage for the next hour of presentations from Acambis.

Acambis is a company that is highly focused on the development of novel vaccines with the majority of our staff working in R&D in Cambridge, Massachusetts.

We also have a manufacturing facility for bulk manufacturing and final fill for final container vaccine.

Following 9/11 there was - and the subsequent anthrax incident, Acambis responded quickly to the government's urgent call to develop a new smallpox vaccine.

ACAM2000 is the result of those efforts. It is a unique vaccine, because it was developed in the absence of a disease. And it's only targeted at those at risk for infection as determined by government agencies.

The question might be asked, why didn't industry just make more Dryvax? After all it's the vaccine that is already licensed.

Well, the answer to that question is illustrated in the next slide. The bottom line is that it was time to update our bioreactors. Dryvax is harvested from calf skin, whereas ACAM2000 is manufactured using modern cell culture technology.

ACAM is purified, homogeneous, clonal isolate derived from Dryvax. It was selected to be less neurovirulent, and tested to be free of adventitious agents.

It is with this type of technology that large amounts of vaccine can potentially be manufactured. Indeed, during the clinical development program, almost 200 million doses of the vaccine were delivered to the strategic national stockpile.

I should add that we have delivered all the doses that have been ordered to date.

I would also like to point out in the slide that the IND was filed less than a year after 9/11, and the BLA was just filed less than a year ago.

That's now I'll introduce the rest of the program. We'd like to begin with a brief review of the history of this disease and the reasons we need the vaccine. Dr. John Neff is well qualified to discuss this subject, having participated in smallpox eradication and safety surveillance programs, starting with the CDC in the early `60s and continuing through collaborations while at Johns Hopkins.

John served as chair of the CDC DOD smallpox safety working group from 2002 to 2004. Following our history lesson, Dr. Tom Monath will review the preclinical and clinical data that supports the safety and efficacy of ACAM2000.

Prior to joining Acambis in 1992, Tom spent 20 years at the CDC, as the division director for the vector borne viral diseases, after which he served as the chief of virology for USAMRID.

He is an adjunct professor at

Harvard School of Public Health.

During our clinical studies we look carefully at all vaccines related to myocarditis, vaccine-related myocarditis, and we learned quite a bit from these studies.

We've invited Dr. Jay Mason to discuss these findings with you today. Jay was the lead investigator in the U.S. myocarditis treatment trials that were reported in the New England Journal of Medicine in `95.

Our concluding speaker will be Dr. Michael Watson. I notice in the speaker roster he was listed as heading up our quality and regulatory; actually that's me. Mike heads up the research and development efforts at Acambis, and he will discuss post-marketing risk management and risk minimization plans.

With that I'd like to turn the time over to Dr. Neff.

DR. NEFF: Thank you very much. I'm John Neff, and I'm going to be talking about

the history of the smallpox disease vaccination eradication. But before I start I would like to acknowledge D.A. Henderson who is present who is really the true expert in this area and responsible as a leader for much of the eradication, and then also my mentor for many years. Glad to see you here, D.A.

These are the topics that I'm going to cover. I'm going to very briefly talk about the history of smallpox, its control, eradication, and potential for bioterrorism use. Talk about smallpox vaccination - its development, protection and adverse events.,

Descriptions of smallpox, the clinical types and expected mortality. And then some concluding comments.

Here's the history of smallpox. It first appeared around 1100 B.C. Its origin was probably from a closely related animal pox virus of the orthopox virus group. And then as it became more epidemic and endemic, it was responsible for worldwide and epidemic

patterns throughout Europe, and certainly caused massive pandemics with high mortalities in the Americas.

There is no doubt that smallpox over the years has changed the course of history several times. It was responsible for an estimated 300 million deaths in the 20th century.

This is just a very brief history of the control of smallpox. Variolation was practiced early on but had relatively little impact on the main control. But it really started with Edward Jenner's discovery and observation that vaccinia based vaccination could indeed protect against smallpox.

That was then used progressively throughout the European world and throughout the world. And by 1967 there was an enhanced WHO eradication program that we all know about.

In 1972 vaccination ended in the United States. Actually the last cases of

importation smallpox in the United States occurred in the 1940s. And endemic smallpox, variola minor form, probably occurred - ended sometime in the early part of the 20th century.

The last natural case of smallpox occurred in Somalia in 1977. But really the last case or death of smallpox occurred in 1978. It was laboratory acquired, presumably through the air vents. And Janet Parker was the unfortunate person in Birmingham, England who died. Her mother also contracted smallpox and survived. Her father had a heart attack and died. And the director of the laboratory where that variola was being tested committed suicide. So it was a very tragic event.

In 1980 WHO declared smallpox to be eradicated. And in 1984 variola was designated to be placed in two secure repositories and nowhere else in the world, in the CDC in Atlanta and in a laboratory outside of Russia.

This is what has happened to our

current concern. Subsequently we have learned that the Soviet government had developed a bioweapons program with the intent to produce smallpox in large quantities and adapt it for use in bombs and ICBMs. Their intention was also to develop industrial capacity capable of producing many tons of smallpox virus annually.

The other thing that happened is that during the latter part of the `70s and `80s the official repository in the Soviet Union was not really all that secure. And there were probably many scientists in and out of the laboratories at that time. And they represented some of the so-called rogue states.

But there is the risk that these rogue states did not destroy the stocks of variola, and that it could be used for bioterrorism purposes. And to my knowledge this concern has not changed in any way since 2001.

This is a little bit about the smallpox vaccination. Vaccinia was obtained from animals originally, presumably cows or horses - it's obscure and not certain. It's certainly a member of the orthopox family, but it's a very distinct virus within that group, and it is related to both cowpox and variola.

It was initially propagated from person to person. In fact it wasn't until the middle part of the 19th century that it began to be propagated consistently through the use of calf lymph or inoculation of calves.

By the 1950s and `60s there were many different strains of vaccinia available in the world, but it became standardized into two specifics strains, the lister and the New York City Board of Health. With these two responsible for eradicating smallpox worldwide by 1980.

The evidence for protection is fairly historical and fairly clear. The cutaneous reaction was what was used for the

demonstration of protection long before there was ability to measure neutralizing antibodies or T-cells. And that was shown, the major reaction, which was defined by WHO, demonstrated protection, provided protection against smallpox.

But also subsequently it noted that the major reaction correlated with the development of neutralizing antibody T-cells after vaccination.

Subsequently in a very small number of studies, neutralizing antibodies or the presence of them certainly correlate with protection against smallpox in humans. And there have been laboratory tests where mice and monkeys with neutralizing antibodies against variola, but who have also been T-cell depleted have been protected against challenge with the corresponding orthopox virus.

Also in some studies passive immunization has been demonstrated to provide some protection both in humans and in animals.

And T-cells certainly may play an important part.

The protection of vaccinia is derived from a variety of different studies, many of them were done between 1950s and 197s. And this is a study that is also published in Fenner that studied all the cases of importation smallpox into Western countries during this period of time.

And from that, anyone who had had vaccination between one to 10 years before exposure, the case fatality rate in that group was 1.4 percent. Eleven to 20 years after exposure the case fatality went up to seven percent, but not much much higher.

But even those individuals who had been vaccinated more than 20 years exposure, about 11 percent of them had a case fatality rate. There is some protection, protection of about 29 percent of those individuals who had been vaccinated immediately after exposure.

But for those who had never been

vaccinated and had no experience with either smallpox or vaccinia, the case fatality rate was 52 percent.

So it's generally felt that complete protection from vaccination lasts from three to five years; partial protection up to 25 years; and there may be some long protection against death that is lifelong.

This is just a summary of the adverse events that were observed during the 1960s in the United States. And the first two at the top, progressive vaccinia and eczema vaccinatum are definitely preventable. Progressive vaccinia is a fairly serious disease - one to seven cases per million vaccinations - that occurs in individuals who have a depletion of T-cell counts. The severity of the disease is highly dependent on how depleted those individuals are. Generally we saw a mortality of between 25 to 60 percent in that particular condition.

Eczema vaccinatum, which occurred

in about two to four cases per 100,000, is a generalized form of generalized vaccinia that occurs in individuals with eczema or a history of atopic disease. The mortality in that group was one percent, but about 20 to 30 percent of those were in context. These two certainly can be prevented through careful screening as we have seen.

Post-vaccine encephalitis, there is no known predisposing cause. It's probably similar to acute disseminated encepalomyelitis. There we observed about one to two cases per 100,000 primary vaccinations with a mortality of about one to 10 percent. And I'm sure both the mortality in eczema vaccinatum and post-vaccine encephalitis has been improved considerably with the availability of modern therapeutic and intensive care support.

Contact vaccinia is simply the transfer of vaccinia from a vaccinated person to a person who has not been vaccinated;

generally requires close body contact. In the 1960s it occurred in about two to six cases per 100,000, and about one-third of those cases were in children with a history of eczema.

Accidental infection is simply an auto-inoculation, often at the time of vaccination, and is fairly mild unless it gets into the cornea, and then it may develop some moderate or severe ocular impairment.

And then there is a whole group of conditions. Into that is often lumped what people call generalized vaccinia. They are erythematous. Some are vesicular. They occur about one per 100 primary vaccinations. They are very mild. They are poorly understood. But they certainly do occur.

Clinical description of smallpox. Very briefly, this is a slide, also from Fenner. During the first 13 days, during the incubation period, there is no contagion; there are no symptoms. But during that time,

after the virus is introduced into the respiratory tract, it appears and then replicates in the lymphatic system, and then breaks out into a viremia fever, backache, headache, nausea and malaise. And it's during that period of time that the patient becomes contagious.

And then that moves on to the rash, which is progressive, going to macules, puples, vesicles and pustules and finally to scabs. In the early phases of that rash, the patients are very contagious. But the patients may contain some minimal degree of contagiousness, because the virus can be found in the scabs, for a long period of time.

This just shows the progression of smallpox from the CDC collection of slides. On day three you can see the papular rash. On day five the vesicle rash. And then on day seven the pustular rash, and it moves on to scabs.

The clinical features of smallpox,

discrete, confluent and flat, and hemorrhagic, and as you project, progress down that ladder, the mortality becomes higher and higher.

This is the discrete form. These are very punctate lesions. They are very well - it shows that the virus has been very well contained dermally. Then it becomes confluent or semi-confluent, moving on to the more confluent form where it's just a massive confluence of vesicles, and the rash actually appears quite flat.

In this form the mortality becomes fairly high. The worst manifestation is hemorrhagic. There are two forms. In the acute form of the disease where there is just an erythematous rash, and the patient dies fairly quickly. And then in the late form where the pustules become quite hemorrhagic, and the patient can die, and this is probably a manifestation of a disseminated intravascular coagulation syndrome.

So mortality from infection of

variola in the unvaccinated individuals can be up to 50 percent, and that of course is going to vary to some degree depending on the virulence of the given strain. But it's expected that in a bioterrorism attack the most virulent strains are probably the ones that have been preserved.

So in conclusion smallpox is a devastating disease with a very high mortality in the nonimmune. Vaccination historically is associated with significant adverse events. The populations are immunologically vulnerable, once eradication has occurred and there are no longer any indigenous cases of smallpox, and at the end of a vaccination program.

In the United States, as has already been mentioned, few people have been vaccinated in the past 34 years, and those who have been were vaccinated a very long time ago.

So as long as variola virus exists

anywhere there will be a need to have a smallpox vaccine available in the event of a bioterrorism threat or possibly a laboratory accident. It's in our best interests to have a modern smallpox vaccine available.

Thank you very much. DR. WONNACOTT: Tom.

DR. MONATH: Good morning.

It is also my pleasure to be able to tell you about the ACAM2000 program. And my job is to describe principally the clinical development program of the vaccine. Most of our goals in this program were indeed met. As you've heard we developed a new vaccine candidate which was derived as a clonal or plaque purified virus from a pool of Dryvax, multiple lots of Dryvax.

We developed a well characterized seed virus which was tested and shown to be free from adventitious viruses.

We engaged in a large scale GMP manufacturing campaign using viral cells and

serum free medium according to modern standards for vaccine manufacturing.

And all of the lots that were produced met an array of quality control tests, and release specifications, including designated potency which should exceed 10 to the 8^{th} plaque forming units per mill.

We showed in clinical trials that the safety intolerability of the vaccine was similar to or better than Dryvax. I'd just mentioned that of course myopericarditis was determined in our studies to be a more frequent event than anticipated by the DOD or civilian experience. We'll say more about that of course.

We demonstrated clinical efficacy, although there are a number of differences from Dryvax, which we will go through.

As you heard, vaccination with this vaccine is indicated for protection of persons who are determined to be at high risk for smallpox infection. It's not for general use

in the population unless there is an event.

And it's stored and controlled by the strategic national stockpile, or SNS, and not distributed outside that government agency.

Briefly mention some salient nonclinical data, which I think would put into perspective some of the things that have been mentioned about neurovirulence in particular. Of course we do rely for a number of these biodefense agents on animal data.

A variety of toxicology studies were done in mice and cynomolgus monkeys which were inoculated by the intracerebral route, and those studies invariably showed that ACAM2000 was indeed less neurovirulent than Dryvax.

Now what does this mean? Of course we don't have enough clinical experience with this vaccine to understand whether these animal data would relate to a lower incidence of post-vaccinal encephalitis. But historical

data quite clearly show that strains that were more neurovirulent than mice - baby mice - those vaccine strains were associated with a higher incidence of post-vaccinal encephalitis in humans, particularly for example vaccine made in China.

ACAM2000 Dryvax have similar immunogenecity in mice and monkeys. And both vaccines protected these animals against lethal challenge with homologous and heterologous pox viruses.

One data slide on neurovirulence: this is the test for neurovirulence that was conducted not only on the seed viruses but on every batch of vaccine that was made, in which three to four day old mice were inoculated IC, statistically powered study to show the difference between Dryvax and ACAM2000. Here you see the survival curves with ACAM2000 being less virulent higher survival ratio than Dryvax. That was a reproducible finding, and it was a good way to test the consistency of

manufacturing using a biological assay as well.

These data show the result of a study of protective immunization in cynomolgus monkeys who received either ACAM2000 or Dryvax or a sham vaccine.

All eight out of eight monkeys in each treatment group developed a typical cutaneous response to the vaccination. They developed high titers of neutralizing antibodies. Here you see the geometric means there that were similar across the treatment groups.

The animals were challenged with a high dose of monkey pox virus by the intravenous route. This is - I'm not quite sure how many LD50 this represents but it results in 100 percent mortality in these animals.

None of the vaccinated animals developed pox on the skin or oropharynx, whereas the controls developed large numbers

of lesions. None of the vaccinated animals in either group developed fever in comparison to the unvaccinated controls which did.

There was little viremia - no viremia in the ACAM group; a little shedding in the Dryvax group but no viremia in the blood in contrast to the controls. And all of them developed no signs of illness and no deaths in the vaccinated group, whereas all eight animals in the control group were euthanized.

So go on to the clinical trials now. I'll first describe safety. This slide just simply lists the two phase-one, two phase-two, and two phase-three trials, the status of the population whether naive or previously vaccinated.

In all trials safety was determined; the cutaneous response to vaccination and antibody response was measured.

In the phase-two program in naive

and previously vaccinated subjects we also did some dose response studies.

In the phase-three naive trial we determined lot consistency with three conformance lots tested in the trial, looking at both cutaneous response and antibody response.

And in one phase-one trial we also looked at the T-cell responses. We looked at shedding of the virus from the inoculation site, both at the skin and on the bandage, and we determined whether the vaccine elicited nonspecific serological test for hepatitis, HIV and syphilis.

The number of subjects in the ACAM2000 program, nearly 3,000 overall; 868 received Dryvax. You can see the numbers here. I won't repeat them. But the main point is that the phase-three study enrollment was curtailed when about 40 percent of the naive subjects, or 67 percent of the previously vaccinated subjects had been

enrolled, because of the incidence of myocarditis which was discovered to be occurring at a rate which was unsuspected at that point.

And the planned number of subjects in these two trials was 2,040 ACAM and 680 Dryvax, so you see that the study was stopped because of those events.

Power calculations were then done. It was deemed appropriate not to continue these trials because we had sufficient power to estimate efficacy.

Nearly all, 99 percent of the subjects, completed the studies, and very few withdrew.

The treatment groups were very well balanced with respect to gender, age and race. I'd just point out that of course the trial - oh, nine involving naive subjects was in younger individuals 18 to 30 years of age who were born after cessation of routine immunization. But the two treatment groups

had a similar age. And the subjects in the previously vaccinated trial were older, ranging up from 31 through about 84 years, with a similar mean age across the two treatment groups.

Now the adverse event profile was that expected based on knowledge of vaccinee in general and Dryvax specifically. The expected adverse events were observed, principally inoculation site reactions; lymphadenitis; feverishness; and some systemic symptoms that you see on the slide. The incidence of these adverse events was slightly higher for Dryvax than for ACAM2000 in both trials. Maybe a little hard to see in the back of the room. This shows the incidence of common adverse events, those occurring at 10 percent incidence or greater. In the vaccinium naive or previously vaccinated subjects, by treatment group, the yellow highlights are those adverse events that were more frequent statistically, and the Dryvax

group and ACAM, those were largely as I mentioned, inoculation site reactions or systemic signs.

And overall the frequency of adverse events, as would be expected, was lower in previously vaccinated than in naive individuals.

We will talk a lot more about myocarditis. That was the most important serious adverse event. This slide shows the serious adverse events in naive and previously vaccinated subjects by treatment group. Overall the incidents of myocarditis was point five to point eight percent. There was no statistical difference between the two treatment groups in incidence of myocarditis.

Other adverse events occurred infrequently, less than one percent. There were some possible cardiac adverse events in the previously vaccinated subjects but these were determined not to fit the diagnostic criteria for myocarditis.

Now myocarditis by protocol design was prospectively ascertained in these trials. And also in the 400-002 phase one trial. So probably the fairest estimate of incidence in our studies is from those three trials in which case ascertainment was performed by a uniform method.

That was done by performing electrocardiograms at baseline, and on day 10 and 21 in the phase-three program, or on day 15 in that phase-one trial.

Cardiac enzymes were measured at screening and on day 10 in the phase-three program and day 15 in the phase-one study. And of course on all clinic visits and in the diaries cardiac adverse events were sought.

Myocarditis was seen only in naive individuals, and as we'll talk more about, the incidence was higher than seen in the DOD program in which the reports were symptomatic patients only, and were spontaneous reports rather than being prospectively ascertained.

In these three studies, or in the phase-one trial and the phase-three vaccinia naive subjects, there were - the incidents of myocarditis after ACAM2000 was 6.6 per 1,0000, and in Dryvax 9.4 per 1,000. It's important to point out that four of the six cases after ACAM2000 were asymptomatic; i.e. they were what we call subclinical myocarditis, and would not have been picked up had we not prospectively done cardiograms and enzyme measurements.

One patient in each group was hospitalized, and of this group of nine subjects, there was another subject in a trial for which the ascertainment wasn't exactly the same; that's where the difference comes.

But among 10 subjects as here, there was only one individual who we will talk more about in Dr. Mason's trial who had any residua, and that was an individual who had a decrease in left ventricular ejection fraction. He's been followed now for two

years, and that persists. We'll talk more about that in the next talk.

Let me turn now to the clinical data on efficacy. Of course as you've heard this is an eradicated disease, so we have to use surrogates or correlates of protective efficacy to measure that.

The cutaneous response is a generally accepted surrogate of protective immunity. Neutralizing antibodies an accepted correlate. In fact, that may be a more accurate reflection of vaccine effectiveness than previously vaccinated subjects, because pre-existing immunity can modify the cutaneous response.

Historical data suggests that relatively low titers of neutralizing antibodies are protective. We don't really know what the protective level is, but in two historical studies low titers were associated with protection.

There were two co-primary endpoints

in the efficacy trials, cutaneous response rate and geometric mean titer.

The statistical methods for evaluation were tested noninferiority against Dryvax, the control group. And in the case of cutaneous response, the goal was to exclude a margin of superiority of Dryvax of 5 percent or greater in the naive subjects or 10 percent in previously vaccinated, the reason for the difference there being the lower expected take rate in previously vaccinated subjects.

For GMT, again a test of noninferiority where the goal was to show that the ratio of the GMT for ACAM2000 to Dryvax was at least point five, or a log value of minus .301. Other secondary endpoints shown here, we will talk about some of these, but in particular of interest was the covariate analysis, which was a planned study that looked at the effect of baseline immunity, that is, neutralizing antibodies in previously vaccinated subjects, and the influence of that

variable on take rate and antibody response.

The cutaneous response, for the two trials, naive and previously vaccinated, as shown here, by treatment group, 96 percent of subjects receiving ACAM2000 developed a take versus 99 percent in the Dryvax group; and we met the noninferiority criterion.

In previously vaccinated subjects, however, the response rate was lower - 84 percent versus 98 percent - and we did not meet the noninferiority endpoint. So we can say that ACAM 2000 was noninferior to Dryvax in naive individuals, but that the take rate was lower than that seen with Dryvax in previously vaccinated subjects.

Now further clarity on this, however, comes from the planned analysis of the influence of preexisting immunity on the response, in previously vaccinated subjects.

And here we look at the response rate by the baseline titer, that is, prevaccination titer of neutralizing

antibodies for each of the treatment groups. The most important take-home message here is that if you have no detectible immunity at baseline, a titer of less than one to 10, the response to ACAM2000 is similar to that seen in naive individuals.

The other point is that while Dryvax is less susceptible to preexisting immunity, ACAM2000, the take rate is inversely proportional to the level of antibody before vaccination.

And I think that is reflective of a certain attenuation of this virus, which of course was seen in the animal studies and also in the dose response studies.

The same analysis was performed for the antibody response. Here again individuals who have no antibody at baseline have a robust 30 fold, 30 - 36 fold increase in antibody titers. That fold increase or magnitude of response declined with increasing levels of antibody at baseline for both vaccine.

And indeed, this level of response is similar to what we've seen in the naive individuals in the -009 study.

Turning now to the GMT endpoint, for naive and previously vaccinated subject by treatment group, the GMT was about 1.5 fold lower in both trials for ACAM2000 versus Dryvax, a relatively small difference. Neutralizing antibody titers were robust in both groups; these are relatively high geometric means. We did not make the noninferiority endpoint in the naive subjects, although the margin, we narrowly missed that statistical endpoint, whereas we did meet it in the previously vaccinated subjects.

Perhaps of interest is the cumulative reverse distribution of antibody titers, which is the proportion of subjects that have a neutralizing antibody titer greater than the value shown on the X axis. And here we display those curves for both the previously vaccinated and the naive subjects.

I think the important points here are that most subjects had relatively robust high neutralizing antibody titers. Previously vaccinated subjects had higher antibody titers than naive individuals. And that over 90 percent of subjects had neutralizing antibody titers that were above those values that we might assume may be protected based on the historical published record.

We measured T cell responses in one study, the 400-002 study. This shows the categorical responses, the incidences of positive responses, for three different assays, CTL, gamme-IFNELISPOT, and lymphoproliferation. And we also display the median values in those groups.

And all the - the vast majority of individuals in both treatment groups - ACAM2000 and Dryvax - had robust T cell responses. In fact ACAM2000 looked somewhat higher than Dryvax in this trial.

Just one of the individual

datapoints for the ELISPOT assay, which probably is reflective of CD8 responses. For ACAM2000 and Dryvax, all ACAM2000 individuals above the cutoff.

And the point here, I think, is that these are robust T cell responses, and hundreds of spot-forming cells per million.

So those three slides to kind of sum up and conclude here. We have developed a new vaccine by modern manufacturing methods, and applied quality control tests for adventitious agents. This is large scale manufacturing, delivered 75 lots and 192 million doses to the SNS. And I think the safety assurance is greater for a vaccine produced under these conditions than for the old animal tissue vaccines.

It's a purified clonal vaccine, less neurovirulent in animal models than Dryvax; is immunogenic and protective against lethal pox in various animal species and models; and the clinical data demonstrated

safety and tolerability that was equivalent to that for Dryvax; and as we will talk more about, of course, there was a vaccinia class effect here, myocarditis occurring in both Dryvax and ACAM2000 treated subjects at a rate of approximately one to 150 in the case of the vaccines, which is of course higher than we've seen in the DOD program.

Primary indicators of immunity support efficacy in naive subjects; 96 percent had a take, noninferior to Dryvax. There were high neutralizing antibody titers after ACAM2000; a geometric mean of 166. Over 90 percent had titers that might be expected to be protective, and we narrowly missed the statistical endpoint for noninferiority on GMT.

There were robust T cell responses, probably most important because it's a measure of immunological memory which is critical for these vaccines.

In previously vaccinated subjects,

neutralizing antibodies may be a better measure because of the influence of immunity on takes. GMT was high following ACAM2000, higher than seen following primary vaccination. The vast majority had titers above 32. Noninferior to Dryvax.

The cutaneous response however was lower, 84 percent; the vaccine was more susceptible to the influence of preexisting immunity on take rate than for Dryvax.

And in those individuals without baseline antibody there was a 94 percent take rate.

So thanks very much. I will now turn the podium over to Jay Mason who will talk about myocarditis in more detail.

DR. MASON: Thank you.

I'll be discussing mechanisms and detection of myocarditis, as well as outcomes and incidence of smallpox vaccine related myocarditis. I am serving as a consultant to ACAMBIS. My academic affiliations are shown

here.

These are the specific topics we'll review: mechanisms of myocarditis; detection; outcomes of myocarditis - and I'll emphasize here that the classic form of myocarditis that clinicians are used to dealing with is really quite different from the smallpox vaccine related disorder.

And finally we will review the incidence of smallpox vaccine related myocarditis, specifically to address the question of whether or not there is an increase in incidence associated with the new vaccine.

Now regarding mechanisms, most of us view classical myocarditis in humans as a triphasic disease.

The initial phase is the phase of viral replication. In most people, this phase is self-limited and no disease, no overt disease, develops.

In some instances viral replication

may be severe enough to induce heart failure in this early period. However most humans with myocarditis present later; some a few weeks to several months later, during an autoimmune injury phase.

This may be followed in some by dilated cardiomyopathy. And in fact dilated cardiomyopathy may develop through several routes. It may result from the initial viral insult. Or that combined with the autoimmune injury. It may also result from an adverse outcome of cardiac remodeling in response to injury.

And indeed there is evidence that mere presence of viral genome in the absence of replication can induced dilatation and failure.

I'd like to point out that the disease that we usually view as classical myocarditis is presenting out here, when the die have been cast to an extent. The smallpox vaccine related cases are occurring here. And

this is a different disease than the one out here.

Regarding detection of myocarditis, I've listed currently used methods from the most sophisticated to the simplest. Endomyocardial is considered by some to be the gold standard for diagnosis of myocarditis. The biopsy tissue examination provides you with histology; the detection of inflammatory markers in the myocardium; as well as evidence for viral presence.

However, endomyocardial biopsy is not generally available. It requires hospitalization. It carries a risk. And it is clearly not appropriate for a large scale surveillance.

There are several imaging techniques - I've listed three of the more common ones here, MRI, ultrasound and nuclear scintigraphy. These are more generally available than the biopsy. However, the expertise to diagnose myocarditis using these

techniques is not widespread.

Circulating immune markers may also be measured to support a diagnosis of myocarditis, but once again this measurement is not appropriate for large scale trial. There are literally only a handful of laboratories in the world that make these measurements.

The last three techniques are ones that are practical, and that indeed are planned for prospective use by ACAMBIS.

The ECG has a sensitivity of 47 percent as shown by a nice study by Morgera, really the only study in early myocarditis. And the observations here were that about half the patients had either significant ST segment shifts, or T-wave inversion, or various degrees of AV block.

Troponin has been reported to have sensitivity varying from 34 to 71 percent, and specificity 86 to 94 percent of these variations being due to different patient

populations as well as varying specific criteria for diagnosis of myocarditis.

The clinical history has moderate sensitivity of 53 percent as we showed in the U.S. myocarditis treatment trial for which I served as the principal investigator. The symptoms specifically amounting to 53 percent, were fever and chest pain.

Now in the next two slides I'm going to review all 10 cases of myocarditis that have been ascertained in ACAMBIS trials in subjects receiving either ACAM2000 or Dryvax.

The points I want to make with this slide are, how frequently are the supposed surveillance methods positive in subjects with post-vaccinia myocarditis. We can see that symptoms were not present in four of these individuals. These individuals would not have been identified unless they had undergone either electrocardiography which would have identified all four and did in fact; or

troponin assessment which was abnormal in two of them; note that those two subjects also had reduced LVEF on echo.

Among the symptomatic patients, you will note the symptoms include exercise intolerance, chest pain, dyspnea, palpitations. We find that the electrocardiogram was positive in four of those five, or rather six, five of those six subjects. And troponin was abnormal in four of the six individuals.

Interestingly echocardiogram showed reduced LVEF in only this one subject, who we may have an opportunity to talk about later if you wish; this is an individual who continues to have cardiac problems.

These are the same subjects listed in the same order. I simply want to make a few more points about these 10 subjects.

First, ACAMBIS convened a panel of cardiac experts to review and classify these cases. And the classification scheme divided

the subjects among those with subclinical presentation of symptoms, and those that did have symptoms.

Among the asymptomatic, there was suspected and probable myocarditis, two in each category. I would like to point out that the day of onset in these patients with subclinical disease, as well as those with symptoms, was early. Again, I want to emphasize that we are looking at this disease process at a very early stage, and one in fact which clinicians rarely have the opportunity to see.

Among those with symptoms there was one felt to be suspect myocarditis, relatively incomplete evidence to make a definitive diagnosis; and there were five with probable myocarditis.

Note that disease resolved in all, and resolution was defined as absence of symptoms; absence of troponin elevation; and LVEF at or above the normal lower limit for

the laboratory.

One case has ongoing disease.

Now regarding outcomes of myocarditis, I've just shown that in these 10 subjects ascertained in the Acambis experience the outcome is quite good with 90 percent resolution. And I will add that there are questions about whether that tenth subject indeed is suffering from a myocarditis related problem.

Outcomes however in what we'll call classical myocarditis are much, much worse. And I show this slide to emphasize the fact that in the case of smallpox vaccine related myocarditis, we are not dealing with the nasty disease that many clinicians view myocarditis to be.

You can see that in the myocarditis treatment trial, independent of whether treatment was given or not, the mortality rate was about 30 percent in two years, and it was above 50 percent, nearly 60 percent, at give

years, obviously a very poor outcome unlike the smallpox related disorder.

Now what is the incidence of smallpox vaccine related myocarditis? There is this perception that it is higher than expected, or higher than it used to be, with the new vaccine. And I'd like to use the following data to demonstrate that there really has not been an increase in incidence. What there has been is a more rigorous attempt to detect the disorder.

So I've divided these data which I realize are very difficult to see in the back between the four studies in which self reporting was relied upon, or other studies in which in addition to self reporting symptoms were sought, and ACG and/or serum markers were measured.

I'll go through each study quickly. The New York Vaccine Campaign of 1947 included 5 million individuals, and there was only one case of myocarditis from that group.

This case actually was only found after death at autopsy.

In the Finnish military experience 60,000 vaccinees; 10 cases of very low incidence rate of .02 percent. We don't have follow up in these subjects, although we know that one individual died. The cause is not known.

In the DOD Dryvax experience which has already been reviewed, you will recall that there were 140 cases, a low incidence rate, and a substantial resolution. I don't know that the data I have is actually as up to date as that which Dr. Nelson showed you.

Let me emphasize that there is an early onset as expected among these subjects. Those three deaths have been discussed.

In the DOD experience there are over 40,000 vaccinees. Twenty-one cases have been found through self reporting. Again, a low incidence, .05.

These of these cases remain

unresolved; that is, there is ongoing evidence of cardiac disease.

Almost all of these patients had onset of disease within two weeks. There were one or two later.

Now if we move on to the studies in which there was active surveillance - well, not surprisingly the incidence rate is higher. And it's my belief that that difference in incidence is solely related to the surveillance techniques, and not to any difference in vaccines.

The Finnish study in `74, very small study. There were eight cases of rather high incidence. We have follow up in six, and all of them experienced resolution.

The Ahlborg study in Sweden, only 286 revaccinees in this case, one percent incidence; we don't have follow up.

Now the ACAMBIS Dryvax vaccinees in the phase-three studies with rigorous surveillance, three cases were identified for

an incidence rate of one percent. And you will note in the studies, additional studies in which there was not rigorous surveillance, no other cases were identified. And the incidence rates for these three subjects is .35 percent.

One of these subjects, a Dryvax recipient, is the one that has not resolved. All these cases presented, these three cases, within three weeks.

And finally the ACAM20000 treated individuals, five had myocarditis identified with rigorous screening, an incidence of .57; two more were picked up in the other studies; all of these particular cases have resolved. All again presented early. Emphasize the difference in this disease compared to classical myocarditis.

I think this data supports the contention that Dryvax using that as an historical control, has a very similar incidence rate when modern surveillance

techniques are used, and there is no real increase in ACAM2000 induced mycoarditis.

My conclusions, at first, the incidence of smallpox vaccine related mycoarditis is, as I've just shown, highly dependent on methods of case ascertainment as well as definition.

When rigorous case ascertainment and definitions are used, the incidence is below 1 percent. And this incidence rate is not increased by ACAM2000.

We've already noted that the majority, more than 90 percent probably, of individuals with vaccinia-related myocarditis, experience spontaneous resolution; quite different from classical myocarditis.

And finally clinical history for troponin and ECG are the only practical methods for detection of myocarditis in large scale studies. And they do appear to have reasonably good sensitivity and specificity.

Thank you.

Our next speaker is Dr. Mike Watson who will discuss the risk map.

DR. WATSON: Thank you very much.

I'd like to finish the Acambis presentations by presenting the risk management plan.

As we've already highlighted today, this is going to be a very important part of the license for ACAM2000.

There are two important elements to the risk management plan. Firstly, the PVG program, the pharmacovigilance program. And secondly, the risk minimization action plan.

The PVG program will allow us to understand better those safety signals already identified, and it will also allow us to detect any new signals that may become apparent when ACAM2000 is used in a larger population.

The risk minimization action plan as the name suggests intends to minimize risk, in the vaccines but also in the case of

ACAM2000 in the context of the vaccinees. Any risk management plan is designed around the safety experience with the product concerned. And in the case of ACAM2000 just to recap what you've already heard, is that ACAM2000 is well tolerated with a similar or better safety profile to Dryvax for all adverse events.

There are really relatively few serious adverse events. But the most important finding, as we've heard from previous speakers, is the finding of myocarditis in ACAM2000 with a rate of .57 percent, and in Dryvax 1.04 percent.

You'll see that myocarditis is inverted commas, and I just want to remake the point that's been made a number of times, and that is, what is called myocarditis depends on the case ascertainment and the definition that's used.

And in phase three in the cases that we've seen and moving into a risk

management program, what we will be calling myocarditis is for the purpose of surveillance and follow up.

In reality most of these cases don't fit the current case definitions for myocarditis. For instance in the clinical study none of the individuals have had cardiac biopsies. None were asymptomatic. And a number had ECG changes alone. And none of those would currently be diagnostic of myocarditis.

I'm going to go through the pharmacovigilance program and then through the risk management action plan.

The goals of the pharmacovigilance program are threefold. Firstly, to monitor for any rare SAEs that may become apparent when ACAM2000 is used in a larger population, so-called signal detection.

Secondly, to establish a more precise instance rate for these possible myocarditis disease.

And thirdly to allow us to assess the short, medium and long term outcome for these potential myocarditis cases.

There are four main elements to the pharmacovisions plan, and there is a fifth which I will talk about in a moment.

The four main elements are the routine pharmacovisions, spontaneous reporting; the enhanced surveillance program; a prospective phase IV clinical trial; and a myocarditis registry to allow us to bring together all potential myocarditis cases into a single long term follow up cohort.

The routine pharmacovisions will be in close collaboration with the Department of Defense. These are the only two agencies that will be using ACAM2000. It will be run under the auspices of an expediting reporting agreement with the FDA. What that means is that we will have a list of adverse events, agreed with the FDA, for which expedited reporting is required. And that's a list

which is longer than it would normally be based on the label.

We will of course meeting FDA regulatory reporting requirements. That means reporting into the VAERS system. That means providing periodic safety update reports, quarterly for the first three years, annually thereafter. And that means including any foreign reports or literature reports in the PSURs.

That will be coordinated through a safety database which we have in house which is operational and validated.

And any cardiac adverse events, any possible myocarditis that become apparent through routine pharmacovisions, will be entered in the myocarditis registry for long term follow up.

As we are all aware one of the inherent weaknesses of passive surveillance is the under-reporting. And even though as we've heard there are great efforts going on within

the DOD to increase the amount of passive reporting, that still remains a concern.

To try and address that we're then going to put in place an enhanced surveillance program, again in close collaboration with the Department of Defense.

The objective of this program, the primary objective of this program, is to collect as large a cohort as possible of myocarditis to follow them up, to get a better understanding of the natural history of this condition.

This will also by virtue of the size of this program allow us to detect any other signals that may become apparent, and to learn more about any serious adverse events or adverse events of interest.

Schematically we expect something on the order of 100,000 plus vaccinees to be entered into this program. These vaccinees will be contacted proactively by email, by cards, by the most appropriatve contact means

for their context, at days 10 and day 21, to solicit symptoms.

Any potential signals, any AES of interest, will then be reviewed by the adjudication committee, and any cardiac events and history - events of interest - will be entered into the myocarditis registry.

Whilst enhanced surveillance is intended to overcome much of the under-reporting, it won't clearly overcome all of it. And it's for that reason that we are putting in play a phase-four trial. That phase-four trial will consist of at least 10,000 individuals. And the goals of that trial are, firstly, to get a more precise estimate of these possible myocarditities and vaccine recipients. According to a range of different criteria, we will be looking at symptoms, signs, laboratory and other investigations.

It will allow us to collect more cases for short, medium and long term interest. And by virtue of the size of the

study it will also give us more information on other serious adverse events.

This again will be in close collaboration with the Department of Defense and deployable troops. We expect this to start within 12 months following licensure, and to be conducted in three to five large military posts.

As I said we hope to be able to recruit 10,000 subjects into the study. And one thing we are looking at at the moment is how we might be able to identify a control group for this group in order to better understand any events that are identified during the course of this study.

Such a study is expected to take two years to complete, and any study of this size in a population as operational as the Department of Defense, we clearly need to take into account the realities of that situation. So we're in ongoing discussions with the Department of Defense to plan this study.

Schematically the 10,000 subjects will be screened, undergo informed consent, and then vaccinated. There will then be medical visits, scheduled for day 10 and day 21.

At the moment we are proposing a screening of troponin and symptoms to try and identify any potential myocarditis cases.

If these are positive they will then be entered into serial follow up as cases of possible myocarditis.

As I said earlier one, these three programs - the passive, the enhanced and the trial - will provide cases which will feed into a myocarditis registry, and we are taking advantage of the registries that exist within the vaccine health care centers which we have heard to allow us to ascertain the long-term outcome for these myocarditis cases.

We hope to be able to follow up all cases for a minimum of two years, and then any cases with persisting signs or symptoms, as

far as is required.

There is a fifth possible risk management activity that we are considering, and that really answers the question. The question being asked her is, is there some kind of subclinical possible myocarditis going on that may lead to long term sequellae.

And we've heard mention that the most likely sequellae would be a dilated cardiomyopathy.

How can we tell that? Well, we can either recruit a large number of subjects with these possible myocarditis, and then follow them up long term.

The other way of doing it is to do a retrospective study. And recognizing that large numbers of individuals were vaccinated prior to 1970, we would expect in a cohort study comparing vaccinate to non-vaccinated, if this was indeed a cause of dilated cardiomyopathy, to find an excess of dilated cardiomyopathy in the vaccinated, and equally

in the case of the control study we would expect to find that the cases were more likely to be in the vaccinated than in the non-vaccinated.

This is something that we need to discuss further with the CDC. But there are clearly some cohorts out there that would lend themselves to this, perhaps the Framingham Heart Study, and perhaps the Swedish and Finnish military recruits, military cohorts, that we have seen in a couple of studies.

I now want to move on to the risk minimization action plan. What I'm not going to do is represent the detailed information that you've seen from the Department of Defense and the CDC, which clearly represent a very comprehensive toolkit of tools to minimize risk in vaccinees. What I will do though is talk briefly about each of the risks to be minimized, and where we see additional possible risk minimization activities.

The (*** 11:38:48) for risk

minimization are the potential vaccinees; because of the nature of the vaccine, the vaccines themselves are a target for risk minimization to prevent secondary transmission, as are the contacts of vaccinees.

The vaccinating physicians and the follow up physicians also need to be involved in any risk minimization action plans.

The risk to be minimized, as we've heard about already, include auto-inoculation, especially auto-inoculation; secondary transmission; eczema in both primary and secondary contacts; prevention or vaccination of the immuno-compromised; prevention of vaccination of pregnant individuals; trying to minimize risk of cardiac events of encephalitis; and also clearly to avoid vaccination of individuals who are allergic to the vaccine or any of its components.

This is really just to illustrate the large number of practical and accessible

tools that are available. And you saw this card earlier. This is a cut out credit sized card, information sheet, the vaccinees can carry with them which gives them an immediate list of contact details should they have any questions following vaccination.

We have also seen from earlier speakers the extensive, repeated and clear advice that is available on preventing secondary transmission. And the impact of that is very clear. There has been one case of eczema vaccinatum, when one would expect historically 20 to 40 cases. There have been tens of cases of secondary transmission when would have expected from historical experience hundreds or thousands. So this is clearly very effective.

The mainstay of the risk minimization program is the screening form. That screening form is currently used to screen out those at risk of eczema vaccinatum. There has been a single case, far fewer than

expected. My understanding is that the information is under review to see whether the visibility of that guidance can be improved to further avoid any additional cases of EV.

Immuno-compromised, my understanding is, the screening form has been very successful in avoiding the vaccination of immuno-compromised individuals, and therefore, there is nothing additional that we see to be done there.

Inadvertent use of pregnancy, that's screened for. There is a pregnancy test prior to vaccination, as we've seen as advice for those concerned. They may be vaccinated around the time of pregnancy, and there is a registry to follow up those individuals.

In terms of minimizing cardiac adverse events, the screening form clearly screens out individuals with preexisting established cardiac disease, or with the risk factors for cardiac disease.

In addition to that, as we've heard, vaccination occurs usually 30 to 60 days prior to deployment. As we've also seen, most cases of myocarditis present themselves around 11 days after vaccination, and that means the vast majority of vaccinees will present themselves prior to appointment.

There is an algorithm for identifying and managing potential cases of myopericarditis, and those that are identified are put on a six-month nondeployable period with specific guidelines for exercise.

There are ongoing immunogenetic studies to try to identify any risk groups to prevent myopericarditis, and we've heard that there have been 140 cases among the 1.2 million vaccinees, the vast majority of which have resolved.

Encephalitis is historically been rare; continues to be very rare. There are no clearly identifiable risk factors that we are aware of. What is sometimes done with

vaccines, where there is a concern about neurological risk, is to exclude individuals with preexisting significant neurological conditions.

Our understanding is that that probably doesn't have a place to play in the Department of Defense.

Compliance is a very important aspect of any risk minimization action plan.

Our understanding is that there are regional analysts who conduct hospital visits within the Department of Defense to check compliance with the use of the screening forms and the educational materials. And we have heard also about the educational materials that are available to make sure that people apply these tools.

In addition to that, we will be developing a medication guide. This is a first for a vaccine. This is a clear guide on what the vaccine is, who should be vaccinated, who should not be vaccinated, and what the

benefits and risks of vaccination are.

And we will continue to work closely with the DOD and CDC to ensure that our information is consistent. We share information, and we explore the possibility of tools for further assessing compliance and the impact of those tools.

So in summary there is an extensive group of proven tools available for risk minimization in smallpox vaccination. There is work ongoing to increase the visibility of the eczema warnings. There is ongoing work to try and identify risk factors for myopericarditis, and we are continuing to explore tools that will enable us to assess physician and vaccinee compliance.

And it will be important to continually review and revise these materials.

That concludes the Acambis presentations. Thank you for your attention.

CLARIFICATION/QUESTIONS

CHAIR KARRON: Thank you very much.

Because we are running a bit behind, and because I think we are going to have ample time in the afternoon to discuss risk math issues, I'd like to ask the committee just to focus their questions on issues related to the trials for the sponsor at the moment.

Questions? I'll start out with one actually for Tom Monath. And this actually has to do with a neutralizing antibody.

And my question is, do you have any information on duration of titers greater than 40 in ACAM2000 induce lower levels of antibody?

DR. MONATH: No, we don't have any information on duration. All of the information on duration of immunity to vaccinia is with older vaccines, either Dryvax or lister, in the literature. So neutralizing antibody studies were not continued after the day 30 endpoint in these trials. So that is something that would have to be looked at

prospectively going forward if further studies were indicated.

But I'd just say that the response was quite similar to Dryvax, and we know that antibodies last - kind of go up early, decline by about a year, and seem to plateau for up to 75 years at constant levels. And the T-cell response was also very long lasting, particularly CD4 cells following vaccine.

CHAIR KARRON: Dr. Teerlink.

DR. TEERLINK: I have a series of questions related to the noninferiority aspects of the trial design.

It's been mentioned before, and I guess one of the advantages of being a cardiologist is, I have the option to ask some stupid questions I guess.

The first question is, it's been mentioned a number of times that the Dryvax potency may have been decreasing in potency over time. And yet for noninferiority design you like to compare it to the very best

available agent.

Is it possible - how confident are you that Dryvax now is the best possible comparator? And if in fact you are being noninferior to that, or may not noninferior to that, how important is that?

DR. MONATH: That's a good question. So the Dryvax lots that are still under license in the repository are tested periodically for potency. Actually, by Acambis, under contract to CDC. So it's an ongoing stability program that looks at potency.

The potency of the Dryvax lot used in all of these trials was about 1.6 times 10 to the 8^{th}. It's very similar to the range of titers for ACAM2000, 1.3 to 2.2 times 10 to the 8, very close; so that's a good match across these trials for Dryvax and ACAM20000.

DR. TEERLINK: And related to that, then, when the statistical analysis plan for the trial, you use co-primary endpoints. And

we have kind of, some made it, some didn't. Was there a prespecified plan in terms of saying what it would take to declare victory supposedly or actual efficacy.

DR. MONATH: That probably is going to be addressed in the FDA presentation. The goal of course was to meet both coprimary endpoints. That was the objective of the trial.

DR. TEERLINK: So is alpha split amongst them? Was alpha split amongst those endpoints?

DR. MONATH: No.

MR. BALSER: John Balser. I'm a statistical consultant to Acambis. The alpha level was not split, because both primary - both coprimary endpoints were required to be met in order to achieve the endpoints of the trials.

The power of the tests, though, were increased in order to accommodate the fact that both were required.

DR. TEERLINK: So to be considered efficacious by the statistical analysis plan, both coprimary endpoints had to be met?

MR. BALSER: That is correct.

CHAIR KARRON: Dr. Jackson.

DR. JACKSON: I just wondered about the workup for the myocarditis cases. Was there any attempt to evaluate things like anti-myocardial antibodies, other marks of inflammation, interleukins and so forth. And was there any correlation between these cases and response to the vaccine?

DR. MONATH: So all the subjects who developed myocarditis were in the naive group, and all responded typically to the vaccine, had a major cutaneous reaction.

There was no planned analysis, and it was felt after discussion with the cardiology advisory panel that we set up, that there really wasn't a good way to address the etiology question directly.

So no - however we do have - the

algorithm that was used for the investigation of these subjects did request a paired sera be collected. We do have stored serum samples, and the thought was that perhaps they would be useful once we could identify appropriate test schemes.

Those serum volumes are quite limited, so I think this would have to be carefully thought through. No specific tests have been done to date.

CHAIR KARRON: Dr. Massie.

DR. MASSIE: I feel funny following my colleague, Dr. Teerlink, in asking questions outside of the realm of my expertise.

But so now that - I was trying to understand whether there was a prespecified, and why it was tested at 97.5 percent in two different things when you might say that you would want to do it at a more stringent level, since there still was sort of a two-sided hypothesis involved.

But the real question that stands out to me, and I'm less concerned about the myocarditis, which seems to be a real issue of concern, but not particularly with this vaccine, is that there were four endpoints. And it was inferior if not significantly inferior to Dryvax in all four. And in two it didn't make the prespecified endpoint; in one it came close to not making it, actually fairly close in both of them.

How confident are we that this is equivalent? Because the chance of that happening is one out of 16, when you miss all four endpoints, or turn the wrong way.

Or are there differences, perhaps - and this is where the experts come in - these are really good responses no matter what. Are these good enough?

Because it doesn't seem to me as a lay person in this sort of area that we are getting the same degree of immunity out of this product as we do out of Dryvax.

DR. MONATH: So I think we developed a vaccine that clearly is a new vaccine. The attempt was to get as close as possible in all the preclinical markers that we had to Dryvax. And clinically when we tested it in large numbers of individuals, we found the differences that you allude to.

Many vaccines that we use today have lower efficacies than we are talking about here. Nevertheless, this is a significant disease, and one would like to get as close to 100 percent protection as possible.

The response in naive individuals I think is very clearly similar to Dryvax, and we are talking about fine points of statistical endpoints. But what is the clinical relevance, and the difference in neutralizing antibody, geometric mean of 1.54. Probably not important.

And if you look at this analysis of titers, you see that the majority of

individuals, over 90 percent in all treatment groups, had these titers that might be considered to be protective, and are known to be - the protection you see years after vaccination is associated with titers, low titers of antibody.

So I think that this vaccine will produce a protective immune response in the vast majority of individuals - probably not quite as effective in previously vaccinated subjects who have preexisting immunity. But remember, in those that are most susceptible and have no neutralizing antibody it is very effective, 94 percent.

DR. HETHERINGTON: What you stated is that you tried to recreate the Dryvax vaccine using modern manufacturing processes. And I wonder if we could hypothesize that these results were about as good as you could expect?

In other words, is the goal of equivalence or noninferiority I should say, is

that realistic? Are there impurities in the Dryvax and the old manufacturing process that act as adjuvants that increase traffic in macrophages and other immune cells that are really acting to boost the antibody response. And you are going to give some of that up if you move to a modern manufacturing process where there is far greater purity; remove the adventitious agents so you can increase safety from that aspect.

But again you have to give up something. There's nothing that's free. And when you go to a pure more modern manufacturing process you are going to give up some of the immune response.

And I wonder if the manufacturer, anybody from Acambis, has thought about this, or if anyone else on the committee would want to make a comment about that.

Maybe the only way to get to the next step is to create a new vaccine, using adjutants or some other process.

DR. MONATH: I couldn't have said it any better myself.

Live vaccines are always a balance of attenuation and immunogenecity. And I think we made the decision to develop a clone, clonal vaccine versus trying to recreate the subpopulation distribution of genetic swarm in Dryvax.

When we passed the virus without plaque purification and cell culture, we actually - the result of that was a more neurovirulent virus than Dryvax. So that evidence underlines really informed that we should develop a plaque-purified population, for a variety of reasons which I won't get into.

When we did that, we were working with a subpopulation compared to Dryvax mixture of strains. And it turned out that there are these fine differences between them. And the biological behavior is quite robust. It does reproduce the effects of Dryvax in

the vast majority of people.

So I think that if you tried to do this again you might get a little different result. This is what happens when you adapt an uncloned genetic swarm to cell culture for modern manufacturing.

And I think probably weighed against these somewhat lower or the attenuation may in fact have a positive side. As I've mentioned with respect to neurovirulence. One of the most feared complications of smallpox vaccination.

So I hope I have addressed your question. But I think your comments were quite germane.

CHAIR KARRON: Dr. Stapleton.

DR. STAPLETON: Yes, Dr. Monath, I'd like to ask two questions. One, I think I'll accept that a take is well associated with protective immunity. But how well are the GMT data with protective immunity?

And the second question is, do you

have any data on the revaccination population, of what their neutralizing antibody titers were in the people who did not get a take with either Dryvax or the Acambis?

DR. MONATH: So I was concentrating on the hard question I forgot the first part. What was the first one?

DR. STAPLETON: The first one was how well it coordinated our geometric mean and titers?

DR. MONATH: As I mentioned, we really don't have an established level of neutralizing antibodies that is known to correlate with protection. The older studies that I referred to were relatively small numbers of individuals, and the design of those studies was limited.

So I think the conclusion that relatively low titers were associated with protection is valid. But it's hard to put a line in the sand. So the one to 32 level is just put up there as a benchmark.

Attempts to find that level of protective immunity by passing immunization studies with VIG for example have not really shed light on the question either.

The individuals who - second question was individuals who did not have a take in the revaccination trial, what was their preexisting level of immunity? It would be helpful to look at a slide. But the majority of those individuals who did not have a take were the ACAM2000 group, and they were the individuals who had neutralizing antibody titers above 20.

DR. WONNACOTT: Let me just add one comment that basically those who had the positive cutaneous response, and 97 percent of those had antibody titers greater than one through 20, those who did not have the positive antibody - or cutaneous response had titers less than one to 20; they all did. That's in the primary vaccination.

In the revaccination, as you saw

from the GMTs, they were all higher than the primary.

(Off-mike voice)

DR. STAPLETON: So you mean whether they had a take or not, they were all high titer post revaccination?

(Off-mike voice)

DR. WHARTON: Melinda Wharton, CDC. But do we know anything about their prevaccination titers in the reactionees? That's what I thought the question was.

DR. MONATH: At baseline in the 012 study, the geometric mean in the ACAM group was 33, and it was about 25, a little lower in the Dryvax group.

CHAIR KARRON: Dr. LaRussa.

DR. LaRUSSA: Just clarify for me, the criterion for noninferiority of the GMT of 0.5, was that based on being able to reliably tell the difference between the twofold difference in antibody titer?

DR. MONATH: Well, the statistical

endpoint was the ratio of the GMTs of ACAM2000 and Dryvax should be at least point five; is that what you are referring to, which is a twofold difference? That is a statistical endpoint.

And I think your question is a little different, what is the variability of the response? Typically one of the secondary endpoints was the seroconversion rate; that is, the proportion of subjects who had an increase in antibody. There we used the fourfold difference between pre and post as the cutoff.

CHAIR KARRON: Okay. I just have one other question for Dr. Mason, and that has to do with slide 68, the issue of resolution of myocarditis. And is that by any measurement? So by EKG? By echo, completely resolved for all of those individuals?

DR. MASON: I can only comment with direct knowledge about the 10 Acambis cases. And they indeed did experience complete

resolution. It was defined - nine of them, nine of the ten did - it was defined as absence of symptoms, no troponin elevation, and an LVEF above the core lab - at or above the core laboratory's lower limit of normal which was point five five for echo EF.

So nine of the ten met those criteria for resolution.

The one subject that did not resolve is an interesting case, because I think it's very difficult to determine or decide if she indeed had myocarditis, and if it had anything to do with her ongoing problems.

She, at the time of vaccination, was 22 years old. She received Dryvax. She was obese, and with a BMI of 45, quite high. And by the way that has continued to rise.

She was and still is a smoker. She had a history of exertional dyspnea, and in my view, the most important observation is that she had long standing extreme sinus

tachycardia. I will describe her Holter results in a moment.

She also had inferior Q waves on her baseline EKG. These Q waves were more narrow than ones on subsequent EKGs. She has met criteria for inferior infarction on several EKGs, and it's notable that she had regional contraction abnormalities on echo consistent with these Q waves.

Her troponin and ECG were abnormal on day 10, but the ECG changes were not changes seen in myocarditis. She did not have ST elevation or T wave inversion. She had sinus tachycardia and these Q waves that I noted.

The troponin was 3.2

A echo on day 15 showed an EEF of .52, and possible concentric hypertrophy. The Holter, very interesting, her mean heart rate was 103. And she had a heart rate exceeding 120 beats per minute for more than five hours during that Holter.

This degree of tachycardia is more than enough to induce a cardiomyopathy independently.

The expert panel that I mentioned that was convened in 2005 suspected that she had preexisting disease, and that it was a major contributor to her ongoing problems.

The echo follow up showed basically ongoing deterioration over a two-year period.

She had a CVA in July of last year, not an unusual adverse event in subjects with cardiac dilatation. Of course she was anticoagulated at that point.

And her last clinic visit, which was not very long ago, she still had sinu9s tachycardia. Her heart rate in fact was 124 at that time. And she has had inferior Q waves present on all follow up exams. The sinus tachycardia on exams. The Q waves on ECG.

Any questions about that particular subject?

CHAIR KARRON: Dr. Farley, did you have a question?

DR. FARLEY: I was trying to remember the screening for cardiac risk factors that had been proposed for the map, risk map. And would she have been screened out based on that?

DR. WATSON: In terms of the current DOD program she would not have been vaccinated, and she should probably not have been entered into the trial.

CHAIR KARRON: Okay, thank you.

We are running behind. We are going to take a very brief break right now, and reconvene at 12:15, and we will hear from the FDA at that point.

(Whereupon at 12:07 p.m. the proceeding in the above-entitled matter went off the record to return on the record at 12:19 p.m.)

CHAIR KARRON: All right, we are going to begin.

Our first speaker for this part of the session is Dr. Rosenthal from the FDA.

FDA PRESENTATION

DR. ROSENTHAL: Good afternoon. My name is Steve Rosenthal, and I'll be presenting Sever's (phonetic) review of the ACAM2000 clinical development program.

As you've heard earlier, smallpox is considered to be a dangerous biological weapons threat. HHS classifies it as a category A bioterrorism agent because a large proportion of the world's population is susceptible; it can be manufactured in large quantities; it can be stored indefinitely; it has a high transmission rate; a high case fatality rate; would cause large social disruption; and the tools are available for public health action.

The only commercial approved vaccinia vaccine available for use in the United States is the Wyeth Dryvax. It is no longer manufactured, and the remaining number

of doses is limited. The vaccine is administered percutaneously with a bifurcated needle.

Effective vaccination was indicated by the observation of the cutaneous pustular lesion seven to 10 days after vaccination at the vaccination site which is classified as a take. The take rate has generally been accepted as an accurate correlate of vaccine efficacy.

Dryvax has a greater than 90 percent take rate.

Potential complications from smallpox vaccination are well documented from the eradication era. Such complications include generalized vaccinia, eczema vaccinatum, progressive vaccinia, post-vaccinial encephalitis, fetal vaccinia, and inadvertent inoculation.

In late 2002 CDC and the Department of Defense initiated a smallpox vaccination program among military personnel and civilian

first responders. Unexpectedly myocarditis emerged as the most frequent serious adverse event. Approximately one case per 2,000 primary vaccinations observed in the civilian program, and one case per 6,000 primary vaccinations in the military.

The ACAM2000 clinical development program was modified to better characterize this risk. The efficacy trials were halted before they reached full enrollment in April of 2004.

In August 2005, the Dryvax package insert was updated with a blackbox warning, the first for a vaccine, and a description of the rates of myocarditis seen in the ACAM2000 trials of approximately one case per 145 vaccinations were added to the package insert.

These data were also made publicly available by Acambis at the October, 2004, ACIT meeting.

The safety and immunogenecity data provided to support license approval is based

on two pivotal clinical trials that demonstrate efficacy by surrogate endpoints, major cutaneous reaction, or take rates; and serum neutralizing antibody.

Both clinical trials' main objectives were, first, to compare the immunogenicity of ACAM2000 and Dryvax vaccines by comparing the proportion of subjects in each treatment group who develop a successful vaccination or take, and the geometric mean vaccinia neutralizing antibody titer on day 30.

And second, to compare the safety of ACAM2000 and Dryvax vaccines in health adults.

Both trials were randomized, double blind, controlled, multi-center studies. Subjects were randomized three to one to receive either ACAM2000 or Dryvax.

Clinical trial, zero zero nine enrolled adults 18 to 30 years of age naive to smallpox vaccine.

Clinical trial, zero twelve enrolled adults 31 to 84 years of age previously vaccinated with smallpox vaccine.

The coprimary efficacy endpoints were, the proportion of subjects with successful vaccination based on natural cutaneous reaction, or take, and the geometric mean antibody titer on day 30.

The endpoints were evaluated based on statistical tests for noninferiority of ACAM2000 versus Dryvax.

The ACAM2000 clinical program was placed on hold in April, 2004, due to concern over a higher number than expected of observed myopericarditis.

This table shows the sample sizes used in the analysis. Both trials had a planned enrollment of about 2,700 subjects. Trial 009 enrolled a total of 1,037 subjects, and trial 012 enrolled a total of 1,674 subjects.

Four study sites, approximately 255

subjects, were excluded in final efficacy analysis due to compliance issues with good clinical practices found on inspection.

These subjects were examined however in the final safety analysis.

Efficacy was assessed with vaccination site examinations on day zero, seven , 10, 21, and 30, evaluating the site for major cutaneous reaction to find as a pustular, vesicular or ulcerative lesion of measurable size on day seven and/or day 10.

Vaccination sites were evaluated by primary investigators in 009, and because vaccination site reactions might be more difficult to interpret in persons with preexisting immunity, site reactions were evaluated by independent review committee.

The primary vaccinees, trial 009, take rates were 96 percent and 99 percent in ACAM2000 and Dryvax groups respectively. ACAM2000 was shown to be noninferior to Dryvax with regard to cutaneous response rates as

lower bound in the 97.5 percent one-sided confidence interval was negative 4.67 percent, greater than 5 percent was needed.

Subjects revaccinated, trial 012, take rates were 84 percent and 98 percent in ACAM2000 and Dryvax groups respectively. ACAM2000 was not shown to be noninferior to Dryvax with regard to this endpoint.

The primary vaccinees, geometric main neutralizing antibody titers were 166 and 255 on day 30 after vaccination in ACAM2000 and Dryvax groups respectively.

GMT in the ACAM2000 group cannot be considered noninferior to that in Dryvax group as indicated by the lower bound confidence interval on the mean difference of negative 0.307 and a lower bound greater or equal to negative 0.301 was needed.

In the previously vaccinated trial, 012, GMTs were 286 and 445 in the ACAM2000 and Dryvax respectively, and ACAM2000 was shown to be noninferior to Dryvax with the lower bound

for the difference that exceeded negative 0.301.

And in summary ACAM2000 met two of the four coprimary endpoint criteria established for the phase three clinical trials. It passed for the cutaneous response in primary vaccinees, and for GMT in those previously vaccinated.

It failed marginally for GMT in primary vaccinees, and failed for the cutaneous response in subjects previously vaccinated.

So its preexisting immunity probably can affect the cutaneous response to revaccination. We feel the data are consistent with ACAM2000 being an effective vaccine against smallpox.

The safety of ACAM2000 was assessed by physical examinations and structured interviews on day zero, seven, 10 and 21. ECGs were done at screening at days 10 and 21 post vaccination.

Troponin was done on screening and on day 10. Suspected cases of myocarditis were identified by clinical symptoms such as chest pain, shortness of breath, palpitations, and with ECG and troponin.

Suspected cases were evaluated by a cardiologist and followed for 12 months or longer if there were any cardiac abnormalities.

No significant difference between ACAM2000 and Dryvax groups was seen with regard to the overall incidence of adverse events. The overall incidence of at least one adverse event in the ACAM2000 groups was 99 percent, and greater than 99 percent respectively.

There was no significant overall difference between groups with regard to moderate and severe reactions.

This table illustrates the rates of selected adverse events, with point estimates generally a bit higher for the Dryvax group

compared to ACAM2000.

The difference of lymph node pain to vaccine groups was statistically significant.

Severe adverse events were infrequent. The most commonly reported severe adverse events for all treatment groups were vaccination site reactions, with severe local reactions occurring in 4 percent and 9 percent of ACAM2000 and Dryvax subjects respectively.

Other adverse events reported occurred rarely at an incidence of less than or equal to 1 percent in ACAM2000 groups. Rates were slightly higher in the Dryvax group in primary vaccinees.

There were 10 cases of suspected or probable myocarditis in the overall clinical development program, with an overall rate of approximately one case for 145 vaccinations.

Seven cases received ACAM2000 with a rate of 5.73 per 1,000 vaccinations, and three cases received Dryvax with a rate of

10.38 per 1,000 vaccinations. This rate was not statistically - this rate difference was not statistically significant.

Nine cases were male with a mean age of 21 years; seven were Caucasian. The mean time to onset was 11 days, ranging from nine to 20 days. Two subjects were hospitalized for acute cardiac symptoms, and the one female case that received Dryvax has persistent left ventricular dysfunction. The ejection fraction is about 35 to 40 percent, and global hypokinesis at followup at 2.5 years.

The safety profile of ACAM2000 appears similar to Dryvax, based on the limited data from the clinical development program.

Since the government's smallpox vaccination began again in 2002, the risks of many of the traditionally known adverse events has been significantly reduced with careful screening for known risk factors and with

education.

However, transmission of vaccinia virus continues to occur, illustrated in two recently publicized cases of eczema vaccinatum in a toddler of a soldier that returned home after being vaccinated. And a case of vulvar vaccinia infection after sexual contact with a military vaccinee. And these, both these cases received some media attention within the past couple of months prior to this meeting.

Serious adverse events including death are likely underreported to the FDA and CDC vaccine adverse event reporting system. The pre-licensure clinical experience for ACAM2000 is limited. Only about 3000 subjects have received ACAM2000 thus far.

So in light of the adverse event profile of ACAM2000, CBER is working with ACAMBIS to develop a risk minimization action plan as a component of the post-marketing commitment.

The purpose of the risk map is to

help ensure that the benefit to risk ratio for ACAM2000 is maintained as high as possible during the entire product life cycle.

Specifically the goals are to minimize the risk of auto-inoculation and transmission; inform vaccinees of the risk of myocarditis and other potential serious adverse events; and ensure that the vaccine is administered correctly both for safety and effectiveness.

We recognize that a risk management program must not be overly burdensome especially in time of emergency. One purpose we have of this advisory committee meeting is to give the various stakeholders a chance to provide input on the appropriateness of a risk map in the initial phase of planning, so that it won't encumber the delivery of smallpox vaccination to those who need it.

The components of the risk map to discuss include the sponsor's plans for limited marketing and distribution in the

United States; targeted education and outreach; expedited reporting of adverse events; post-licensure pharmacovigilance commitments; and program assessment.

Acambis has stated that the company has no intention to distribute ACAM2000 in the United States outside of sales to the U.S. government for the strategic national stockpile. We agree with that plan. This will help ensure that vaccine will only be given under controlled conditions that would minimize risk.

Health provider education stresses the knowledge of known relative contraindications of smallpox vaccine such as a history of eczema, cardiac risk factors for coronary artery disease, correct vaccination technique, and counseling for vaccination site care to avoid transmission and auto-inoculation.

Examples of provider education include the package insert, again, this will

have a black box warning like the Dryvax vaccine; and provider continuing education programs; vaccinee education to prevent transmission and auto-inoculation, and to communicate risk, should include a medication guide, which is an FDA-approved patient labeling which would be required to be provided to every vaccinee.

This would be the first med guide ever for a vaccine.

In general adverse events listed in the package insert do not need to be reported in an expedited manner unless an expedited reporting agreement has been made.

There has been underreportingn of adverse events after Dryvax vaccination to the FDA and CDC, and to those who are using the vaccine are encouraged to report this as well. Therefore we would require an adverse event expedited reporting agreement to include terms listed in the package insert, such as myocarditis, contact transmission, death, and

auto-inoculation among others.

Acambis has proposed several pharmacovigilance activities with the following goals: to study ACAM2000 in the larger population than possible in the pre-licensure studies, looking for known and unknown adverse effects; to further study cardiac complications after smallpox vaccination such as long term clinical outcomes and potential risk factors, that which can be genetic immunologic risk factors, or demographic such as behavioral risk factors such as exercise and things like that.

The proposed post-licensing pharmacovigilance program will be carried out in the military population, and includes a phase four cohort study and 10,000 vaccinees. They will be vaccinated and followed up in eight to 12 days with structured interview, and will have proponent tests on day one, and I believe there will be a follow up visit on day 21 as well.

ECGs would be done if clinically indicated or if elevated troponin was detected.

A second component is an enhanced surveillance program in about 1 to 200,000 vaccinees over a one to two year duration. And the goal of this as well is to establish a myocarditis registry which Acambis hopes would be able to accumulate up to 150 cases for further study for up to two years following onset of disease, and for up to five years for those with persistent cardiac abnormalities.

Some possible concerns with such a pharmacovigilance plan. There might be inadequate case ascertainment to be able to determine the natural course of disease associated with ACAM2000. To improve case ascertainment one could increase sensitivity with the addition of laboratory tests such as ECGs and additional follow up with clinical and laboratory visits at day 30.

Or one could also increase the

sample size for the phase four cohort study. However resources will be needed to be made available.

Other issues for case detection: for example, a soldier that is vaccinated and is going to be deployed into the theater, he might develop chest pain but choose not to report it because he knows it will preclude him from being deployed into the theater.

Other issues for example can be long term follow up which can be particularly challenging for persons who go from the military health system into the civilian or VA health systems, and if we want long term follow up, 10 or plus years on these cases, this could be very difficult and expensive.

And again the vaccine adverse events surveillance, we always have concerns on completeness and timeliness of reporting, even of nonserious adverse events. But two recent cases described in the media - actually we found out about them in the media and not

through the VAERS reporting system.

Evaluation of the risk map will depend on a high functioning VAERS system that will detect the serious adverse events in a complete and timely manner. Adverse event data would be used to detect areas in which compliance with risk minimization activities are weak.

And VAERS (phonetic) information could also be used to guide improvements for these activities as well. We might want to suggest other process audits, for example, compliance with medication guides; how the education programs, how frequent they are being given; how big - and how they are performing; things like that.

So in conclusion data from phase three clinical trials provide reasonable indication that ACAM2000 would be effective and relatively safe for persons at high risk of exposure to smallpox.

However we have to recognize the

ACAM2000 safety data is limited, and that the ACAM2000 risk profile is clinically important and unusual for a preventive vaccine. A risk map would be a valuable addition to a risk management program.

I'd like to acknowledge my colleagues.

Thank you very much.

CHAIR KARRON: Thank you, Dr. Rosenthal.

Yes, Dr. McInnes?

DR. McINNES: Will you entertain questions?

CHAIR KARRON: Yes, I believe so. Dr. Merchlinsky is just going to be reading the questions? Is that the presentation? Yes, we can entertain a question.

DR. McINNES: I have two questions. One is around whether the company is making this vaccine for other governments or entities that we might actually gain additional data from if there was going to be additional

pharmacovigilance program put into place.

And the second question is around the subjects enrolled in the trial who have ongoing myocarditis. I want to know if that, retrospectively, or even at the time, constituted an enrollment violation. I understand she would have been captured under what you now have as exclusion criteria under the military program. But I want to know whether she did fall within the inclusion or exclusion criteria for the trial.

DR. WONNACOTT: I think that, I guess, is a question, at least the first part, to us.

At the current time none of the foreign countries that we have had any interaction with have specific programs that are ongoing or policies that we are aware of. But that is a very good point - we could look further into that.

The second part of the question, though?

DR. McINNES: Subjects with ongoing myocarditis issues and whether she was a violation of protocol, enrollment violation.

DR. WATSON: Prospectively she probably wasn't in the eyes of the investigator. But retrospectively we look at the ECG, she probably should have been.

So if that makes sense.

DR. McINNES: Wasn't there the catch-all phrase, in otherwise good health? I'm just interested in what the inclusion criteria were.

DR. BLUM: Paul Blum, operations at Acambis.

Yes, there were general criteria of good general health, and there were specific criteria similar to the ones Colonel Ford presented for risk factors. And while she strictly met the specific criteria, one could say that the general, she probably was not in good general health.

I hope that answers your question.

CHAIR KARRON: Dr. Word.

DR. WORD: I guess this is a follow up with Dr. McInnes. When you look at the exclusion criteria, it says you have to have three. Now she may have had two or one, but she technically would still have been eligible. So she wasn't ineligible. So I think that's where you go down to, you are saying, how many. And it says, you are excluded if you have three or more risk factors.

DR. WATSON: In retrospect she has preexisting contact disease, a long history of sinus tachycardia. She in retrospect had a childhood history of being told she had a murmur. She has some very suspicious QAS on the ECG. She was obese; she was a smoker. So it comes back, it was a judgment call by the investigator.

Hence my answer at the time. You can see why the judgment call was to include the subject. Retrospectively probably the

judgment call should have gone the other way. But it was one of those judgment calls.

CHAIR KARRON: I think we will go ahead with Dr. Merchlinsky reading the questions.

DR. MERCHLINSKY: All right, at this time I'd like to reintroduce questions to the committee.

First of all, are the efficacy data sufficient to support the use of ACAM2000 in situations where it is determined that there is a high risk of exposure to smallpox virus?

Second question: are the safety data sufficient to support the use of ACAM2000 in situations where it is determined that there is a high risk of exposure to smallpox virus?

And the third discussion point: please discuss the benefits versus the risks of ACAM2000 for the use in high risk situation.

And with regard to the post-

marketing or phase four, does the committee agree that a risk minimization action plan, which is referred to as a risk MAP, for ACAM2000, composed of the following, is needed: including A, vaccinee education; B, health care provider education; C, expedited reporting of certain serious adverse events; D, phase four studies to better define the safety profile, long term outcomes and risk factors for myocarditis; and E, evaluation of the risk MAP.

And again, we'd like the committee to discuss the methods to increase the sensitivity of case ascertainment of myocarditis and long term follow up and methods to evaluate the effectiveness of this.

I think that's the last one. I'll leave question one on it.

CHAIR KARRON: Thank you.

Further comment or questions from the committee?

Yes, go ahead Dr. Farley.

DR. FARLEY: I have one quick question about the myocarditis. And I think someone earlier was asking about other attempts, looking for etiologies that might be unrelated to the vaccine if I remember correctly.

But I wonder, have we been told whether there was ever any clustering of the cases, the myocarditis cases?

DR. WATSON: In the clinical study and in the literature there does appear to be this clustering of cases around 10 to 11 days.

DR. FARLEY: I mean case to case, that there might have been an outbreak of enter (phonetic) virus or coxsackie virus, particularly in a community or a troop, that sort of thing, clustering cases together.

DR. WATSON: Within the clinical trials, there is no indication of that, no.

CHAIR KARRON: Dr. LaRussa.

DR. LaRUSSA: Could somebody just remind me what the plans are to induce better

access to records, once people separate from the military? It seems to me that the long term follow up here depends on getting better follow up than you are getting now.

DR. NELSON: I guess everyone is looking at me.

I can speak to the fact that there are certainly very active efforts to improve the communication between the active duty military and the Veterans Administration. So both on an electronic data transfer model as well as physician sharing. So the barriers to that transfer and handoff of care are much more systematic.

So I see clear improvements in that arena already. And from the outlines I'm looking at, for all clinical conditions cross the board, as our service members are being discharged from that service, we are seeing improvements across the board.

The communication with the civilian network is not so regimented from our

perspective, at this point, but there is clearly sentiment on both sides that there needs to be committed effort to improve that data sharing.

And it has occurred at the level of the Vaccine Health Care Center and the Centers for Disease Control and Prevention with regard to these myocarditis cases. But actual sharing of data records and HIPPA issues have not entirely been overcome to date.

CHAIR KARRON: Yes.

LT. COL. FORD: Just to follow up on Dr. Nelson's comments, there also is an effort within the Department of Defense to obtain secretarial designee status for people who are enrolled in the myopericarditis registry, so if they choose upon separation to continue to receive care through the Department of Defense they will be eligible for care as the secretarial designee.

CHAIR KARRON: Yes, Dr. Stapleton.

DR. STAPLETON: I guess I'm still a

little confused on the plan. Will this vaccine be used in place of Dryvax? Or will it be administered in the military simultaneously? And if so that would seem to be an opportunity to gain further data prospectively upon the comparison of these two vaccines.

CHAIR KARRON: Dr. Nelson, I don't know if you want to comment on that?

DR. NELSON: I don't think we've set a clear plan in that regard. I think the question came up earlier, which are we going to use first versus the other, and at this time I don't think there is any plan in place.

CHAIR KARRON: Colonel Alvarez.

COL. ALVAREZ: So I'm Colonel John Alvarez. I'm the joint vaccine acquisition program manager. It's a tough question. It has a lot to do with what the intent of Wyeth is to manage the Dryvax license in the long term.

Is there an opportunity to study if

both are available at the same time? Yes. The probability of that is probably very low, and I think the long-term intent is going to be to replace it.

CHAIR KARRON: Dr. LaRussa.

DR. LaRUSSA: So it seemed to me that in the vaccinees that develop myocarditis that the most screening tool is the EKG, but in the plan to study the 10,000 vaccinees, symptoms and tropanin levels were to be used as the screening tests.

I can understand where doing 10,000 may be a little bit onerous. But would it be conceivable to do EKGs on people without symptoms on a subset of that 10,000?

DR. MASSIE: I think it's a good time to chime in.

I think the key thing from the point of view of the myocarditis issue is that we really have a prospective way of knowing not only who gets it but what the consequences are. And it's a key thing for the government

and the society as a whole.

Because I can easily envision, as has happened with Persian Gulf syndrome and Agent Orange that anybody who has ever been vaccinated who develops heart disease will be service connected unless we can really track what's happening here.

It may be expensive; it may be difficult. But it will be very cost effective to get the various agencies that have to deal with it.

So I think it gets down to the 10,000 patient study as a start, but there are not going to be enough case there. But there will be controls. Because the only way to understand what happens with this is to be able to check controls. We have no signs of early myocardial damage and myocarditis. They should include EKGs. They should include troponins. They should perhaps in some include echos. But certainly in anybody who then develops a symptom, an ECG or a troponin

level, they need an echo, and then they need a mandatory echo that the government should be willing to go to all extent to do and get to a corps lab down the road.

And without that I don't think there is much point in having a phase four study. We have to have a control group. This is a unique group of people. They are exposed to lots of stresses which can cause heart disease -- T-wave inversions and all these types of things. Lots of substance abuse, alcohol, and actually that was one of the questions for the sponsor, is there any connection between these people and -- any evidence of substance abuse, or were they systematically excluded adequately.

So getting information about the next group of 50 people, which I guess is the odds out of the 10,000 patient study, without knowing what happens to people who are in the same situation over that period of time, to me won't help us a bit.

CHAIR KARRON: Other comments? Questions?

DR. WATSON: Can I just make a comment?

It's an important question. It's not set in stone. We clearly need to find the right balance between the sensitivity, specificity, and practicality of the screening test to get the greatest compliance. That's something we need to work through.

And they'd be coming back, though, to the value of the retrospective study, I think given that the hypothesis is that smallpox vaccination may be responsible for some future cardiac disease, a retrospective study would be a very quick way to address that question. And you saw that in some of the published studies. There are some Finnish cohorts, conscripts, 30,000 a year vaccinations, `77 and `78, and then subsequent cohorts who weren't vaccinated. And that would seem to lend itself to a cohort study.

To look retrospectively at whether there is an overrepresentation of significant cardiac diseases in the vaccinees compared to the non-vaccinees.

DR. MASSIE: I think that is a good point. But I think it may be very different in service men going to Iraq. I think there are very different socioeconomic issues perhaps. There is certainly different exposure to all sorts of things. And to decide - and there may be some synergism between those things and developing this syndrome which may not be myocarditis in the traditional sense. What do we know about ST T-wave changes and funny troponin abnormalities? But whatever it is, I bet there are a fair number of servicemen who are having those without the smallpox vaccine.

DR. WATSON: Absolutely. And hence your point about the control group, which is going to be very important to be able to balance out those other things.

CHAIR KARRON: I'd just like to make a comment before I take some more questions abou8t the retrospective analysis. And that is the question about, are we considering all smallpox vaccines the same?

Were those early vaccinations in the `70s in the Finnish populations with Dryvax? Or were they with other smallpox strains that, at least in my understanding, were thought perhaps to be more myocardiogenic, if you will?

So could we perhaps get some information from that, but that's not the same thing as getting prospective information on the Acambis product.

DR. WATSON: Clearly the totality of the program will be important. Hence all these questions; absolutely.

The historical studies, yes, there are a range of different vaccines used, at least three or four different vaccines used in those studies.

But it's the totality of the program, and hence the way the program is structured, that we hope will allow us to answer most of those questions.

CHAIR KARRON: Dr. Jackson.

DR. JACKSON: Or in the retrospective study. I mean the role of the question is, of course, among persons who receive smallpox vaccine, are those who have evidence of myocardial inflammation at higher risk long term than other people? And you can't look back at the `70s and know what that - who those subsets were.

So I think those results will be very difficult to determine. And that also goes toward what we should be doing now. And I think we need much more complete identification of the persons who appear to suffer this consequence so that they will be identifiable for later term follow up among other reasons.

DR. FARLEY: Where there any signals

in any animal model that has been used that would have predicted myocarditis? You know you've mentioned that there was a decrease in the neurotoxicity which was an encouraging finding in your preclinical stages.

Is there anything we can do in a preclinical - would there be a better clone in the future that we could look forward to that might actually reduce both the neurotoxicity and the mycoardial findings?

DR. MONATH: I'm not aware of any animal model of vaccinia related myocarditis. We made an attempt in the laboratory to induce this condition in mice by making repeated cardiac passages of the virus to try to adapt it, and by looking for pathological changes. And that really didn't - we were not able to succeed in developing a myocarditis model.

That is not to say that one couldn't try other avenues. The etiology or pathogenesis is certainly obscure with respect

to direct viral injury, autoimmunity and so on.

I might just mention a favorite observation of mine that I brought up before that I think is very intriguing.

In our trial in the study where we look for nonspecific effects on serological tests we found that 18 percent of subjects in both treatment groups developed biologically false positive tests for syphilis.

This was actually reporting in the literature before, but this is an antibody to cardiolipin, the reagent in the test. And of course it's associated with autoimmune diseases like lupus and so on.

I think this was transient, and it was shown to be a biologically false positive, i.e. treponema specific tests were negative, and all these subjects became seronegative by the RPR test within about two months; most of them earlier.

But it's an intriguing finding, and

it suggests that the inflammation induced in the local site probably does lead to at least some antibody responses to host proteins, and could be a signal of what happens in patients who develop myocarditis.

That's the only light I can shed on this subject at this point.

CHAIR KARRON: Other questions or comments?

DR. NEFF: I just wanted to add why it's very difficult to do retrospective studies going back to the `70s. The vaccinations that were done in the `60s were all in children, and for whatever reason, myocarditis was not observed in the United States.

There were a fair amount of military, though, that were vaccinated from 1970s through the `80s. And I think the problem going back and looking at that is, when we were looking at this with the Smallpox Vaccine Safety group there was really a

paucity of data on the prevalence of dilated cardiomyopathy in the population. So you really don't have - it's very difficult to go back and sort that one through.

(Off-mike voice)

OPEN PUBLIC HEARING

MS. WALSH: As part of the FDA advisory committee meeting procedure we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the committee.

Dr. Karron, would you please read the open public hearing statement.

CHAIR KARRON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is

important to understand the context of an individual's presentation.

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of the statement, it will not preclude you from speaking.

MS. WALSH: I have received one request to speak from Dr. Robert Jordan representing SIGA Technologies.

Dr. Jordan.

DR. JORDAN: Thank you. Thank you for this opportunity to show our support for Acambis' ACAM2000 product.

Currently we have no direct financial connections with Acambis, but we are planning to conduct some joint studies to follow up some of these ideas that I'm going to be presenting today.

Our company is developing antiviral drugs to a variety of biodefense targets. Our lead program is a program for an antiviral against smallpox. This product is called ST-246.

We feel that the use of this product in combination with the live virus vaccine could potentially reduce some of the serious side effects that are associated with the live virus vaccine as well as protect

individuals who have been vaccinated but who haven't yet acquired protective immunity. So it essentially expands the product value of ACAM2000.

And so while this doesn't have anything directly related to the issues that were on today's table, this may come up in the future as we conduct our joint studies to explore this hypothesis further.

You can imagine in an outbreak there will be a period of time before the sentinel cases are observed. At that time point vaccines will be administered to the population. ACAM2000, a third generation vaccine, and maybe even an antiviral.

However there is a time period before. People would exhibit symptoms and acquire protective immunity where they are vulnerable to disease from smallpox attack.

We feel that co-administration of an antiviral drug would protect those individuals while they acquired their

protective immune response.

To give you a brief overview of the ST-246, it's a small molecule, potent, nontoxic, and it's a specific inhibitor of orthopox virus replication.

It's effective in all the animal models that we have tested against a variety of orthopox pathogens including monkey pox virus and variola virus in a nonhuman primate model (*** 1:05:36) virus disease.

It's orally bioavailable and has excellent PK and safety parameters. And currently it's in phase one human clinical trials for safety and PK.

ST-246 targets the F13L gene product. As you know the majority of virus particles produced during productive infection are intracellular mature virus. They are responsible for local infection and cell to cell spread. A small portion of these viruses go on to form extra-cellular envelope viruses which are involved in systemic spread, and are

the disease-causing form of the virus.

The F13L gene product is required for production of extra-cellular virus particles. The ST-246 inhibits F13L activity; prevents formation of extra-cellular virus particles; and in animal models we see no disease.

And interestingly in animals that have been infected in the presence of 246, they all develop a protective immune response.

And this is just some visuals to show you clearly that the administration of 246 protects animals from disease, compared to a mouse that's been treated with placebo.

So just again an overview. 246 protects animals from all orthopox pathogens tested. We can administer the drug at 72 hours post-inoculation and still see 100 percent protection from disease and death.

The compound reduces systemic virus spread, especially in the lungs. And we've been looking at studies using 246 in

combination with Dryvax, and we can show that it elicits a protective immune response equal to that of Dryvax alone, and we plan to continue those studies with ACAM2000.

So the indications we are seeking are prophylaxis, post-exposure prophylaxis, and therapeutic, as well as an adjunct to vaccination. We feel that the use of 246 in combination with these live vaccines could prevent smallpox disease during the time period where the vaccinee is acquiring protective immune response.

In addition we may be able to prevent some of these vaccine related complications, especially those that may be related to systemic spread of the virus away from the site of inoculation, and potentially prevent disease in those populations that have typically been contraindicated for use of these live virus vaccines, and those would be the immuno-compromised people.

So our initial studies have been

done in mice, where we have inoculated mice via scarification with Dryvax in the presence and absence of 246. And interestingly, what we see in the presence of 246, there is a delay in lesion formation. However this does form the same type, size lesions, forms about one to two days later.

When we look at a variety of immune parameters, we see equal to if not better immune response with the combination of 246 and Dryvax. And this is just a cytokine release assay looking at the acute immune response, and this is 246, and this 246 plus vaccine and 246 alone, and memory response.

Additionally with looking at neutralizing the antibodies to vaccinia virus, we see, especially in the memory response, almost equal titers of neutralizing antibodies with the vaccine or the vaccine plus 246.

So the combination of 246 plus vaccine seems to generate at least an equivalent if not better immune response than

the vaccine by itself. In addition to data that did show that the combination of 246 plus vaccine elicits an equivalent protective immune response when we rechallenge animals.

And we feel that using this combination treatment with the vaccine and 246, could protect individuals from severe disease prior to development of protective immune response.

Thank you again for allowing me to share our views and our support for ACAM.

CHAIR KARRON: Thank you very much, Dr. Jordan.

Are there other individuals who would like to make a presentation at this time?

Yes. Dr. Mendelman.

DR. MENDELMAN: Paul Mendelman, pediatric infectious diseases.

My question is, what is the pediatric dose? There is no age indication that is being proposed. It's those who are

going to have significant or serious potential exposure.

There was a publication I think a couple of years ago, Dr. Belshe in the New England Journal, diluting Dryvax, and showing you could boost the responses to people who had previously been vaccinated with a much lower dose.

And obviously some of the primary endpoints, Dryvax gives you a better booster response to Dryvax than Acambis did. Now with Acambis out there, one can do a study with Acambis, and then follow up with booster doses of Acambis versus Dryvax and see if one is a better booster to Acambis which is going to be the only vaccine available.

And if one does appropriate dilutions with Dryvax, one could use Dryvax as a dose ranging or dose finding for both booster response in terms of duration. My memory is that if I get smallpox vaccine I think I got a booster vaccine 10 years later.

But I could be confused about that.

But I'm more concerned about my children who are going to be exposed. So is this only going to go to military? I understand, first responders, health care workers like myself. But if there truly is a smallpox risk that is real within the community, I don't think from the data I've heard today th8at we know what vaccine and what age they should be given to in children, understanding it's very difficult to get any children or parents, altruistic, to enroll in these trials. It was tried by the NIH and didn't do well.

So I think we need to understand more about primary responses with dose ranging. Maybe 10 to the 8th PFUs per mill isn't the right dose, as you go across the age spectrum from 18 to 81.

And I think there needs to be some dose ranging studies in adults, under informed consent obviously. They need some booster

studies in adults that are dose ranging so we can do some more dose ranging and dose finding so that we have something. Maybe there are just separate - we have other live viral vaccines like MMR and varovax that are two doses. Because of issues with primary vaccination and getting a better take with a second vaccination that is long lived and durability of response.

So I think those kinds of studies ought to be done in the phase four scenario under the IND. In adults. We can all be the experiments and the guinea pigs, not the children; but something to help us understand a little bit more about the immune responses so we have a plan if we need to ever go into children.

Thank you.

CHAIR KARRON: Thank you, Dr. Mendelman.

Dr. Henderson.

DR. HENDERSON: There have been

questions raised about do we have a risk with regard to smallpox today. And I have heard this in many quarters. We haven't had an attack. Why are we concerned?

I would take you back to November, 2001. There aren't too many here who participated in the discussions we had, and to realize why ACAM2000 came as it did.

We knew in 1991 that there was work going on in the Soviet Union with regard to smallpox virus. The first hint we'd had that there was anything going on in the Soviet Union at that time.

Shortly after that Ken Alibek defected and presented a horrific tale of all that was going on; it was enormous; and talked about the fact that they were working with smallpox virus at a couple of plants; that they were producing it in ton quantities at a particular place called Sergiyev Posad. This was not really for awhile believed, but as we had more confirmation it was quite clear that

there was a lot going on, and it had a lot to do with smallpox.

We met in I think 1993 with a group of the primary Russian bioweaponeers at the National Academy of Sciences who provided us a lot of information. The door was open briefly there for awhile.

The top of their list was smallpox, and the next two were anthrax and plague.

So that there was a lot of work going on at that time in the Soviet Union. These were their priorities at that point.

We came to 2001, and we had the anthrax attack as you all know, and there was a lot of intelligence chatter at that time that there was going to be a second event; that the event would be biologic; and the question was, what would it be? And the two that were highest on the list were certainly smallpox and anthrax from the experience in the Soviet Union; and of course Russia was not exactly, at that time or now, all these

supplies they had, how tightly controlled they were was a real question.

We realized at that time, in that November, that we had no vaccine production facilities anywhere in the U.S. or the world. We had a limited amount of vaccine, 15 million doses; and only 90,000 of that could we use at that moment for other reasons.

We knew that there wasn't all that much internationally, and if smallpox was released anywhere there was going to be a problem, and it was going to be o8ur problem as well as the rest of the world's problem, no matter where it was released.

And so the desire to move as quickly as possible on getting a vaccine. And we thought at that time, do we go back to calves and do this on an emergency basis. This was going to be a problem setting up stables and shaving these damn animals and doing all the other things you were going to have to do.

We should go to tissue cell culture, and we should do that rapidly. So at that time when we sat around and we said, let us all do everything we possibly can to move this as rapidly as we possibly could to get something in the stockpile.

And of course that was now six years ago, but we are still getting the licensure, bu9t that's another story. But at any rate we do have vaccine.

So things have been - it's been a problem to know what to do. Beyond that, such alternatives as we have possible in the pipeline, you wonder how well they will work. Will they work in protecting humans against smallpox? And of course that is beyond the range of testing that we can perform now. I don't think the institutional review boards would permit that.

So we are faced with some real dilemmas as to what to do about smallpox. I think in looking at the issue of how we would

use smallpox vaccine, the feeling of having this available as an emergency, being prepared to respond quickly is what the strategy is at this particular time.

So the question is, how much more do we need to know about the vaccine. And of course we'd like to have more or less an infinite amount of additional information about the risks of the myocarditis and outcomes and so forth. Inevitably if this is going to be done, it's going to have to be done with DOD and the VA, and VA as we know at this present time is stressed. Are they prepared to take on elaborate studies? And this is a matter of priorities and decisions that will have to be made.

So I'm not sure where all it goes in terms of how far we go, but practically at this point the question is, what do we do if we have an epidemic? Whom do we vaccinate? What do we do about it? And there is indeed a utilization policy that has evolved, and I

think has been discussed widely at this point in time, and I think soon will be made more widely available for discussion; but it is basically that we would not use it extensively unless we have an attack.

And I think we need to keep this in mind, that we do not expect to use this other than in an emergency. We would not expect, based on what we know, to need to worry about long term immunity. We would be worrying only about comparatively short term immunity. And that we don't foresee at this point the situation where we'd have to use a vaccine on a routine basis simply because of the risks that are there, and the difficulties in getting vaccine across to any population in the United States, whether it's influenza or what have you, simply as a routine vaccination. This has not been an easy task.

But finally I'd just like to say I think the one thing that continues to worry us now is the question of, suppose we have a new

bug, whether artificially created or coming out of Africa; we don't have a vaccine; we don't have any treatment at this point in time.

How long would it take us to mobilize enough to develop - work with the manufacturers, the basic research people, to get something to counter that agent?

And I think now we have an opportunity to have a learning experience by going back and looking at 2001 where this was high priority, top priority, to get anthrax vaccine and smallpox vaccine. And here we are six years later, the anthrax vaccine is sometime in the future; the smallpox vaccine is not yet licensed; and I think just a matter of going back to do a detailed review of this, what could we have done to move this faster? It might be an illustrative piece for whatever we need to do in the future, because we are going to be faced with that problem with an agent that we are going to need help on in a

hurry. And right now it's quite obvious we are not well prepared to deal with that.

CHAIR KARRON: Thank you, D.A. And even though everyone in the room knows you, I was wondering if you could identify yourself for the record.

DR. HENDERSON: Well, I had something to do with smallpox eradication at one point, and in 1980 thought we closed the door and I would not be talking about it again. Subsequently I've been, since 2001 I was the first director of the Office of Public Health Emergency Preparedness with the secretary, and worked in that pretty much full time for the next three years as we dealt with many of these issues.

I'm now at the Center for Biosecurity at the University of Pittsburgh Medical Center.

CHAIR KARRON: Thank you.

Yes?

DR. ZINK: Thank you, if I may be

recognized.

I'm Tom Zink. I'm with Emergency Biosolutions. And in following that great rendition from our esteemed colleague I would just like to add for the record that we do have an FDA-licensed vaccine against anthrax currently available to our armed forces and those who determine themselves to be at high risk.

I just didn't want Dr. Henderson's last comment about us still waiting for an anthrax vaccine to go uncorrected for the record.

Thank you very much.

CHAIR KARRON: Thank you.

Seeing no other people - ah, one more person, yes?

DR. UTEFF: My name is Peter Uteff. I work for the public health agency of Canada. And I have no conflict of interest.

I try to put myself in the seat or shoes of the panel. And I wanted to know

whether the panel members had a really good understanding of what the definition of high risk of exposure was.

Because if you are to be asked to comment on that I would imagine you would need to have a definition.

And the second question I had was, a point maybe more than a question was, will the same indications or contraindications used in the clinical trial apply to the licensed product?

CHAIR KARRON: I just want to make sure that I - it was a little bit difficult to hear you, and I just want to make sure that I heard the questions.

Were the questions for the committee?

DR. UTEFF: They weren't questions. I was trying to put myself into your shoes, and I wanted to know how you are going to answer the question about high risk without knowing what the definition of high risk of

exposure was, or perhaps you do have a definition and could provide it.

And the second thing was, were you made aware of the exact contraindications which will be stated in the licensure product.

CHAIR KARRON: I think those are both issues that we will get into in our discussion that goes on after lunch. And seeing nobody else who wants to make a comment, we will now break for lunch.

Because I expect that we are going to have a fair amount of discussion, I would like to ask that we all come back at 2:15 rather than 2:30, so it will be a quick lunch.

Thank you.

(Whereupon at 1:24 p.m. the proceeding in the above-entitled matter went off the record to return on the record at 2:15 p.m.)

CHAIR KARRON: (In progress) - who need to leave on the early side this

afternoon.

COMMITTEE DISCUSSION AND RECOMMENDATION

CHAIR KARRON: What we are going to do is, we are going to have a very focused discussion from about 2:15 to 2:45. And at 2:45 we will vote.

What I've done is, the questions before the committee you have already heard. They were introduced by Dr. Merchlinsky.

You will note that the first one that I've put up here for discussion is actually the second question, which is a question about safety data.

I purposefully moved ahead from the efficacy data question, because I think that many of the issues have been addressed this morning.

If committee members feel that we need to have more discussion on this point, let me know now.

Okay. In that case I think we will

then move on to the second question and talk about committee members' feeling relative to safety data. And if you recall, and you have it in front of you on your handout, the next question is about benefits versus risks. And obviously we had some similar discussions yesterday. And I think that we have to think about the safety of this vaccine perhaps in that context, if in fact we are able in this instance to assess benefits.

So with that I'll open it up to discussion.

Dr. Word.

DR. WORD: I don't know if Dr. Baylor can address this one. But I'm still troubled by the last part of the question. If there is a high risk exposure. Because I think if there was a high risk exposure, or if it was there, I think we wouldn't be having this discussion.

Because really what you are asking, or the question is, can we use - is it

sufficient to utilize right now in our armed services.

CHAIR KARRON: Dr. Baylor.

DR. BAYLOR: Let me clarify.

What we are asking for is a situation where it is determined that there is a high risk of exposure. The military but also Dr. Parker presented a slide where there were recommendations in the civilian population. There is not per se a civilian program, but he did show a slide where there were certain areas of recommendation. Certain areas - I'm trying to pull that slide up now - available, recommended.

So I think you have to take that whole scenario when you think about this question. But probably what's facing is most is the military because they are actively immunizing when they are going into those regions.

CHAIR KARRON: Yes, Dr. Stapleton.

DR. STAPLETON: So one question that

arises then in the military, and I know a lot of this is policy and not necessarily the purview of this committee, but it would seem that opting out options, based on very extensive - or very thorough educational opportunities to recipients, would be important, particularly about the cardiovascular aspect.

Because the incidence of myocarditis of one in 150 is far beyond anything else we deal with in preventive vaccines.

CHAIR KARRON: Did someone from the military want to comment on that?

DR. NELSON: Reluctantly.

In certainly scenarios opting out is certainly a viable option. And I'm not going to make a decision today whether today's situation is one of those.

When the Department of Defense approaches these issues in general, they take into account the risks and benefits for the

individual and the organization and unit as a whole.

So when we do have situations with true bonafide high risk exposures, it may in fact affect a certain portion of a deployed unit; that in fact imperils more than just that single individual.

So that balance of when a decision is made, whether a vaccine is mandatory or not, takes into account all these things. Currently the smallpox vaccine is mandatory for individuals deployed to these areas. There are exemptions as we talked about for medical reasons, but not quite for opting out.

So yes there are individuals over there who are not actually vaccinated, but who would be in the setting of a true high risk exposure.

DR. MASSIE: Refresh me, do people who enroll in the military get - what type of workup do they get going in nowadays? Do they get ECGs? Do they get - how careful - in

other words, would all the information be available to make such a decision as to if they meet the high risk categories if they don't actually know to answer all the questions.

And I would say another thing that clearly would concern me about the heart in that age group would be alcohol abuse, which certainly can cause cardiomyopathy in its own right. Now I wouldn't imagine the average service person would be willing to discuss that, perhaps, which may be an issue as well.

But certainly if everybody had an ECG, and that were reviewed at this point in time before they were given the vaccine, that would be at least a start, and a careful medical history.

The question is, do they have a form that says, do you have heart disease, and they check yes/no, that probably would not be adequate.

To answer your question about

inductees into the Department of Defense, they do not currently have a mandatory ECG that is done or serves as a reference baseline for future consideration.

And I can tell you however that everybody who is inducted must undergo a history and physical examination that is thorough and addresses all chronic medical conditions, not only at induction, but at a minimum at least every five years, and this is tracked centrally.

CHAIR KARRON: Dr. Teerlink.

DR. TEERLINK: I'm following up on Dr. Massie's question. It seems then that whereas we are saying that baseline ECG abnormalities we're concerned may put a person at increased risk for development of myopericarditis, or at least increased risk for bad outcomes in relation to that, then it would seem to be prudent to have that be a requirement before vaccination.

As we are trying to grapple with -

this is clearly a risk benefit question. And we are right now giving ou8r service personnel a vaccination to prevent something that as of yet hasn't happened but may be a high risk event, we don't know. But there is a clear risk involved.

And it's interesting to me that if in fact the appropriate surveillance is done, which is that we get ECGs and follow up on symptoms and follow up on troponins in these patients, that the U.S. military is willing to give a vaccine that will knock out one ou8t of 145 people who get the vaccine for a six-month period. If in fact the policies are put into place that we have been talking about where we follow up these patients to see whether they have ECG changes, whether they have changes in troponin in relation to the vaccine, if you then - and we see that it's about one out of 145, we are going to be eliminating, by giving this vaccine, getting rid of whatever percent of our armed service personnel that is.

So is the plan to do pre-ECGs in this, and this will help us evaluate the risk MAP. And is there a plan to do follow up troponins and follow up ECGs to actually look at what the risk is?

DR. NELSON: So across the board in looking at follow up ECGs and triponins certainly is done in our cohort of index cases. But there are also studies underway, the immunogenetic study done in conjunction with the Centers for Disease Control and Prevention and the University of Washington, with a target enrollment of 3,000, does just this. So it has periodic assessment of enzymes and EKGs in a symptomatic individual. So we hope to get that data at least for the current Dryvax vaccine.

Your point about the ECGs as a mandatory screening step for receipt of the vaccine is a little bit problematic for me. I think it may be in some circumstances the right thing to do. But in my position as

assistant department chief and a true foot-on-the-ground implementer at the clinic level, which is my main reason for being here today, I see some very practical issues with that.

And I think that making the leap that a finding on an EKG increases your risk for myopericarditis cannot be made at this time.

As part of that same study with a target enrollment of 3,000, there was a control group of 200 influenza vaccinees. That cohort has been closed out at its target level of 200; 11 percent of those individuals had some EKG change from baseline. None of them were adjudicated as really causative or associated with vaccinia myopericarditis. So I think we may be setting ourselves up for finding spurious EKG findings during the baseline studies that would be problematic to interpret with respect to risk factors for myopericarditis or what else needs to be done with these individuals since some of these

normal variant EKG findings really are quite prevalent.

DR. MASSIE: What about follow up troponins?

DR. NELSON: As a mandatory for all recipients? Practically again I think that would be problematic because of the fact that these individuals are often deployed to austere locations, and the control for samples and ability to assess these individuals may be an issue.

Certainly doing an answer to these questions in a research setting in the right cohort that we can do very active follow up on I think is the right thing to do. And as a scientist in addition to a clinician these questions intrigue me greatly and I think should be addressed in a systematic research setting.

CHAIR KARRON: Dr. Self.

DR. SELF: So one question that reminds me of yesterday's discussion, is the

consideration we are supposed to be making about safety and efficacy data relative to Dryvax? Or is it in some absolute sense?

If it's relative - I'm kind of thinking about this as if it's relative to Dryvax which has had extensive use. And I see no data that would suggest the risk profile for myocarditis is any different between Dryvax and Acambis.

And so I guess I'm wondering, why we are - whether that's the reasonable benchmark. If it is, then my suggestion would be to really focus on simple but clearly clinically relevant outcomes in large numbers of vaccinees as you have in Dryvax for as long term follow up as you can. Because all the rest, given the use in the context that Dr. Henderson provided, just seems out of place to me.

CHAIR KARRON: Actually, before I call on Dr. Farley, Dr. Baylor, do you want to answer that question?

DR. BAYLOR: Sure, I'll come on that. I think it has to be both, because when the vaccine was evaluated, when Acambis 2000 was evaluated, it was evaluated against Dryvax. Dryvax, it's a vaccine of a different era. This, the ACAM2000 was a new, quote unquote, vaccine manufactured somewhat differently.

We are talking about using this vaccine for a specific program as a licensed product. There are stockpiles of Dryvax available. This vaccine if licensed will probably be used in much larger quantities.

I think you have to look at the data as it was generated against Dryvax, but in the larger sense looking at this product, how this product will be used, based on the data that you have seen in the clinical trials, and using this product, ACAM2000 in a population, and considering the safety and efficacy data in that context.

DR. HETHERINGTON: I wanted to make

a comment very similar to what Dr. Self has said, in that whatever we are discussing here about what is necessary for screening patients or follow up or risk-benefit really applies to both vaccines. The total number of cases, or the case rate was actually higher in the Dryvax group than in the Acambis group, although it wasn't statistically significant.

I guess the question is, given those numbers, what's the likelihood that the risk would actually be higher in the Acambis group. And I would guess that it's probably pretty low.

So with regard to this question about, are the safety data sufficient to support the use of ACAM2000 in situations where there is a high risk of exposure is as sufficient as the data is for Dryvax I believe based on what we've seen today.

That doesn't mean we can't make additional recommendations on what should be done. And I don't think we should shy away

from doing things that might seem onerous, such as screening people with EKGs. If you are a pharmaceutical company and you are developing a new chemical entity, you are going to do a fully powered QT study which will involve about 2,000 EKGs on about 2 - 400 patients. So it's not out of the realm of what is ordinarily done for new therapeutics anyway, and one at an early stage even before you get to the phrase three studies.

CHAIR KARRON: Dr. Farley.

DR. FARLEY: I have a question for the military in terms of whether the availability of the licensure specifically of the ACAM2000 will change how you prioritize, or will it involve, likely involve, an increase in the number of doses given?

I mean at present it sounds like you are actually going through an algorithm of the highest risk exposure individuals. And you are not immunizing the entire - everybody in the military. Is that because you have

been trying to preserve the number of doses available and not use up more than necessary, and if it were more widely available you would go ahead and just do a universal immunization of the military. That would be I think of interest to know.

LT. COL. FORD: The policy is based on the threat, and it's mandatory for again service members who are deploying to those higher threat areas currently assigned to the U.S. Central Command area of responsibility or for Korea, for emergency essential civilians and contractor personnel performing mission essential functions in the same area.

I don't expect the policy to change as a result of licensure of ACAM2000 or not or the use of Dryvax. The policy will remain unchanged for the target group.

DR. NELSON: This is Dr. Nelson again. To state that in a different way there is no current rationing in place based on the levels of vaccine in the current stockpile.

DR. MASSIE: Maybe I misunderstood. So in terms of - it's deployed did I hear only to Korea at this time? Or is it deployed to anywhere abroad?

DR. NELSON: There are high threat areas, and there are multiple areas.

DR. MASSIE: Oh, you are not able to tell us - okay. I mean I agree - certainly I don't see a signal for myocarditis that is higher with this vaccine. It happens to be the way the question is worded, however, which doesn't say it is a comparator; it's just - is it the - oops - but basically I mean clearly myocarditis, we don't know how serious it is. We have two different - two roadblocks to making a reasonable decision. One is, we don't know how serious this syndrome is, because we don't have follow up data on what happens to these people, and we are not going to get it for awhile. And the second thing is, we don't know how serious the risk is.

So it's a little difficult frankly

to answer the question. But I think that along the line of what we could do, there is reason to believe that people with preexisting heart disease, or at least to have a belief of it, are at higher risk because that's how people designed the studies, and that makes some sense.

So I don't know which question in point of discussion it comes to. But it seems to me that we should encourage people to do all the things that we think might limit the risk of individuals getting this. And assuming that there will be situations that are deemed by people high enough risk to make it worth giving, I guess the payback is that you have to screen out the people at risk.

CHAIR KARRON: One last comment on the previous question. Dr. Jackson.

DR. JACKSON: I was going to move on to four because I was assuming you would be moving us there momentarily.

Anyway, since we are getting near

the end of our time, I have a major concern I guess about the adequacy of the post-licensure risk minimization action plan in that looking at identification of people who may be at increased risk down the road because they have experienced this event. I mean it seems to me that the registry is not adequate if it only identifies the small subset of cases that are symptomatic, and that we don't know what the long term consequences are. Perhaps people completely recovered from this, and there is nothing that happens after that; but perhaps there is not.

And if there is not then it seems like we want some ability to be able to identify those persons who fell into this risk group as a consequence of their vaccine exposure.

I'm not a cardiologist, but it seems possible that these people may be at higher risk of cardiac decompensation on subsequent insult, such as uncontrolled

hypertension, alcohol abuse, or some things like that that are potentially preventable or modifiable. So you could imagine scenarios where this knowledge may be beneficial down the road.

So I'd like to say that I think this plan is built along the lines of more traditional post-licensure and intent on identifying signals, which is fine, except that in this case we already have a signal that seems to be quite robust and quite serious.

So I think that some aspect of the plan needs to accommodate that consideration.

CHAIR KARRON: Since we are jumping around a little and our time is limited, I actually did want to make a comment about the risk MAP, in addition to, I actually agree with everything that you said, Lisa.

But one of the things was about vaccinia education. And I did note, when Colonel Ford put up the original trifold,

which is I believe what troops are getting currently, there is actually very little information there as I saw it on myopericarditis, myocarditis, chest pain, transient, rare event. And I guess I would suggest that probably given new information about both Dryvax and ACAM2000 that particular attention be given to that, and that additional information be included there.

DR. COLLINS: There is information - remember you also indicated that there is a video, there is a provider brief that is given, and that information is included in that brief. But we are actually relooking at the trifold to try to incorporate more information.

But information regarding the myopericarditis is given in there.

CHAIR KARRON: Since we've skipped around a bit, and skipped ahead to this question, are there other comments the committee members want to make that address

the risk MAP? I know that we had deferred a lot of this from this morning.

Dr. LaRussa.

DR. LaRUSSA: I'll just bring up again the idea about doing the EKGs on the 10,000. And I think it would give you an opportunity to sort out what are the real nonspecific findings that mean nothing, and the ones that may really be associated with long term sequellae. So I would encourage you to do that.

CHAIR KARRON: Dr. Farley.

DR. FARLEY: This has been mentioned before, but I just wanted to emphasize it again, that I think for the phase four trial the idea of having a very well thought out control group is really essential.

But I just wanted to make sure that that is part of the planning, which might be as much the company as it is the military. But I'm sure it will end up being a joint venture.

The other thing is, and it's not necessarily the risk MAP, but it's the pharmacovigilance, or somewhere in this, is to really make sure that this is permanently and indelibly on their record if they had myocarditis, whether it be on the DOD side, as well as the service connected side that we see on the VA side . But just making sure, regardless of their recovery, even with full recovery, at least apparent full recovery in that short term, that it be mandated that it be put in their records, that that will be something they can fall back on later and will be of interest.

CHAIR KARRON: Dr. Massie.

DR. MASSIE: I mean the other thing, and I've said it before, and I don't want to get lost at this moment, in that phase four study there has to be mandated, and if the government doesn't get it done they should be penalized for it, long term echos. Otherwise we will never know. And so I think they need

an echo when they get - have the disease. They need an echo one year later. And the military has got to find a way. And if they can't find a way they shouldn't vaccinate the people.

CHAIR KARRON: Actually I want to follow up on something you just said, Dr. Farley, which is the issue of a controlled phase four trial. And my question is, how do you do that? If you could perhaps use the controls for people not being deployed to that area as controls. But that is not an optimal control group. They are not the same.

And if you can have controls among the people who are being deployed to those areas then you probably don't need the vaccine in the first place if you are willing to accept a control group among the deployed.

So how to do a controlled phase four trial?

DR. FARLEY: Well, I guess I was thinking more in terms of those who did not

develop myocarditis but received the vaccine would potentially be - some group of them would be followed with the same kind of EKGs, troponins, that sort of thing, to match the activity of those who developed clinical myocarditis.

CHAIR KARRON: Dr. Self.

DR. SELF: So I think we are talking about a cohort study, but a nested case control design within this.

I mean we don't know anything about how these vaccines will be used in the military that could inform study design. In listening to the discussion there are lots of good ideas, but I think that we don't have enough information to try and talk about what the most efficient way is to do the (*** 2:41:34) and learn what we need to learn.

It does seem that with the plan of a cohort study of 10,000 that is more than adequate for most of the studies that we have talked about so far. It may not be adequate

in size for defining very low risk events long term follow up, and so there may be two phases to it. That may be as a statistician about as far down the design road as I think I can see.

DR. NELSON: One other very practical issue of looking at a study of 10,000 in this setting is that we are making the assumption that we are going to be able to devote any reaction that occurs specifically to the smallpox vaccine, when in real practical use this vaccine is administered in the context of other vaccines, same day, same month, same couple of months.

So we need to look at, when we do design that specific cohort, whether or not we can isolate the vaccine, which may be impractical in a lot of situations. It may also set you up for some selection bias for the cohort you are able to do this on.

DR. SELF: I guess I would just say that that argues even more for being very specific about the clinical endpoints.

CHAIR KARRON: Other comments?

One question that we skipped, and we are actually going to go to the vote in a couple of minutes, we did skip discussion of three, which is please discuss benefits versus risks of ACAM2000 for use in high risk populations.

Unless people feel we need to discuss that right now, I think we will discuss it in the voting situation.

Okay. Are there other comments that committee members want to make?

Dr. LaRussa.

DR. LaRUSSA: So just for point number five, methods to increase sensitivity of case ascertainment and long term follow up, the only other thing I can think of is, there are CDC-funded VSD, and centers that could potentially help with long term follow up. And it might be possible to either give people referrals or get permission to have them contacted by CESAR (phonetic) or VSD

investigators after they leave the military, and that way ensure follow up with some of these people. CHAIR KARRON: Okay, seeing no other comments, I think we are going to move to vote.

Just a couple of things I just wanted to make clear. One is that if you look at the questions and the discussion items, there are three questions, and there are two discussion items.

I think for simplicity sake what we are going to do is go through each of the questions, which are yes/no questions, which are actually one, two and four, and then we are going to go to the two discussion items, which are three and five. And also again because I think really of time constraints, I am just going to call upon the voting members of the committee to speak in answer to the questions.

So I wonder if we could have the first question.

The first question is, are the efficacy data sufficient to support the use of ACAM21000 in situations where it is determined that there is high risk of exposure to smallpox virus?

And Dr. Aziz, we'll start with you.

DR. AZIZ: According to what we've heard today, I really believe that, yes, the data is sufficient.

CHAIR KARRON: Thank you.

Dr. Massie?

DR. MASSIE: I think of people who know how to answer that question say yes, I would agree. There is a difference, but I don't know the clinical or biological significance of that difference. But it looks more similar than different, I guess.

CHAIR KARRON: Colonel Schultz.

DR. SCHULTZ: I have to go along with Dr. Massie that those who should know, and given the indication, the difference is so slight that there is no reason not to say yes.

CHAIR KARRON: Thank you.

Dr. LaRussa?

DR. LaRUSSA: Well, assuming that there is somebody who knows that there is a high risk of exposure I'd have to agree that the data support the use of ACAM2000.

CHAIR KARRON: Dr. Self.

DR. SELF: Well, first of all, I object to use of the term, efficacy data, because we have none. These are data on surrogates, and we are trying to infer efficacy.

There were some statistical issues raised about coprimary endpoints and alpha spending and all. I think all of that was fine, however, there was discussion about missing the preset criteria. And usually on these committees that's a rather big deal.

In this case I don't think so. I think the criteria were unusually strict, actually. And in looking at the RCD curves for antibody titer, I don't see that these are

different in any important way.

So in the end I would answer the question yes.

CHAIR KARRON: That's a yes, is that correct, Dr. Self?

DR. SELF: That would be a yes.

(Laughter)

CHAIR KARRON: Dr. Teerlink.

DR. TEERLINK: With all of the foregoing caveats and comments I would say yes as well.

CHAIR KARRON: Dr. Jackson.

DR. JACKSON: Yes also.

CHAIR KARRON: Dr. Word.

DR. WORD: Yes, I agree.

CHAIR KARRON: Dr. McInnes.

DR. McINNES: In looking at these four endpoints for noninferiority, I think the take rate in the naive is the most important and the dominant one and the one on which we have the most experience, and has meaning way back to the smallpox eradication time.

I think the others we've backed into in some ways, hoping that we would see some nice clean correlation with plaque neutralization assays, et cetera. I really hold less water in those, and certainly take in vaccine previously vaccinated I think we don't really know a whole lot about what that necessarily means.

So with some hesitation only because I don't want this to set a precedent for future that you can fail endpoints and still make it okay, and that this gets pointed to as an example. I think this is a unique setting. I think this is a unique disease, a unique vaccine, a unique procurement for the government, a unique target population.

So I think it's important to enunciate that. I don't wish this to be viewed as precedent setting that you can fail noninferiority endpoints and still be licensed. But I think in this particular case, and the historical basis of this

vaccine, and it was highly efficacious in eradicating a disease. I am persuaded by the take rate in naive, and so I do think this efficacy is an efficacy surrogate that will support the use of this vaccine in what I hope is really a - I hope it's only used where there is a risk of exposure.

So I say yes.

CHAIR KARRON: Thank you. Dr. Farley.

DR. FARLEY: I very much agree with what Dr. McInnes has just stated. And I think in particular since most of the military personnel, or at least the young people who are fully susceptible coming in, are going to be in that naive category; that the idea that the take rate was high in that group with some of the ancillary immunologic data persuaded me as well. So yes.

CHAIR KARRON: Thank you.

And I would also vote yes, particularly though underscoring what Dr.

McInnes said about not setting a precedent.

So our second question if we could have that. The second question is, are the safety data sufficient to support the use of ACAM2000 in situations where it is determined that there is high risk of exposure to smallpox virus.

And this time, Dr. Farley, we are going to start with you.

DR. FARLEY: Okay. Well, again, going back to what was just stated, I feel as if - and this came up somewhat, the pandemic flu vaccine discussion a few months ago - that it would - I think this committee who is used to setting a high bar for things, as is the FDA, for safety and for efficacy, would - if we were looking at a vaccine that was coming through for routine use in the general population, having this kind of myocarditis signal would be unacceptable.

And so I think that raises our concern level, but then we have to put it into

context. And I wish there were some kind of a special licensure process for these kind of diseases that we are dealing with in this setting and also in some respects pandemic flu.

Bu9t having said that, we are facing what now I think just has to be balance of high risk exposure versus - to a very significant disease - versus the safety profile.

And so I think that after all of the discussion today, that given all the restrictions that we have discussed, including that this would be restricted to only being used and not in a commercial setting but in a governmental setting in a high risk exposure situation, and given the screening and pharmacovigiliance that has been also - will happen further down the road; given all that, in this context of this disease and this situation specifically, I would vote yes, that the safety data are sufficient.

CHAIR KARRON: Thank you. Dr. McInnes.

DR. McINNES: In follow up to my colleague, it's clearly significant reactogenicity (phonetic) in - there is an adverse event profile that does cause one to pause.

I feel very strongly that the vaccine should not be used lightly, to be used in a setting where there really is risk, I think all we are told, and this has been the same way for years is, we are not going to quantify the risk, but it's not zero. And so that's the best that we know.

And I think about it really in terms of public sector use the same way I think about an emergency use vaccine. I know that that raises issues that are sort of operational and somewhat strategic.

So with those caveats in mind, and that I still - all I know is that the risk is not zero - I vote yes.

CHAIR KARRON: Thank you.

Dr. Word.

DR. WORD: I think everyone has that feeling of ambivalence when it comes - because you are looking at that signal that is coming out.

But when you put in that caveat of high risk exposure, then you automatically switch gears. A number of us do anyway in terms of saying the risk and the benefit for them.

And so if it is strictly limited to specific targeted group and not for the general population as proposed right here, then I would say yes.

CHAIR KARRON: Thank you, Dr. Word.

DR. JACKSON: I agree with the previous comments, and would also vote yes.

DR. TEERLINK: I agree with the previous comments, and also vote yes, and encourage the military and the Department of Defense to do as you have been doing, but

really take into account that this safety signal seems to be much stronger than I think we previously had guessed, and take that into account in terms of who you give it to.

DR. SELF: Agree with the previous comments and vote yes.

CHAIR KARRON: Dr. LaRussa.

DR. LaRUSSA: Yes. Nothing further to add.

CHAIR KARRON: Colonel Schultz?

COL. SCHULTZ: Yes.

CHAIR KARRON: Dr. Massie.

DR. MASSIE: Yes, but with all the provisos and the fact that it really depends on further pinning down the safety. We don't know now. It is as safe as the vaccine that is being used. But unless there is further data I think that yes has to be revisited at some point in time. And maybe when we discuss the risk management, we say no, that will be a chance to try to develop something that would maybe make this risk benefit more appropriate.

But yes, I think it's as safe as what we are doing now.

CHAIR KARRON: Dr. Aziz.

DR. AZIZ: And I agree with Dr. Massie. I think what we know right now is sufficient for us to say yes. But on a future date it might be helpful; so it's yes.

CHAIR KARRON: And I would also say yes, and I would underscore the second half of this question, which is really only in situations of high risk of exposure to smallpox virus. Because this and Dryvax are the least safe vaccines that we will have licensed in this country. And I think we have to weigh that against the risk of smallpox.

Okay. The next, as I said before we are doing the yes-no questions first, and then we are going back to the discussion questions.

So the next question is question number four: Does the committee agree that a risk minimization action plan for ACAM2000

composed of the following is needed.

I won't read each of these, but you can see them. And what I'd like to do in this vote is actually you can say yes, or you can say no. Whether you say yes or no, if you would like to underscore any of these individual points, A through E, we would appreciate those comments as well.

So this time, again, Dr. Aziz, we are starting with you.

DR. AZIZ: I think I can say yes for all, and with number four, what was discussed also in the committee with the need for a controlled study, control group.

DR. MASSIE: Well, the question is whether it's needed, and I think there is no doubt that the answer to that should be yes.

Whether what I've heard today is sufficient, the answer no doubt is no, and I think somebody has to come up with a better plan. We can't micromanage it, but I think that should be determined before approval and

be agreed upon by people. Where is it insufficient? We need to know the outcomes of the people who have it. We need to know - that's one aspect. And that's the phase four trial design which may have to be expanded to a larger size.

We also need to do a better job of screening out the high risk patients. That's part of risk management.

I do believe an ECG, such as it is, and before the patient gets it, is part of that. And then I need to think follow up ECGs in all patients, at least in the phase four trial, and perhaps as Dr. Teerlink has suggested, in all patients at that 10-day check on them visit, would also be good.

But I think that there is a big gap here between what is, handing out pieces of paper and getting the information we need and protecting the people who are getting this.

CHAIR KARRON: Col. Schultz?

COL. SCHULTZ: I will say yes. But

I would like to make a comment about the phase four study. If it's going to pose a horrendous problem for the military long term to try to follow through on this. And I think someone has to take a look at that, see some way to get around it.

CHAIR KARRON: Okay, Dr. LaRussa.

DR. LaRUSSA: So yes, and yes the studies - the phase four studies need to be improved. And I think unfortunately regardless of the problems it poses to the military, it really has to be done.

CHAIR KARRON: Dr. Self.

DR. SELF: Yes.

CHAIR KARRON: Dr. Teerlink.

DR. TEERLINK: Yes.

DR. JACKSON: I think the current plan is not adequate so I would vote no. I would say the vaccinia education would need to be bumped up considerably and include statements such as, you have a one in 100 or one in 200 risk of sustaining myocardial

injury following vaccination; and that there has to be some way of identifying persons who were not part of the formal phase four study who have myocarditis by means other than voluntary self report.

CHAIR KARRON: Dr. Word/

DR. WORD: I'm sorry. I actually will say yes with the caveat that more improved phase four studies. And I do think the military, if you can find a way to deploy people, you can do anything - as Kennedy once said, if you can get a man on the moon, I think you can find a way to conduct these studies.

CHAIR KARRON: Dr. McInnes.

DR. McINNES: I think these as a minimum are absolutely fine, and I say yes. And I think many views have been expressed today that could be embraced into a little bit of an expansion of this.

And I am supportive of what is laid out, and hope that it will in fact become even

more robust with time.

CHAIR KARRON: Dr. Farley.

DR. FARLEY: I would vote yes, and I agree with all the comments, and would just add that I think that taking a good look at the cardiac bullet points - this may not have been an exhaustive list, but very carefully looking at the cases that have occurred; what we currently know; discussing it with cardiologists; and coming up with a good list of exclusion criteria would be very helpful.

CHAIR KARRON: And I would also vote yes with all the qualifications given as ways to improve the risk MAP plan.

Okay, we are now at the point of going back to our two discussion questions. The first one that we will put up is, please discuss the benefits versus the risks of ACAM2000 for use in high risk situations.

And here this is just - Christine, correct me if I'm wrong - but this is just going to be an open discussion. So we'll take

a few minutes on that for people who would like to comment.

DR. MASSIE: My comment would be, I think that's what we've been doing for the last 15 minutes.

(Laughter)

CHAIR KARRON: Okay. Well I actually have a comment to make about this, which is that I think that yesterday you heard us all trying to look at issues of risks and benefits and talking about whether we should be or not.

But there I think relative to today it was kind of easy. Because I think we all know what the risks of influenza in children are. And we can look at the vaccine, and we could do a comparison.

Here I think quite frankly our hands are tied. We only can talk about the risks. We have no way of knowing information about the potential benefits of this vaccine relative to credible threat risk information.

So my feeling is, honestly, I think the people who are in a position to make that decision have to take the safety considerations very seriously; think particularly about this one in 150 risk of myocarditis; and put that into the equation as they are deciding for - about issues related to vaccinating military populations.

Other comments? No? Okay.

So we are up to the last - the very last item, which is - and we have discussed some of this today, but maybe we could just underscore it, people who have made these points earlier, if you could just make them again for the record.

Discuss methods to increase sensitivity of case ascertainment of myocarditis and long term follow up and methods to evaluate the effectiveness of the risk MAP.

DR. MASSIE: Since I've been doing it I'll go back, I think the studies were very

nicely designed that we saw. I think they have a good time point to look at the myocarditis developing at that point. They have ECGs. They have troponins. They have CPKs. I think probably the CPKs are probably not worth if you have troponins.

So I think that they probably had a good risk ascertainment process. The long term followup is what we really need I think at this point in time. And I would continue that ascertainment process as it was done in the studies and not cut back on it just because we are rolling it out to other people, because we really have to know.

And so the question is, what is the long term? I mean I think if you give people a Amazon dot com certificate and say, when your echo is sent to us, you get this certificate, they'll get them. And any VA hospital will get $25 for doing it.

It's not hard to get people to do things with the right incentives, and I think

those ought to be there.

And I think the other thing is, we do need to get an echo. Whether you need the echo at the 10 day when the troponin and the ECG is positive, or you get the echo at some expert determined time thereafter to see if there is anything residual. And then later, too, because clearly there are many people - and Dr. Mason left - but that believe a lot of the cardiomyopathy we see that's not due to coronary disease is due to subclinical myocarditis.

This is not subclinical, and if we can find nothing delayed on that that would be very important for lots of people who are exposed and may worry for the rest of their life, and for the people who may be bothering the VA about all their cardiac complaints. We really need to know that information.

So that would be my point, to emphasize the long term follow up, but not to cut back on what you have done in the studies

for the people getting the vaccine now.

CHAIR KARRON: Just to be clear on that, Dr. Massie, so what you are really recommending is the EKGs and the troponins, to not cut back on those specifically as you are assessing prospectively?

DR. MASSIE: Right, and then adding an echo and later historical information and follow up information to find out the significance of the people who have it.

And again the devil is in the details about the control group. But I'm afraid there will be people who don't get this myocarditis from the vaccine and people who wouldn't get the vaccine who might have some of these same things.

So we need to figure out a way to get a comparator group as well.

CHAIR KARRON: Yes, Dr. Teerlink.

DR. TEERLINK: So just to extend upon what Dr. Massie just said, I would also encourage that there be an echo substudy of

echos at baseline, where you actually get - and it may have to be in 500 or 1,000 patients or people - and then you get some serial follow up. Because otherwise you will be stuck with issues of people - of not knowing what your actual attack rate is.

And then I would reinforce the importance of having serial studies on patients who have now become index cases of the myocarditis and following serially. And I think that is absolutely essential.

I agree in terms of the CKS, dripping those. But the (*** 3:07:43) and the ECGs would also be very useful, both as baseline screens - because as you have said, my guess is, they are going to be very nonspecific - but it would be useful to demonstrate in this context that they are in fact nonspecific.

CHAIR KARRON: Yes.

DR. ROSENTHAL: I'd like to ask Dr. Massie, Dr. Teerlink, how long is long term

follow up? What would you recommend?

DR. MASSIE: I wish Dr. Mason were still here in terms of that. But I think that at least one year and two years.

But my guess is that if you can't see anything at two years that probably these are not the people who come with low ejection fractions after 10 years. But I don't know, I think you would have to get a variety of opinions.

But it presumably is a matter of some time later.

CHAIR KARRON: Dr. LaRussa.

DR. LaRUSSA: So just because we are being asked to repeat things, I would like to see some at least formal mechanism of referral for follow up care once people leave the military.

DR. MASSIE: For the people who got myocarditis in particular?

DR. LaRUSSA: I would think that if you got this syndrome you should leave the

military service connected. I mean it would be nice to make sure we collected that data, and the computerized record theoretically could be queried and found out whether they got it or not.

But I would think that that should be available and free to both the military - if not the country - and to the individual.

CHAIR KARRON: Dr. Jackson.

DR. JACKSON: Again, since we were asked to repeat, I would say that what the Acambis study makes clear is that symptoms are a very insensitive way to identify persons who have evidence of myocarditis.

And so an important way to increase sensitivity of case ascertainment is to use methods other than report of symptoms. And I think that is along the lines of the discussion of other committee members.

CHAIR KARRON: Other comments?

Dr. Word.

DR. WORD: In terms of the

individuals who develop myocarditis, and when you - the cardiologists suggested doing serial echos. I guess the first model that came in my head, I was thinking that like so the adult - the child - Kawasaki, where we continue to follow them out for X amount of time until, you know, then we just stop.

And I don't know how frequently you would propose that they should follow the echos.

DR. MASSIE: I'm not sure - I know I'm not the right person. I think that Dr. Mason who was here is one of the right people.

But I think it should be long term. I would say a minimum of the two years, and I just don't know whether people feel it would be likely - and of course there will be inter-current events that begin to effect other people too.

DR. TEERLINK: So one of the other titles is the head of our echo-cardiography department. So I agree with Dr. Massie that

two years would be at a minimum follow up. A five-year cohort would probably also be useful. And that - as Dr. Massie pointed out, the further you get along, the more intercurrent events you can have that can complicate this. Fortunately, you are starting out with a group that has such a relatively low event rate in terms of cardiovascular illness. They are being selected to be healthy cardiovascularly. And so they are a perfect group to actually study the potential additional risk of this agent on cardiac outcomes.

CHAIR KARRON: Other comments? Yes, Dr. Goodman.

DR. GOODMAN: I just wanted to ask especially the cardiologists if you are accepting the comments about the high risk individuals being the subjects who had received the vaccine.

I heard a lot of comments about screening tests before they are enrolled. But

I've also heard about the high incidence for example of nonspecific EKG findings, even in relatively healthy young populations.

And I was wondering if you have any guidance about what kind of findings would really make you concerned about an individual receiving the vaccine other than actually having known disease.

And the other thing I was going to ask is whether there is any evidence from the DOD cases - I know there isn't from Acambis, because in general these people were excluded - but presumably most of these cases are occurring in people without a history of cardiac disease.

So I'm just wondering why that would be a risk factor. Obviously you wouldn't want to give it to someone with active disease.

And then what kind of things you would look to somebody - a practitioner or a health system like the DOD using this vaccine

- what kind of things would concern you, and what kind of things wouldn't?

DR. TEERLINK: Thanks. So we don't know. We don't know what are the real risk factors that predispose. So we have to take extensions from what we've learned from other cases of cardiomyopathies and myocarditis and things and try to extend that into this realm.

That being said, certainly people who have evidence of - strong evidence left ventricle hypertrophy, I'd be concerned about. People who have evidence of potential ischemic disease that is more clear than just some nonspecific ST-T-wave changes, and then they would have to be followed up for evidence of apicardial (phonetic) coronary disease.

Any of the familiar cardiomyopathies, any histories along those lines, should also be excluded.

In terms of the conduction abnormalities that I'd specifically exclude, I'm not sure I'd know which of those to go

after. Bivesicular block (phonetic) would probably be one that I'd be concerned about.

DR. MASSIE: I would certainly rule out anybody with a left bundle (phonetic). First of all, because you can't say anything else about the ECG, and at that age range, left bundle branch black (phonetic) would be a remarkable finding. I don't know about right bundle or the other types of bivesicular (*** 3:14:30) but we know that the epidemiologic risk of the left bundle, I'm sure it's true in kids and it certainly is true in adults, is pretty high; whereas the others are not.

CHAIR KARRON: Other comments or questions?

If not, we are adjourned. Thank you all.

(Whereupon at 3:15 p.m. the proceeding in the above-entitled matter was adjourned.)

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