

MEETING OF

ARMED FORCES EPIDEMIOLOGICAL BOARD

Dalymple Conference Room (1425)

The U.S. Army Medical Research Institute

Infectious Diseases

1425 Porter Street

Fort Detrick

Frederick, Maryland 21701

TRANSCRIPT OF PROCEEDINGS

MAY 11, 2004

Reported by: Donna Evans
Tri-State Reporters, Inc.
43 Summit Avenue
Hagerstown, Maryland 21740

1 FREDERICK, MARYLAND, MAY 11, 2004

2 1:00 P.M.

3 ARMED FORCES EPIDEMIOLOGICAL BOARD MEETING

4 MR. STEPHEN OSTROFF:

5 (PRESIDENT OF BOARD)

6 Let me welcome everyone and thank
7 you for a very interesting session this morning
8 for those who had attended. What I'd like to
9 try to do before we get started is since we're
10 now formally in session if we could possibly go
11 around the room and have folks introduce
12 themselves. And in particular there are some
13 new board members if they would just take a
14 minute or two to give us a little bit of their
15 background as we go around the table.

16 (BOARD MEMBERS INTRODUCED THEMSELVES)

17 PRESIDENT: Thanks very much.

18 Sorry to diverge a little bit from the schedule.

19 Before we go ahead and turn the
20 podium over to Colonel Henschel, what I'd like to
21 do is ask Colonel Gibson if he wants to make a

1 couple administrative remarks.

2 COLONEL GIBSON: (Making remarks
3 about dinner plans for members.)

4 CME Credits, we have CME credits
5 for this meeting. 10.25 credits for the whole
6 meeting. There are forms over here on the side
7 if you want to fill them out. We'll get them
8 taken care of.

9 PRESIDENT: Why don't we go ahead
10 and get started and let me introduce Colonel
11 Henschal to give us a brief on USAMRIID.

12 COLONEL HENCHAL: I want to
13 welcome you all. I'm Colonel Erik Henschal, the
14 commander of USAMRIID and welcome to the home of
15 medical biodefense and actually for about fifty-
16 eight years the AFEB has been dedicated to
17 preventive medicine and to sustain health of
18 service members worldwide.

19 For about thirty-five years
20 USAMARIID has been producing the research
21 province the Department of Defense needs for

1 protecting against not only biological warfare
2 threats, but also several very hazardous
3 infections diseases.

4 Here at USAMRIID we have all the
5 biocontaminants, we have the largest collection
6 of bio safety level for the large collection in
7 animals under containment in order to test and
8 evaluate medical products for biodefense.

9 In the future USAMRIID is going to
10 be working very closely with its inter agency
11 partners, many of which are in this room.

12 We all recognize that we have a
13 changed world. It's not about the traditional
14 threats. In the future we're going to be
15 getting many new agents and new infectious
16 diseases such as SARS, which is on our horizon;
17 medically engineered bioterrorism agents as
18 well.

19 In the past USAMRIID was dedicated
20 strictly to ten or twelve traditional biological
21 warfare agents. In the future we recognize

1 there may be as many as fifty different
2 biological threats that we may have to respond
3 to.

4 The job ahead for all of us is
5 much more than any single agency can handle.
6 The number of medical products of the future can
7 overwhelm any single agency. And, so it's
8 necessary that we work together in this new
9 inter agency community in order to produce some
10 medical products, not only academies, but also
11 the medical product to protect the nation.

12 We're already seeing the fruits of
13 their work. I can point to SARS as an example
14 for the inter agency community working with
15 industry partners in academia, produced in a
16 little less than eight months. The animal
17 models for SARS, the isolation of the virus, the
18 diagnostics. USAMRIID was involved by testing
19 over two hundred thousand compounds against the
20 virus identified forty leads and one of those
21 leads is already in clinical trials in Canada.

1 That's an example of the kind of
2 work that we can do as an inter agency
3 community.

4 I can also point to the
5 development of the Anthrax vaccine. Many of us
6 know that the current AVA vaccine is cumbersome
7 to administer; eighteen months, six shots. And,
8 the next generation of vaccine we hope is going
9 to be a safer product and one that can be
10 administered in as little as two doses.

11 At the same time we've been
12 working closely with our NAID partners at NIH to
13 develop the next generation ebola vaccine. So
14 it's going to be an exciting future for us all
15 as we continue to address the needs of the
16 country and develop these medical products.

17 So I welcome you to this meeting
18 today at USAMRIID which should be a very
19 productive meeting and vigorous discussion as we
20 continue to sustain the health of not only the
21 DOD, but also the nation as a whole. Thank you

1 very much.

2 (APPLAUSE)

3 PRESIDENT: We are going to come
4 up and present you a certificate as a way of our
5 thanks for hosting the meeting and while I'm
6 walking up I neglected to let Dr. Kilpatrick
7 make the comments that he's required to make as
8 the designated federal official to the meeting.

9 DR. KILPATRICK: As the designated
10 federal official for the Armed Forces
11 Epidemiological Board and Federal Advisory
12 Committee to the Secretary of Defense which
13 serves as a continuing scientific advisory body
14 to the Assistant Secretary of Defense for Health
15 Affairs and the Surgeons General of the Military
16 Department I hereby call this Spring 2004
17 meeting to order.

18 PRESIDENT: Thanks very much.
19 Here's a certificate of appreciation and an the
20 AFDD coin.

21 (APPLAUSE)

1 PRESIDENT: We actually have a
2 fairly busy afternoon, there were a number of
3 issues that were raised at our previous meeting,
4 particularly regarding the smallpox vaccination
5 activities and we had requested a number of
6 updates at this meeting, so I think that why
7 don't we just go ahead and get started. Our
8 first presentation is from Colonel Engler who's
9 going to update us on Anthrax/Smallpox Vaccine
10 Adverse Event Reporting.

11 COLONEL ENGLER: Actually I was
12 asked to update on the VHC, I would have done
13 that for you if that would have been clear but
14 we'll basically move forward.

15 PRESIDENT: You're correct. It's
16 the program that's incorrect.

17 COLONEL ENGLER: I can switch, but
18 certainly I just wanted to announce to the board
19 that we had the second official opening of a
20 regional vaccine health center network site at
21 Portsmouth on the 25th of April and the other

1 site's at Wilford Hall and Fort Bragg
2 operational that have to have their formal
3 opening ceremony.

4 The funding for these four
5 additional sites is adequate for this fiscal
6 year, but we are asked for a unfunded
7 requirement for FY05 with work completed to
8 submit this enterprise to the budget submission.

9 We've continued to be extremely
10 busy in terms of providing consultative support
11 in case management and the infrastructure to
12 support the work that you will have presented
13 this afternoon and the increasingly interesting
14 work surrounding myopericarditis for Smallpox
15 vaccination.

16 PRESIDENT: If I could just
17 interrupt one second and mention that your sites
18 are in Tab No. 5 in the book and I think they're
19 also back on the table.

20 COLONEL ENGLER: Yes, they are on
21 the table as well. Since the opening in 2001

1 indepth case reviews and consultations support
2 for medical exemptions has exceeded a thousand
3 cases and the emergent response in 2003 to
4 support indepth VAERS review and become the
5 formal registry entity for myopericarditis.
6 Since that time as of today we have 71 cases
7 that meet CDC/DoD case definitions. 6 are under
8 additional review. We have 23 additional cases
9 that for a variety of reasons don't meet the
10 case definitions. But are being followed for
11 outcomes and will be at a future date reviewed
12 as requested.

13 There were a radial questions that
14 raised at the beginning of the program and still
15 regarding oropharyngeal shedding of vaccinia
16 post immunizations and at the start of the
17 Smallpox program a protocol was established in
18 collaboration with USAMRIID.

19 In that protocol both cultures and
20 specific antigen by electrochemiluminescence and
21 specific DNA by PCR technology were applied to

1 forensial swab work, 144 subjects were studied
2 with 89 completing all post vaccination swabs at
3 the time frames listed on the slide.

4 A copy of power summary point of
5 this study is also available on the table and
6 there's not sufficient time to go through it,
7 but sufficeth to say that despite rumors and
8 anecdotes that we've heard regarding the
9 potential sharing, in this study we found
10 absolutely not one sample that had evidenced by
11 any of the three methods described either for
12 vaccinia. So these data support the ACIP
13 guidelines and have reassured those with
14 continued concern about respiratory
15 transmission.

16 We've also supported the work of
17 the vaccinia contact transmission investigation
18 with indepth VAERS report and actually this work
19 is being presented tomorrow or Thursday at the
20 National Immunization Conference on vaccinia
21 contract transfer, The US Military Smallpox

1 Vaccination Experience as shown.

2 The risk factors for contact
3 vaccinia in 29 cases that were reviewed in this
4 report are limited to intimate and/or close
5 personal skin-to-skin contacts, particularly
6 wrestling activities and sleeping in the same
7 bed. There were no unexplained transmission
8 events in contrast to the historical reports of
9 contacts of Smallpox.

10 Myopericarditis, the greater event
11 that we anticipated, but not to the degree that
12 we've seen it. Cases have continued to provide
13 some considerable challenges in terms of the
14 review process. I'm very proud of the fact
15 today that Colonel Atwood is here, Dr. Eckart to
16 present the indepth work from this review
17 process with the consultant cardiology groups
18 from the three services and the VAHC staff.

19 I also wanted to report that the
20 prospective myopericarditis protocol is now
21 fully approved at Walter Reed and at Brooke Army

1 Medical Center. And, will be starting in June
2 or July. That particular study, for those of
3 you who had not been at the last meeting it will
4 be six hundred vaccine recipients. Initially it
5 was going to be Smallpox only, but in view of
6 reports and discussions regarding the ACAMBIS
7 study and the fact that many service members in
8 our system receive not Smallpox alone but with
9 other multiple vaccines we are just now
10 submitting a slight modification so that we'll
11 be enrolling primary vaccinees but not excluding
12 other vaccinations, since we are told that
13 within the next six or twelve months the ACAMBIS
14 study will actually give the prospective data by
15 a large co-court of not only vaccinees but
16 Smallpox vaccine alone and no others.

17 We also were asked under the CDC
18 contract to include 200 influenza vaccinations
19 and the hypothesis here being historically
20 there's a 2 to 3 incidence of subclinical
21 myopericarditis. I was asked to kind of rush

1 through because of the time constraints. The
2 factors, there will be addressed and again this
3 is a collaboration with the CISA group and the
4 University of Washington Molecular Immunology
5 Department.

6 A companion protocol developed by
7 our cardiology colleagues to study — to address
8 standardization specific cardiac studies for
9 detecting low level inflammation for better
10 appreciation of outcomes in regards to
11 myopericardia function now is currently
12 underway.

13 I did want to share with you the
14 presentation for the National Immunization
15 Conference tomorrow is available for you. The
16 result of our four and a half year work to
17 establish a web-based interactive learning
18 management system for immunizations designed by
19 medical technicians, nurses and clinical
20 providers, their 21 modules that are available.
21 All of these were developed in a curriculum

1 consensus committee involving all of the five
2 services. It's a web-based education
3 development company that has a lot of experience
4 doing this at NIH that has partnered with us.
5 Each of the module story boards are peer-
6 reviewed and coordinated with the help of
7 Colonial John Ravenstein with a large population
8 of stakeholders. These are self-paced objective
9 testing education modules available on the VHC
10 web-site with the pre-test, post-test
11 interactive process and we have as part of the
12 quality evaluation of this program built-in the
13 ability to assess or engage the users, and not
14 to belabor it, but a variety of personnel who
15 have utilized this research demonstrate
16 including folks who's been through the DoD
17 training and CBC training for Smallpox
18 demonstrated significant learning gauge by going
19 through such a module.

20 The other thing that we're proud
21 of with regard to the VHC work and its focus on

1 rare adverse events is that the blistering skin
2 rash or oral ulcers post Anthrax vaccine in
3 question has been evident through a number of
4 venues. The last time I told you we had three
5 cases identified with history of new onset
6 pemphigus vulgaris where no autoantibodies were
7 skin specific, desmoglein skin antigen presence
8 prior to the Anthrax vaccine using the DoD serum
9 repository in partnership with Dr. Stanley at
10 the University of Pennsylvania who performed the
11 autoantibodies studies. There was a question
12 raised of molecular mimicry in relation to this
13 very rare event. We reviewed the various
14 reports. We'll have those in the next slide.
15 There's a total of 34 blistering skin rashes
16 with Anthrax in one of more vaccines exposures.

17 The protocol has been approved
18 that will screen for the presence of
19 autoantibodies in a population of Anthrax
20 vaccinees versus non-recipients to determine
21 whether the subclinical reduction of

1 autoantibodies occurs. As the next step in the
2 context of the VAERS update we have held over
3 1.1 million Anthrax vaccine recipients with four
4 point two million doses. There are 34 VAERS
5 with Anthrax vaccine and the terms, the rash for
6 pemphigus vulgaris, 19 were Anthrax alone, 4
7 were hospitalized. A lot of these cases have
8 not been entered into the registry of the VHC,
9 so we have not had an indepth case review or
10 investigation. 29 of the 34 occurred within the
11 first 30 days and there are four — there were
12 additional oral ulcer reports four of those with
13 prolonged symptoms presumably not recovered.

14 So the hypothesis that pemphigus
15 vulgaris specific antibodies against skin
16 antigens may develop following immunization with
17 the anthrax vaccine in a subpopulation of the
18 vaccinated individuals is being pursued in the
19 context of its protocol. Persons who have
20 received both smallpox and anthrax together may
21 through the TH1 immune activating properties of

1 smallpox vaccine perhaps have a higher rate of
2 these autoantibodies is another hypothesis and
3 then within the existing serum repository and
4 database there are about 41 cases of Pemphigus
5 vulgaris, some of which have received the
6 anthrax doses and sera are potentially available
7 for study.

8 The prevalence will be measured at
9 baseline, pre anthrax versus post anthrax and
10 populations about 300 para samples will be
11 pulled from these existing databases and of the
12 ones who have Pemphigus 11 of the 42 received
13 anthrax vaccine based on the existing records.
14 I think in this kind of work addressing — have
15 implications for clinical guidelines that will
16 make certainly Pemphigus and blistering and oral
17 ulcers and/or blistering skin rashes are a
18 relative contraindication to the currently
19 utilized anthrax vaccine. Certainly further
20 studies with regard to the epidemiology of this
21 adverse event are needed and needless to say it

1 is unlikely that patients who present with these
2 problems may have a VAERS completed. In talking
3 to the oral surgeons and dentists they certainly
4 don't take immunization history when they see
5 these lesions.

6 When using the serum repository,
7 immunization registry and defense medical
8 surveillance system and in the interest of time
9 since you have this I'll just run through it and
10 go on.

11 We would ask for the board to
12 consider, it's not a formal question, but we
13 felt in a clinical perspective that we've
14 experienced considerable challenges in terms of
15 trying to do a good job with the myopericarditis
16 case management and surveillance and tracking
17 trying to work through civilian and smaller
18 facilities and have worked despite many, many
19 hours of intense labor on the part of the VHC
20 network pieceworkers, continues to be challenged
21 and it's the consensus opinion of the

1 cardiologists involved in this as well as the
2 VHC staff that these patients should be referred
3 to either Brooke Army Medical Center or Walter
4 Reed for standardized evaluation and follow-up
5 processes and for certain scans that have been
6 considered to be useful potentially for the long
7 term assessment of any injury to the myocardia
8 that may have long term sequela and certainly
9 that would be addressed in Dr. Atwood's and
10 Dr. Eckart's talks.

11 The myocarditis registry as it was
12 initially tasked with a one year follow-up. But
13 due to subjective symptom persistent that will
14 be discussed we recommend that that follow-up in
15 terms of outcomes of the quality of life impact
16 be continued for at least two years and beyond
17 that should symptoms persist. And, then
18 consideration as a start of this work that
19 blistering skin disease and/or ulcers following
20 vaccination with the sera repository be coupled
21 with a formal guideline to establish a registry

1 on these types of VAERS cases for indepth case
2 follow-up that may be needed so that we may
3 understand this rare event.

4 I thank you all for your time. I
5 didn't bring tool kits this time since I thought
6 you all got last time but please I'd be happy to
7 make those available to the board or anyone here
8 that may not have gotten one. And, we thank you
9 for your time this morning.

10 PRESIDENT: Thanks very much. The
11 board continues to be extremely supportive of
12 the work going on at the Vaccine Health Center.
13 You know, I think collective estimations it has
14 been a success story and one that we would like
15 to certainly see the work continue.

16 Let me open it up to any questions
17 or comments. If I could just ask one, do you
18 know, or has anyone gone back to look at the
19 prior experience related to anthrax vaccines and
20 history skin disease?

21 COLONEL ENGLER: You mean beyond

1 the VAERS creed?

2 PRESIDENT: That or the large
3 program that was done in the mid 1990s?

4 COLONEL ENGLER: You know, I just
5 didn't know, if someone points us in the right
6 direction I didn't have any access or awareness
7 that there was data available beyond what exists
8 in the repository and unfortunately in regards
9 to the DMSS in searching for oral ulcers the
10 coding is a problem and it's not necessarily
11 visible.

12 So, you know, other than
13 potentially doing a protocol or a registry
14 process where we advertise for people who may
15 have these lesions so we can do a more indepth
16 case review and get their serum, the nice thing
17 about this entity is that there is a pathogenic
18 sera marker and that is the antidose on bleeding
19 antibodies and it's Dr. Stanley's opinion with
20 us based on what we know with the
21 immunologically that we would expect there to be

1 a variety of people who might have the antibody,
2 but not go on to Pemphigus vulgaris and who
3 might just have transient lesions and sort of a
4 form of crust or subclinical. But I don't know
5 what other places. I'm very open to direction
6 or guidance from the board.

7 We thought we had exhausted all
8 the existing resources that are available to us.

9 DR. KILPATRICK: It's an
10 incredible resource and a very valuable resource
11 that I don't know how it could be duplicated
12 anywhere else. It's wonderful to have.

13 BOARD MEMBER: I have one question
14 on the slide where you asked the AFEB support
15 requested. It's the second bullet about
16 following the extended for 2 years. Can you
17 clarify, do you mean within the military system
18 or...

19 COLONEL ENGLER: Well, when the
20 myocarditis cases started to accumulate and we
21 are a real time operationally responsive

1 enterprises, okay, you guys with the registry
2 because you've got the, sort of the structure to
3 do it and the initial direction, you know, there
4 was nothing in writing, but certainly from the
5 consensus was that we would try to do a one year
6 follow-up.

7 I speak for Colonel Ravenstein as
8 well and I think all the cardiologists that we
9 feel very strongly that given the continued
10 questions that will surround cardiac issues in
11 smallpox vaccine, that it is prudent not only
12 for the purpose of knowledge for the future if
13 there needs to be a mass immunization, but also
14 for the Department of Defense to understand, you
15 know, if we can tell people we've got better and
16 two years later you really were great and we
17 worked through some of the vagaries that still
18 exist in the context of our trying to understand
19 these cases there's a lot of complexity in our
20 weekly case conferences with the cardiologists
21 involved. We all agree that having at least two

1 years of follow-up is our directive, if you
2 will, would make sense.

3 It's just like following ones that
4 didn't fit the case definition for a variety of
5 reasons, we felt it was the right thing to do
6 because there are some issues there that I think
7 may become, questions that need to be pursued.
8 And, we really have never been defined in terms
9 of this kind of case management registry
10 function. Frankly, my struggles with the
11 business cases and trying to justify and explain
12 how much work goes into what was presented to
13 you all and funding support for this effort.

14 DR. KILPATRICK: Just a reminder,
15 this meeting is being transcribed, so state your
16 name when you ask a question and speak into the
17 microphone. Thank you. Sorry, Dr.
18 Philen and Dr. Haywood.

19 DR. PHILEN: The web data learning
20 management system that you described here what
21 you've been treating is very, very valuable to

1 — is that universally?

2 COLONEL ENGLER: Extremely
3 valuable.

4 DR. PHILEN: Is that universally
5 accessible?

6 COLONEL ENGLER: Right now what
7 we've been doing is if you write in from a
8 government e-mail then you get a password
9 automatically. Public Health and other entities
10 we've given passwords to and right now working
11 with our JAG to have permission and it looks
12 good so far to allow the Health Soft that's done
13 a lot for the American teachers preventative
14 medicine to take our work and also host it for a
15 potentially civilian. Nursing schools have
16 approached us and said this is wonderful. We
17 have tried to incorporate the current state of
18 the art. The question about how do you show
19 that something's real worth it, that the people
20 want to get up and seek and take some competency
21 knowledge with them. And, we've have the

1 training center at Walter Reed has great
2 interest in this and again we think it's a
3 wonderful thing that's been done. We haven't
4 been funded to support the world. We welcome
5 any ability to partner, because it is my firm
6 belief that immunization helps our education is
7 in need of improvement across-the-board in and
8 out of DoD and it will make our credibility and
9 our vaccination programs better.

10 MEMBER: I found that that
11 recommendation has been inclined to extend the
12 authority to do this. (inaudible)

13 COLONEL ENGLER: Thank you.

14 PRESIDENT: Thanks very much. Why
15 don't we move on to our next presentation so
16 that we try to stick with the schedule and the
17 next speaker is Major Robert Eckart. He's from
18 the DoD smallpox vaccination critical evaluation
19 team at Walter Reed and he's going to brief us
20 on the follow-up of the myocarditis cases in DoD
21 and his slides are under Tab No. 6.

1 MAJOR ECKART: Actually I
2 apologize for the change in the rank, actually
3 my date of promotion isn't until Monday. So
4 when I thought the meeting was next week
5 officially I would have been a major but —
6 clearly this work could not have been done
7 without the cooperation of the entire department
8 smallpox vaccination to include (inaudible).
9 This article, the final copy was accepted for
10 publication on Friday. It's a publication in
11 the Journal of American College of Cardiology.

12 So if you talk about the incidence
13 and follow-up of these patients and you may or
14 may not be aware these cases were identified
15 through both monitoring passive surveillance
16 through DMSS as well as accurate solicitation
17 as well as publications which now I've been in
18 MMWR and JAMA, there's a pending publication to
19 the American Journal of Epidemiology.
20 (inaudible) and others highlighting positions to
21 raise the awareness of (inaudible) myocarditis.

1 To date there have been approximately seventy-
2 six cases identified, those numbers vary
3 depending on — you've already mentioned 71
4 cases and then 6 pending review, so these
5 numbers start to fluctuate, it is a dynamic
6 process. What I'm going to present basically is
7 67 cases of data available to review greater
8 than 60 days since diagnosis, since diagnosis as
9 this topic is about prodromal by follow-up.

10 As I alluded to you earlier the
11 data was collated and centralized by the vaccine
12 health care center in Washington, D.C., as well
13 as regional sites in Portsmouth, Fort Bragg, and
14 San Antonio.

15 Back in June the guidelines for
16 follow-up were developed through the VAC, the
17 military vaccine agency in collaboration with
18 clinical cardiology and college and civilian
19 facilities that called for a clinical evaluation
20 and certain studies, electrocardiology,
21 echocardiology and treadmill testing at 6 to 12

1 weeks and patients with persistent symptoms is
2 encouraged that they stay their transfer at the
3 regional military treatment facilities for
4 further evaluation.

5 The guidelines for this can be
6 found on at sites listed on the bottom of your
7 handout.

8 What we're representing at this
9 time and some of you may or may not be familiar
10 with, but again these are commonly younger
11 individuals around 27 years old (inaudible.)
12 It's statistically seems a predilection for
13 Caucasian males. The means time for vaccination
14 to evaluation was approximately ten days. This
15 is very consistent of means 10 days to 25 days.
16 But again that was the time to evaluation not
17 necessarily a time of symptoms.

18 Other times that follow up on the
19 data that I present data on today the means was
20 approximately 31 weeks median 33 weeks.

21 These cases all presented with

1 chest pain. The documentation of cardiol
2 symptoms was 91.1% with a relatively good
3 reporting through (inaudible) as well as
4 solicitation. General symptoms were fever,
5 chills, myalgias, arthralgias, viral syndromes,
6 were relatively consistently reported.
7 Approximately 15% of patients had documentation
8 of absolutely no prodromal system but they
9 started they got the chest pain syndrome.

10 Data was available on 64 patients
11 to 67 patient, 96%. Two patients were self-
12 reported as healthy, and basically declined
13 further follow-up, although all contact with
14 them has been — but they are self reported as
15 healthy.

16 As you're aware, one patient died
17 during hospitalization. Her case was very
18 atypical of this case definition of having
19 cardiac enzymes in a chest pain syndrome within
20 thirty days of a smallpox vaccination although
21 two independent groups have basically decided

1 that her case was uncharacteristic of the
2 smallpox vaccination experience.

3 In the meantime the follow-up was
4 32 weeks. A couple things I would look at. I'm
5 a clinical cardiologist and so we're the ones
6 that's getting called first of these patients.
7 It's a little bit different for the group, but
8 this is going to be more clinical. Original
9 tracings were available for review and very high
10 percentage basis, recognizing that this is a
11 multi-centered collection of things in the VHC.

12 We had identifiable abnormality in
13 75% of the patients most predominately a
14 isolated ST7 abnormality and you round up 9%
15 basically you had to what I called earlier,
16 (inaudible) or a normal finding for agents in
17 individuals and isolated a T wave abnormality in
18 approximately 20%.

19 72% of the patients had follow-up
20 ECG that was sent to us specifically for review,
21 the median time that this ECG was obtained was

1 approximately three months and there was in 100%
2 of those tracings reviewed and 100% of those
3 tracings that were reported to have been done
4 there was clear normalization of pathologic ST
5 segment elevation and T-wave inversions in all
6 patients. There was complete normalization on
7 all EKG's and CG's that was for review in those
8 patients.

9 One of the problems initially in
10 some of our report in JAMA, was concern about
11 one patient having persistence changes of their
12 electrocardiogram and this was relatively
13 fortuitous in this particular case although
14 these are digitalizations of these tracings
15 this one provider in Germany wasn't sure what to
16 do with this particular patient. So he just
17 brought him back for an EKG and he just kept
18 getting them. And basically — which was great
19 for us, because basically what we saw was a
20 serial documentation of repolarization
21 abnormalities in this patient. So much not

1 unlike acute myocardial infarction, although the
2 pathogenesis was different that it can't —
3 normalization of those changes and this patient
4 was subsequently seen without normalization.
5 When I saw him it was 54 weeks.

6 This is important because when we
7 look at the electrocardiograms because there is
8 some concern that with their serial changes that
9 these patients have that the period of
10 repolarization or when the electrical activity
11 within the heart allows it for relaxation that
12 if there's an abnormality in this space the
13 patients can have sudden cardiac death. And we
14 saw this repolarization, this repolarization in
15 the '80's, within these ECG's that we saw in
16 these patients.

17 One of the things we looked at was
18 something called the QT interval dispersion and
19 the QT interval is, here's the beginning of a Q
20 wave and it goes out to the end of the T wave.
21 And if you look at several portions of any one's

1 patient's ECG at any one time if they have a
2 variancy within 150 of tracings then they still
3 call that the measurement of dispersion and
4 basically we found that there was elevated QT
5 dispersion at baseline and basically what we
6 call complete normalization anything less than
7 40 is considered completely normal. But clearly
8 normalization at follow-ups.

9 We looked —unfortunately for
10 cardiology when a patient comes in with a heart
11 attack we know that because we base it on 5000
12 patients. When a patient presents with a
13 smallpox vaccine associated myocarditis we don't
14 know what this means. So we make a lot of leaps
15 of faith. But when you do extrapolate this data
16 notifications of — sudden cardiac death, this
17 normalization of QT interval dispersion is
18 thought to be associated with lower risk of
19 sudden cardiac death. And we've proved that
20 basically all patients that had the follow-up
21 ECG's all had normal parameters for measure of

1 unpolarization and therefore we suspect it
2 reduced in a sense or reduced risk of sudden
3 cardiac arrest, but again recognizing the
4 rotations that I've described.

5 Furthermore, there are concerns
6 about arrhythmias in this patient population.
7 All patients basically were both in sinus rhythm
8 at presentation as well as follow-up and there's
9 no statistically significant differences in any
10 of the intervals that we measure on routine
11 electrocardiography except for complete
12 normalization of pathologic (inaudible)
13 elevation similarly there were some concerns
14 raised about hypertensive response in these
15 patients and basically that was not seen in any
16 patients either with a normal systolic and
17 diastolic blood pressure on follow-up.

18 One of our problems, as Dr. Engler
19 alluded to, is that concern that we had as
20 clinical cardiologists about the variable workup
21 to date. There is laboratory variability in

1 things of for example of Component I, BNP which
2 is the marker of stress within the heart.
3 C-reactive protein, which is a mark for
4 inflammation. Using each flat as its own
5 comparison or its own control basically there's
6 been no abnormalities in any of these markers on
7 followup examination indicating basically that's
8 there no ongoing mycardionecrosis or ongoing
9 cell death to heart. At the time of followup
10 using BNP as a circuit marker for heart failure
11 there's no ongoing volume or pressure overload
12 within the heart on followup and using BNP as a
13 circuit marker for just generalized information,
14 appears on followup as relatively routine work.

15 Dr. Atwood will talk in just a
16 moment about dilated cardiomyopathy and the
17 concerns that — looking at our index cases,
18 around 85% of these patients had
19 echocardiography during their acute illness. We
20 had followup in 40 of these patients in median
21 approximately three months after the diagnosis.

1 The mean, that follow up was 60%, but the range,
2 the lowest reported was 64%. There was no
3 evidence of ventricular dilatation, diastolic
4 dysfunction or relaxation abnormalities,
5 regional wall motion abnormality, or pericardial
6 effusion.

7 It took a long time for clinical
8 cardiologists to convince the non cardiologists
9 and the ejection fraction of 60% and 55% of
10 cases is normal. That's a normal number — 100%
11 is distinctly abnormal. So in normal reference
12 value there will basically be anything from 50
13 to 55% to be considered normalization. Basically
14 you'll see that 100% of patients had
15 normalization. There was one patient that the
16 ejection fraction was 54% when two weeks earlier
17 his ejection fraction of 62%. Well, we took the
18 worse case scenario on him which was, out
19 thinking at the time we did it 62% he had that
20 documented and he had full recovery and from a
21 clinical cardiology perspective we would look at

1 that is there's no difference in those two
2 parameters.

3 The point is that 100% of these
4 patients had complete normalization of all
5 parameters on echocardiography within a median
6 of 8.6 weeks and that's important.

7 Again looking at the time and
8 looking at these surrogates looking this is
9 their initial cardiographic ejection fraction
10 and this is a time relative to the diagnosis.
11 The graft basically again is times 0 is our
12 baseline echocardiography on 67 patients and the
13 followup studies on the 55, 55 studies on 40
14 patients and again it puts us in some
15 perspective a normal (inaudible) ejection
16 fraction basically considered.

17 Some people say 50%, some people
18 say a low number of 40% they would consider a
19 normal ejection fraction you look at it as an
20 outcome marker of risk. We thought we were very
21 conservative and basically chose 55%, again,

1 clear normalization of all patients early in the
2 process.

3 And, again when you look at those
4 patients at a mean of 14 weeks after diagnosis
5 again the mean ejection fraction of 55 to 61%.
6 When you look at functional assessment in these
7 patients we've been able to clearly objectively
8 find that their heart muscle recovery returns to
9 normal. That their electrical characteristics
10 of their heart return to normal. The question
11 is basically how well can they perform. 36
12 patients went on treadmill testing at a median
13 of 75 days. Exercise duration was 12 plus or
14 minus minutes on the treadmill. Maximum heart
15 rate was basically what we would consider to be
16 indicative of adequate testing and again rate
17 pressure product was 31,000, 25,000 is a
18 surrogate marker for is this considered an
19 adequate stress test and so these patients met
20 those objectives. In no case were Electro
21 cardiographic abnormalities or cardiac symptoms

1 provided in these patients undergoing maximal
2 stress testing.

3 So again in clinical cardiology we
4 can work this time to what's called a metabolic
5 unit and this is the results of our patients and
6 again to put this in some degree of perspective
7 you can see that these are patients that had a
8 median of 75 days after being on some sort of
9 profile, that don't do anything but relax, we're
10 able to go through a median of 75 days of
11 deconditioning and yet still had performance
12 levels that basically were approaching endurance
13 athletes in many of these patients. So these
14 guys basically as far as clinical cardiologists
15 are concerned had full recovery of functional
16 status in all cases.

17 They perform well, their heart
18 muscle works well, their electrical risk is
19 thought to be reduced. There's no evidence of
20 myocardial necrosis. There's no evidence of
21 inflammation, but how do they feel? Well, we

1 have the red line here as any reported symptoms
2 in these patients and the green line is near as
3 that for those symptoms that were felt to be
4 referable to cardiac disease or basically just a
5 non-descript chest discomfort. You see that not
6 all patients recovered completely the patients
7 continued to report symptoms,

8 Ending followup of 32 weeks of
9 these patients, in 64 patients 88% that's been
10 recorded for complete resolution of any symptoms
11 even remoting referable to cardiac disease. No
12 chest pain of any sorts.

13 Characteristically, chest pain was
14 atypical non-descript and dissimilar to that
15 when they originally presented. I just saw a
16 guy recently and the graph needs to change,
17 because I just saw him on Friday. I gave him
18 his antacid and he said he feels great, he feels
19 great. But we couldn't discern that at the
20 time. But that's sort of what we're fighting
21 right now.

1 Three patients basically report
2 continued fatigue, two patients report continued
3 headaches and one patient reported shortness of
4 breath with the extremes of exertion.

5 When you compare those
6 persistently symptomatic patients to those that
7 report full recovery there was no statistically
8 significant or unstatistically significant in
9 terms of their age, their time for vaccinations
10 to evaluation, the mean time of followup. There
11 was a clinically, but not statistical
12 significant in the number of those that had
13 continued symptoms with abnormality on initial
14 echocardiography. (inaudible) had a significant
15 abnormality on initial echocardiography compared
16 to one-third of that sub report to recovery. So
17 it was a statistically significant decrease in
18 their baseline ejection fraction for those that
19 (inaudible) when you compare those when you
20 compare those that reported full recovery.

21 There is no clinically or

1 statistically significant difference. In our
2 followup ejection fraction there are — or
3 subsequent treadmill — there is no significant
4 differences or insignificant differences in
5 clinical differences in those two groups.

6 So again looking at the same graph
7 where the question is when do these patients
8 recover their ejection fraction. Are these the
9 cases down here? Now, the solid dots basically
10 are those that reported persistent symptoms.
11 You can see clearly these cases all have clear
12 early normalization of ejection fraction. You
13 know, the worldwidens here, although completely
14 normal are completely asymptomatic as well, so
15 in case there's any concern in that regard.

16 Similarly things can be said for
17 treadmill testing. Those with the solid dots
18 are basically those that had persistent
19 symptoms, and you can see basically they're
20 packed in the middle. Those are not necessarily
21 the low liars of what we're considering normal

1 testing. These guys were right in the middle.
2 When you looked at all symptoms in
3 these patients, such as headaches, dyspnea,
4 fatigue as alluded to statistically significant
5 difference in those that had the initial
6 depression ejection fraction, and so then the
7 concern was were these patients more sick or a
8 more dramatic illness at baseline. Overall when
9 you looked at those symptoms — when you gratify
10 these patient for those symptoms that were
11 referable to (audience noise) disease there
12 really was no significant statistical
13 significance and you can see a much closer
14 proximation of the lines. So these patients
15 that had initially depressive ejection fractions
16 when you looked at them by symptoms referable to
17 cardiac disease there is no statistical
18 difference and as alluded to before there was no
19 objective differences in functional cardiography
20 laboratory testing or echocardiography.
21 When you look specifically at

1 those patients that had initially depressive
2 ejection fractions these 18 patients their
3 initial ejection fractions by design was
4 statistically significantly lower. There was no
5 statistically difference in the amount of
6 cardiac isoenzymes which we sometimes used as a
7 surrogate marker for the amount of myocardia
8 that was damaged. There's no statistical
9 difference in that as measured by the component
10 creatine kinase. As I mentioned before there's
11 no statistical difference in great excess
12 testing on metabolic units.

13 So, as I said, there's no change
14 in the follow-up exercise, they were more
15 symptomatic on followup, but they didn't
16 necessarily have symptoms of irreparable cardiac
17 disease. The question was what about
18 normalization of the ejection fractions in these
19 patients.

20 So, those that had initially
21 (inaudible)ejection fraction continued to have a

1 completely normal ejection fraction. Those that
2 had reduced ejection fraction had a less than
3 55% of baseline. Again there's clear
4 normalization of their ejection fraction as
5 well. (inaudible)

6 So again looking at
7 electrocardiography clear normalization in 100%
8 percent of patients. You look at ejection
9 fractions times normalization complete
10 normalization.

11 There is this concern about
12 ongoing chest discomfort and resolution of
13 symptoms.

14 So, in conclusion, and as
15 Dr. (inaudible) article recently presented to
16 cardiologists, plus the fact that
17 myopericarditis should be considered in those
18 patients with chest pain, we know that objective
19 testing are normal. When we looked at the time
20 that we had recommended for follow-up all
21 patients that were basically tested within that

1 interval all had normalization in that period of
2 follow-up.

3 Around 22% of the patients
4 continued to have persistence subjective
5 complaints, 40% of those are not referable to
6 cardiac disease. As I alluded to, the data
7 presented the worst case scenario, not
8 necessarily when the patient said that they
9 recovered, but when we got around to asking them
10 if they had recovered they said they felt fine.
11 We asked them various other questions, but we
12 couldn't say "when did you start to feel fine?"
13 So again this is the worst case scenario in that
14 regard.

15 A concern that we have is that he
16 continues the presence of symptoms. And they
17 get better they get deployed is a double-edge
18 sword. We've had, some people do acknowledge
19 that once they get better they're off. At the
20 same time, even more concerning, was when we had
21 a patient that reported to us that he reported

1 to his commander that his cardiologist said he
2 shouldn't go and the commander said, "The
3 cardiologist doesn't want you to get on the war
4 fighter," you know, get on a plane and you'll be
5 fine. And somewhere between Iraq, Turkey,
6 Germany, and Brooke Army Medical Center he's
7 routed back home with this persistent chest
8 discomfort I imagine somebody thought that was
9 probably a bad idea to put him on a plane when
10 he had those symptoms before he even got on the
11 plane.

12 Some of the cases, as I alluded
13 to, we've included as a case definition, but as
14 a clinician I don't think some of these patients
15 should be included. We mentioned that in the
16 case of reflux in a 25 year old male. Now, he
17 clearly had symptoms at presentation, you know,
18 he had abnormalities in his EKG, the case
19 definition. But when we saw him, it's very hard
20 to differentiate over the telephone and when
21 this young man says he has chest pain what

1 exactly is without referring for further care —
2 similarly one of our patients had a preexisting
3 migraine disorder. And he continues to have
4 headaches and we can't pick it out, and
5 unfortunately he just ends up a case definitions
6 in that fashion. And, then unquantified
7 symptoms like fatigue. It's very hard to sit
8 there and tell a 22 year old that you can't feel
9 fatigue, because you just ran 15 minutes on my
10 treadmill, so you must feel fine, I mean he
11 feels fatigue and we have no test for that.

12 There's a clear need for objective
13 data. I absolutely concur with Colonel Engler
14 that patients with postvaccine cardiac disease
15 need to be referred to comparable to Walter Reed
16 Army Medical Center. We have the most
17 experienced with it and the concern that has
18 been raised by others is that how come we don't
19 have followup echos on 67 patients; how come we
20 don't have followup treadmill on 67 patients.
21 These patients got better in two weeks. Their

1 clinicians out in the field say, "do you feel
2 fine?" And, they say, "Yeah, I feel fine."
3 Then they go off on their way, they never did
4 any followup testing.

5 Then we called them a year later
6 and they're still doing fine, so we got lucky
7 and we did okay with that, but there's too much
8 about the disease process that we don't
9 understand to allow it to undergo that sort of
10 risk.

11 Dr. Love, who was the Portsmouth
12 VHC has worked with Dr. Atwood and Dr. Engler
13 with a very structured questionnaire followup
14 trying to justify things like fatigue and
15 shortness of breath to know exactly what those
16 things mean.

17 And, again perhaps it's out of
18 ignorance about the disease process, but unless
19 we are on the field doing follow-up with these
20 patients for two to five years and whether I can
21 get — these patients should undergo repeats

1 testing of these objective parameters. For the
2 following years they should undergo a screening
3 questionnaire.

4 These patients have recovered.
5 These patients have done fine. And, we've been
6 fortuitous in that regard and they've been
7 fortuitous in that regard. But I don't think as
8 I alluded to before with coronary artery
9 disease, when I look at a coronary disease
10 patient when I see him in the emergency
11 department I'm basing my treating on him on 5000
12 patients, 10,000 patients on a study that just
13 came out last week, not to mention the hundreds
14 of thousands that came out in studies before
15 that. When we're looking at 76 cases of this I
16 don't think we know enough to say that in two
17 weeks if the soldier feels fine, we can pat him
18 on the back and put him on an airplane and call
19 him a war fighter. So far we've been lucky.

20 One of the concerns was for the
21 ones that had clinical followup compared to

1 objective followup was there any difference and
2 looking at the two groups there was no
3 statistical significant difference and either of
4 the patients left at the time of vaccination,
5 their initial depressed ejection fraction,
6 followup was slightly shorter because they only
7 had clinical followup, time resolution symptom
8 was no difference, persistence symptom was no
9 different, so we take out those patients that
10 would represent the type of cardiography
11 treadmill testing electro cardiography are
12 representative of the patients as a whole. But
13 it would be nice to say that without the
14 caveats.

15 Are there any questions on this
16 subject?

17 PRESIDENT: Thanks very much for a
18 very comprehensive presentation. I'm sure that
19 represents a phenomenal amount of effort in
20 working. We appreciate the care with which
21 you've taken to be able to follow these patients

1 and document all of this. I can't imagine what
2 you do in your spare time. Let me open it up to
3 the board if there are questions.

4 MR. HERBOLD: John Herbold. Are
5 these patients profiled at all or put on any
6 type of (audience noise)

7 MAJOR ECKART: We found out that
8 each service has different regulations in that
9 regard. However, the DoD guideline basically
10 recommend either a like DD profile or an
11 elective profile to meet every services but for
12 a minimum of six weeks or until clearance by a
13 cardiologist prior to resumption of full
14 activity.

15 The concern was in the initial
16 period when we didn't know enough and we
17 actually see one of the cases at our center, he
18 had been out of the hospital three days from a
19 center in Alabama and we said, "Well, go be a
20 war fighter" and he did, he came back from
21 Afghanistan a year later, felt great, followed

1 up with us and we got lucky. We didn't know any
2 better at the time.

3 But as you start to look at the
4 risk of some cardiac death is in animal models,
5 there's no risk showing in animal models, it is
6 felt to be associated with exertion during the
7 time of active myocarditis.

8 We have other data that we've not
9 done at this time, but, you know, we've shown
10 that the active myocarditis is a broad
11 definition, depending on which test you look at
12 and one of the advantages to sending these
13 patients at either Walter Reed or Brooke Army
14 Medical Center is their expertise in echo
15 imaging an MRI where we can set there and show
16 with a high degree of sensitivity resolution of
17 these changes of active myocarditis, so when we
18 look at normal components two weeks later and a
19 normal EKG and a normal Echo I don't know if
20 that means the soldier or marine or sailor is
21 safe to go at that time, but within a relatively

1 conservative practice to place all of these
2 patients on light duty profile for six weeks.

3 MEMBER: I want to ask you, what
4 are alternate etiology with this syndrome? Are
5 there viral associations that are — I can't
6 recall, it seems to me there are...

7 MAJOR ECKART: For myocarditis?

8 MEMBER: Yes.

9 MAJOR ECKART: And, you're right,
10 absolutely, the list is voluminous. The concern
11 is that these patient's were evaluated at I'm
12 going to say forty-six different facilities
13 initially. One of the reviewers from one of our
14 articles said, "why did all these patients come
15 in for a heart catheterization? Only emergency
16 medicine physician is seeing a patient. An
17 independent agent comes in a cardiac elevated
18 enzymes, has C segment elevation on their EKG
19 and chest pain that's obstructing coronary
20 disease and the only thing that says that these
21 cases were myocarditis was in four other cases

1 was biopsied but in 56% of them was a normal
2 coronary angiogram. And, so certainly echo
3 viruses can cause myocarditis.

4 The number of bacterial ideologies
5 that — the list is voluminous.

6 MEMBER: My followup question
7 would be was there any effort to look at those
8 potential agents and another issue would be if
9 you would be doing long term followup how would
10 you rule out during the (inaudible) period of
11 exposure of infection and other known causes?

12 MAJOR ECKART: Sure. That's one
13 of the limitations of having these individuals
14 going to 46 centers. They follow-up with either
15 myself or Dr. (inaudible) or Dr. Atwood for
16 persistent chest pain and they said, "well, I
17 was told I had myocarditis, I don't have an EKG,
18 I don't have any of my blood work, I don't have
19 — we'll throw up our hands and say let's start
20 from scratch. At the Water Reed Medical Center,
21 the Brooke Army Medical Center and to as many

1 people as we talk to there is a variable degree
2 of evaluation viral illness – but unfortunately
3 not much is known as to how to interpret that
4 data basically there is no baseline data. And,
5 I don't — again this is the worst case
6 scenario, that's what we've been saying. There
7 may be some cases that's not anti-viral
8 myopericarditis. And that's okay, we'll treat
9 it the same way, but we don't know that
10 question.

11 In those cases that we have done
12 biopsies on and even on florescent staining and
13 cultures we have not been able to isolate
14 smallpox or any other applicant in these cases
15 and the results of the biopsies have been very
16 limited in and of themselves. Again they're
17 calling for a need for more standardization of
18 that testing, the facilities. But unfortunately
19 we can't tell the community hospital, "we want
20 you to do a cardiac aline nuclear study, et
21 cetera, et cetera, et cetera. We would bankrupt

1 tri-care for certain with some of these tests
2 and the degree of interpretation required which
3 means more complex tests. I think is beyond the
4 scope of many community hospitals, as it should
5 be. They don't need to necessarily have that
6 experience. That's what referral centers are
7 for and I think we need a little more of it.

8 PRESIDENT: Let me just ask one
9 more question before we take a break. Do you
10 have any recommendations at this point, you
11 didn't say really anything about treatment.
12 What are the current recommendations about how
13 to handle these individuals?

14 MAJOR ECKART: Because this was a
15 brand new experience for us there is no standard
16 of care. At Brooke Army Medical Center we took
17 the approach of following the natural history of
18 the disease and not treat them. And so we
19 didn't. And, these patients basically did not
20 get normal treatment of what we'd consider heart
21 failure or things of that nature. And, so we

1 were allowed to watch them and saw complete
2 normalization of objective parameters.

3 For those patients that have
4 persistent symptoms, and again I refer to the
5 article by (inaudible) a short course of
6 non-steriodal anti-inflammatory drugs, generally
7 what I have been doing is two weeks, if that's
8 does not completely resolve their symptoms then
9 that is followed up with six weeks and then if
10 they still have persistent symptoms
11 consideration for steroids only after a biopsy
12 excluding active medicine.

13 PRESIDENT: Thanks very much. I
14 think what we're going to do at this point is
15 take a break. Why don't we take a ten minute
16 break. It's quarter after two, so that will
17 have us come back at twenty-five after two and
18 when we return there will be another
19 presentation and this one will be related to
20 dilated cardiomyopathies and then we have some
21 additional time for discussion.

1 (Whereupon, off the record for break)

2 (Whereupon, back on the record)

3 PRESIDENT: Okay, our next two
4 speakers will be Colonel Atwood, the Director of
5 Cardiology at Walter Reed. He's going to brief
6 us and there's going to be other issues related
7 to smallpox vaccine which is dilated
8 cardiomyopathy. But before we get to that
9 Colonel Gibson has one quick question for the
10 group.

11 DR. KILPATRICK: Colonel Atwood,
12 go ahead.

13 COLONEL ATWOOD: Thank you very
14 much. It's a real privilege to be here,
15 although it's a somewhat daunting task to follow
16 two follow to superb presentations like that.

17 The clarify that we've heard in
18 the first two talks may be changed at this
19 point, but my job or what I wanted to talk about
20 today was smallpox vaccination and dilated
21 cardiomyopathies. Is there a connection?

1 Now, my name is the only one
2 there, but I should be the last there. The
3 Action Health Care Center under Renata Engler;
4 the military vaccine agency under John
5 Ravenstein and everybody else, Roger Gibson and
6 also the armed forces surveillance group, John
7 Brundage, a whole host of people participated in
8 this but I am the lucky one to present so on we
9 go.

10 I don't know if you all know this,
11 but this is the Grand Canyon, you may not be
12 able to see it and there's myocarditis and there
13 is a canal between the two. This answers some
14 of your questions, these are very busy slides,
15 but they're only meant to put an impression in
16 front of you. But I think somebody asked a
17 question of Dr. Eckart what are some of the
18 causes of myocarditis. Here are two slides of
19 cardiomyopathy and dilated cardiomyopathy and
20 these don't even include the ones that come to
21 mind so-called secondary cardiomyopathies

1 including ischemic, coronary artery disease, or
2 multi-infarction reduced to Jackson fraction,
3 valvular heart disease, hypertensive heart
4 disease is a dilated cardiomyopathy. So just
5 this these two small lists are examples of the
6 causes of dilated cardiomyopathy. These are all
7 in your handbook.

8 Here is your list of causes of
9 myocarditis. Just a few viruses, about two
10 dozen, and lots of bacteria, lots of toxins,
11 hypersensitivity reaction, so there's a whole
12 host of huge differential when it comes to
13 myocarditis and also dilated cardiomyopathy.

14 The World Health Organization came
15 with a definition in around 1996 saying that
16 dilated cardiomyopathy is dilatation and
17 impaired contraction of the left ventricle or
18 both ventricles. It may be idiopathic, familial
19 or genetic, viral or infectious or immune,
20 alcohol toxic or associated with recognized
21 cardiovascular disease in which the degree of

1 myocardial dysfunction is not explained by the
2 abnormal loading conditions or the extent of
3 ischemic damage.

4 This is just a hedge to allow us
5 to include multi-infarction ideology as well as
6 valvular as an underlying element, but again it
7 wanted to stress the primary cardiomyopathy may
8 be different than the secondary
9 cardiomyopathies.

10 Histology is not specific,
11 presentation is usually what's heart failure,
12 again, which is not an easy diagnosis to deal
13 with given both systolic dysfunction and
14 contraction dysfunction versus relaxation
15 dysfunction, there's an enormous differential
16 with this.

17 The failure may be progressive, it
18 may even be asymptomatic which we'll discuss
19 later.

20 Now, the CDC task force came up
21 with the definition of dilated cardiomyopathy

1 after smallpox vaccination and it also follows
2 many of the World Health Organization's
3 definitions. Cardiac muscle dysfunction exists,
4 it's characterized by ventricular dilatation,
5 left ventricular-end-diastolic dimension,
6 greater than 55 and impaired contraction of one
7 or both ventricles with a left ventricular
8 ejection fraction of less than, or equal to,
9 45%, as Dr. Eckart mentioned 55% is normal.

10 There's no evidence of dilated
11 cardiomyopathy or congestive heart failure prior
12 to vaccination, either by history, dyspnea on
13 exertion, fatigue, or cardiac evaluation
14 including chest X-ray or echocardiogram when
15 available.

16 And, then as a third kind of
17 caveat no other cardiac or non-cardiac disease
18 can likely account for the symptoms or
19 abnormalities present. If another cardiac
20 disease co-exists it is not sufficient to cause
21 the degree of myocardial dysfunction present.

1 In other words, does a previous disease explain
2 the cardiomyopathy.

3 So myocarditis this is quite
4 simplified part of two — for two reasons, one
5 it's difficult for me to understand and two,
6 it's better stated in another article. But
7 basically the definition of myocarditis is
8 inflammation of the myocardium. There are three
9 basic mechanisms. One is direct invasion of the
10 myocardium, myocardial toxicity, direct side of
11 toxicity, myocardial toxins, immunological
12 mediated myocardial damage. Of course this has
13 been simplified. This is your classic acute
14 myocarditis, viral myocarditis mechanism and
15 it's in the Journal this is a very lovely
16 article, nice review article, but basically
17 states that you have acute myocarditis where you
18 may get viral infection and myocyte necrosis,
19 acute injury.

20 It then moves on to an immunologic
21 or autoimmunologic phenomenon and immunologic

1 clearing and intense killer cells, et cetera,
2 leading to further myocardial or myocyte
3 necrosis and then chronic myocarditis is kind of
4 this end stay or final common pathway for all
5 kind of mild carditis or damage to the heart and
6 sometimes we may not be able to find any virus
7 or any clues to a virus here or rather just
8 fibrosis, chronic dilatation and the
9 presentation of heart failure.

10 Then I wanted to include just a
11 partial list of the viral myocarditis. These
12 so-called cardiotropic viruses and needless to
13 say I suspect at least 70% of us in this room
14 have been exposed at one time to one of these
15 viruses. It's almost leading me to wash my
16 hands more frequently as the infectious disease
17 people suggest anyway.

18 But the big picture is viral
19 myocarditis given the presence you think of its
20 nature all of these organisms why would some
21 patients recover completely and some patients

1 progress to cardiomyopathy? Now, in the animal
2 model in the mouse model it seems fairly easily
3 documented and well-documented that there is
4 viral myocarditis leads to dilated
5 cardiomyopathy. This is not necessarily true.
6 It's mainly circumstantial evidence from a human
7 point of view.

8 So, I like this slide because it
9 kind of typifies life in general and perhaps
10 whether or not you have a viral infection it
11 could go badly or it could go well depending on
12 whether it goes badly or well. So that often
13 goes in terms of a talk. But the long and the
14 short of this is this is just a small list of
15 the cardiac tests that we can do in evaluating
16 somebody who comes in with heart problems.

17 I only list this to really show
18 that the history and physical is the presenting
19 components and when a patient is asymptomatic
20 that leaves us out of the loop. In addition
21 most of these tests ECG, cardiac enzymes, have a

1 subjective component to each one of them. And,
2 what somebody might call an ejection fraction of
3 45%; somebody might call it a 50%, somebody
4 might call 40, so there is this element. They
5 all have different test characteristics in terms
6 of one magnetic resonance imaging center may use
7 a certain type of imaging process, whereas
8 another one might not.

9 Nuclear imaging, all of these have
10 different technologies and experts at each
11 institution. Even autopsy and endomyocardial
12 biopsies have problems. Needles to say the
13 patchy elements and the patchy necrosis and the
14 patchy areas of involvement, then a myocardial
15 biopsy leads to mis-diagnoses. In addition, the
16 characterization of abnormalities on biopsy
17 range from the quote "the Dallas criteria," in
18 which there's some disagreement to other
19 controversial pathological definitions.

20 Autopsy has its problems and
21 obviously there's plenty of tissue, but it's

1 just a little bit late. So I thought I'd just
2 throw out some dilated cardiomyopathy
3 interesting facts. The incidence is about 5 to
4 8 per 100,000 patient years. Prevalence is 36
5 per 100,000, coronary artery disease is the most
6 common cause of congestive heart failure as well
7 as dilated low ejection fraction heart.

8 What's interesting to me is that
9 14% of middle aged to elderly men may have a
10 dilated cardiomyopathy and be totally
11 asymptomatic. That's very dramatic. In
12 addition 70% of the population will be exposed
13 to some cardiotropic virus. Myocarditis in only
14 about 40% of patients present with an antecedent
15 viral illness within one month.

16 So given that I think you can
17 understand it's a perplexing problem. You have
18 multiple possible diagnoses and found
19 invariable. Multiple and perfect diagnostic
20 tests, inconcise mechanisms and imperfect
21 therapies, which I won't go into at this time.

1 What I'd like to do is just
2 present some of the cases, some of the
3 confounding variables with each case and some of
4 the difficulties that we've come up and found.

5 It should be mentioned that
6 Dr. Eckart presented earlier his case of a
7 definition for myocarditis is there's a 30 day
8 window. So all of these cases you're going to
9 see don't fit the diagnosis with myocarditis.
10 However, most of these are in retrospect and
11 we'll just go over some of these. These are
12 listed in your handout. At the very end there's
13 a little table.

14 But Case 1 is a 37 year old male
15 revaccinee. Day 5 he may have had chest pain
16 and kind of a band like chest pain across his
17 chest which prevented him from doing pushups.

18 It's unclear whether or not the
19 huge left axillary lymph node and the soreness
20 in that area was the cause of what? Again, this
21 was a retrospective complaint. Day 163 or

1 roughly there, he was diagnosed with near
2 syncope in Kuwait. He had an ejection fraction
3 of 35 to 45%. He had no coronary artery disease
4 to rule it out in terms of a cause of dilated
5 left ventricular dysfunction. But also because
6 of his history of chest pain and he had a
7 history of hypertension, proteinuria and
8 hyperlipidemia. His exercise capacity, just to
9 point out, he went on the treadmill and he
10 walked on a Bruce 13 minutes and you're
11 wondering what that is, but that's 13 mets. 13
12 mets is — a met is a multiple aggressing energy
13 expenditure. The activities of daily life are
14 around 3 to 4 mets. Showering, brushing your
15 teeth. This is the ability to jog probably
16 about an 8, 7 to 8 minute mile. So you get a
17 sense that this guy is pretty asymptomatic if he
18 can jog an 8 minute mile.

19 The next one. This was another
20 interesting case. A 42 year old again male
21 revaccinee. He could not recalled any acute

1 symptoms. But on Day 151 post vaccination he
2 had flu-like symptoms in Iraq. They evaluated
3 him, they noticed an ejection fraction of 10 to
4 20%. Again, the normal being 55%. We evaluated
5 and he had no coronary disease and he had an
6 exercise capacity of only 4 mets.

7 Interestingly enough, when we were
8 looking at all of these titers of viral titers
9 he did have a positive adenovirus of 1 to 32 and
10 a coxsackie, and I'm not sure if it was B1
11 through B5 or whether it was and B5. Not being
12 a virologist I'm not sure what these mean except
13 that somewhere he was exposed to this virus. We
14 don't have convalescent titer and it should be
15 mentioned Dr. Engler brought up that in many —
16 there were a lot of viral studies and seravocic
17 studies in Dr. Eckart's room, but it was
18 sometimes a little hit or miss and we weren't
19 trying to mean anything that seemed significant.

20 Case 3, 44 year old, again a
21 revaccinee. Day 14 had acute squeezing pain,

1 but this only lasted one minute and sort of
2 atypical for angina. And, Day 30 to 45 he was
3 noted to have dyspnea while in Qatar and on
4 echo/cath he had an ejection fraction of 15 to
5 25%. His coronaries were normal and he had a
6 past history of micro valve collapse, but again
7 look at this at that capacity. You get a sense
8 that at 10 mets that's the ability to walk about
9 six miles in an hour. So in somebody who's not
10 particularly active and not in a stress
11 situation this is pretty good functional
12 capacity.

13 So Case 4, 34 year old male
14 primary vaccinee presented with chills, flu-like
15 symptoms; then presented with cough and dyspnea.
16 Noted to have an ejection fraction and no
17 coronary artery disease. His compounding
18 variable was 15% deficiency. History of
19 migraines. We don't know how far he was able to
20 exercise. Much of this data is pulled out by
21 old hospital records and the so-called chart

1 biopsy that's done by the Vaccine Health Care
2 Center and other people which is extremely
3 useful and incredibly difficult, as you can
4 imagine, trying to get records from various
5 hospital centers and clinic notes, it's a tour
6 de force that none of us has really set up.

7 These next two cases are from the
8 CDC and I haven't really seen them. I just have
9 the little biopsy that you have in the little
10 material there. But basically a 53 year old
11 female vaccinee, Day 7, perhaps retrospectively
12 noted some chest pain and fatigue; had an upper
13 respiratory illness, had more fatigue, shortness
14 of breath, a new murmur that was noted, hence
15 she was sent for an echo, noted to have an
16 ejection fraction of 35%. No coronary artery
17 disease. But compounding variable, hypertension
18 and mild obesity; both known to be causes for
19 dilated left ventricular dysfunction.

20 Another CDC case, 55 year old
21 female revaccinee. Day 9, myalgias, fatigue,

1 palpitations. No chest pain. Day 99 continue
2 fatigue and again a new murmur. Echo ejection
3 fraction 25 to 30%. Has negative perfusion scan
4 with coronary artery disease. She had just a
5 few variables for — compounding variables,
6 including diabetes, hypertension, hyperlipidemia
7 and again mild obesity. So all of these had
8 compounded variables.

9 This is a data sheet prepared by
10 John Brundage and reviews basically any medical
11 challengers in the ICP 9 codes and trying to
12 define — this is a busy slide, this is in the
13 back of your handout. In the back it we chose
14 any medical encounter, but this was hospital or
15 ambulatory diagnosis, the primary or
16 cardiomyopathy other, and Roger may be able to
17 handle some of the questions you may have, but
18 what's interesting is that this one right here,
19 relate for a 100,000 patient year the background
20 rate for 2002 to 2003 really was 5.7 for 100,000
21 patient years, which is in keeping with that of

1 the civilian population and other population
2 studies.

3 Of note, the incidents here of
4 171.749 patient years for smallpox vaccinees
5 there were only 2 observed cases. And, needless
6 to say I just presented 6, so you're probably
7 saying "Oops, another cardiologist you can't
8 trust them. Anyway, the cute picture is that
9 this is a work in progress. We can't define
10 getting materials, reviewing the ICC 9 codes.
11 The other thing that's real important to notice
12 is that both of these cases have no relation to
13 the other cases that I put in, so none of them
14 have been captured. So there's inconsistent
15 database and we know this probably brings in how
16 accurate is our misinformation and I think
17 that's what we struggle with most.

18 So the question is can we really
19 draw a line from myocarditis to dilated
20 cardiomyopathy and then perhaps with some
21 science and observation and epidemiology maybe

1 we can do that, but I'm not certain. It's a
2 pretty long gap from here to here and a lot of
3 blank canyons and steep walls to overcome.

4 So in summary, dilated
5 cardiomyopathy and myocarditis are difficult to
6 diagnose and to connect. Variable
7 presentations, imprecise tests. Does smallpox
8 vaccines associated myopericarditis lead to
9 dilated cardiomyopathy, my opinion is not likely
10 causal and probably not related given the data
11 that Bob Eckart has presented and the baseline
12 cardiomyopathies values that we have so far.

13 I think what's important here is
14 that a centralized evaluation in care process is
15 needed in which the vaccine health care center
16 has really provided.

17 Collecting all these pieces of
18 information is time intensive work and it never
19 could have been accomplished and I think it's a
20 tribute to the Armed Forces that this has
21 occurred. I'm open for questions.

1 PRESIDENT: Thanks very much. Why
2 don't we open the floor to questions. One
3 comment that I would make is that those six
4 cases you presented were not on active duty
5 personnel, so you wouldn't expect all of them to
6 be in that database.

7 COLONEL ATWOOD: That's right,
8 except they were all older than 30, so we're
9 looking at that and when I was reviewing all of
10 the inconsistencies those two cases we're going
11 to chase down and my suspicions actually are
12 that when I was looking at them with John
13 yesterday that they may be the myocarditis cases
14 that we already have. But we need their Social
15 Security number and all of the information.

16 MR. HAYWOOD: I have a couple of
17 comments. These were both superb presentations
18 and extremely thorough. I would just — to hear
19 that the Armed Forces took a golden opportunity
20 to look at that intensively and we need
21 consultation and I would endorse the efforts

1 brought in both directions (inaudible).

2 MR. ATWOOD: You know just from my
3 personal opinion as I've been reading all this
4 material it's just very rare to have a group of
5 population with clear-cut myocarditis that we
6 can follow even with all of the compounding
7 variables I think it presents just a terrific
8 opportunity to find an actual course of this and
9 define it for later on.

10 PRESIDENT OSTROFF: Thank you very
11 much.

12 (APPLAUSE)

13 PRESIDENT OSTROFF: Okay, our next
14 presentation is going to be multiple presenters,
15 I believe. We're going to be hearing from the
16 Navy Health Research Center in San Diego and our
17 first presenter will be Colonel Wells, who is
18 going to talk about the Case-Control Center.

19 LIEUTENANT COLONEL WELLS: Good
20 afternoon. I would like to brief you on the
21 Myopericarditis case control studies that we

1 studied a while back. This is our research
2 group here and then we have a group at the Naval
3 Health Research Center that are working on the
4 study. We had Dr. Eckart and Dr. Atwood as
5 consultants.

6 As a quite a lot of you know, the
7 program in the DoD started back in December of
8 2002. We began seeing the cases in February
9 2003. That initiated a series of telephone
10 conferences amongst the DoD/CDC and also FDA.

11 At one of these conferences it was
12 suggested that case-control studies be
13 accomplished. We volunteered to do that. We
14 wrote a protocol and submitted it to Colonel
15 Ravenstein's team and that was funded in August
16 of 2003.

17 It was our design to limit it to
18 males, primary vaccinees between twenty and
19 forty-five years of age serving on active duty
20 for six months or more during December 1st, 2002
21 through August 31st, 2003.

1 The reason we set the deadline at
2 August 2003 was to allow cases to accumulate
3 with data. That could take approximately six
4 months. So we wanted to ascertain all the cases
5 that we could so that's why we set the August
6 timeline. We're going to get our population
7 from DMDC defense manpower data center. We
8 planned to enroll four cases with subjects with
9 the same criteria as the case, except they will
10 not have myopericarditis following the smallpox
11 vaccination. We plan to enroll individuals
12 using the postal mail. Once we've consented
13 them then we're going to have a time drafted on
14 the internet so it will be computer assisted
15 telephone interview.

16 We wanted to get the cases through
17 M2. SIDR, for those that aren't familiar with
18 it, it is a standard data record. SADR is the
19 standard amitoid data record. These are both —
20 SIDR is for inpatient within a DoD medical
21 facility. SADR is an ambulatory within a DoD

1 medical facility. HCSR health care service
2 records if for either hospitalized or seen on an
3 ambulatory basis outside of the DoD, but it's
4 paid for by Tri-Care. We'll have visibility of
5 those individuals in the database.

6 You can see the list of ICD-9
7 codes that we're going to use. The analysis or
8 logistic analysis. We want to look at a number
9 of variables, some of them are standard, fairly
10 standard; exercise, smoking, alcohol usage,
11 prescription and over-the-counter medications,
12 dietary supplements. One of the eye openers
13 that I had with deployment was how many
14 individuals used say body building type dietary
15 supplements. Some of you might be interested in
16 looking at that relationship. Look at the
17 finals also. Colonel Atwood talked about the
18 relationship between myopericarditis and past
19 illnesses to see if there's anything there.
20 And, then this is what we want to look at during
21 the analysis.

1 Here's our timeline. IRB was
2 approved in November of 2003. We're working on
3 the case ascertainment right now as we speak.
4 Procuring the DMDC report control symbol that I
5 need to survey individuals within the military.
6 We're supposed to be in a contract to do
7 telephone interviews. We anticipate potentially
8 enrolling individuals in the June/July time
9 frame. Interviews then in July and August and
10 hopefully we will have the results in
11 September/October 2004.

12 And, if you keep going way past
13 the Grand Canyon to the DoD center for
14 Deployment Health Research, this is our group.
15 Thanks.

16 PRESIDENT OSTROFF: We'd like to
17 open that up for questions. Dr. Herbold.

18 DR. HERBOLD: The selection of
19 controls you said is the same as the cases that
20 were hospitalized controls. What's the process
21 for the control selection?

1 LIEUTENANT COLONEL WELLS: There
2 will be a random selection of individuals who
3 are males twenty to forty-five years of age,
4 been in the military six months or more and have
5 been vaccinated. So we're using vaccinated
6 controls.

7 MR. HERBOLD...pursue that more
8 off-line it looks like you're developing one arm
9 case retroeffectively working for variables and
10 the other arm you're developing exposure and
11 then going forward and looking for — and that's
12 find of catty wamper. So perhaps I don't
13 understand what you're saying, but we can talk
14 about that later. There is something not clear
15 to me.

16 LIEUTENANT COLONEL WELLS: Okay.

17 MR. CLINE: I'm having a little
18 trouble connecting the pericardia with the
19 myocardia. Looking at the pages you show on the
20 ICD-9 categories and they are either
21 pericarditis or myocarditis. I don't see a

1 myopericarditis, is there such a category?

2 LIEUTENANT COLONEL WELLS: No,
3 there is not. This is — we have become
4 accustomed to following either myocarditis or
5 pericarditis as myopericarditis. And, so we —
6 what we're really looking at is a combination of
7 either myocarditis or pericarditis.

8 MR. CLINE: For example, the paper
9 that we have a copy of is myopericarditis
10 following smallpox vaccination. I just have a
11 little trouble with the definition. I just want
12 to make sure we're all talking about the same
13 thing?

14 LIEUTENANT COLONEL WELLS: Yeah,
15 it is. Rather than taking the time to say
16 myocarditis or pericarditis we've been called
17 myopericarditis.

18 DR. GRAY: In the analysis you
19 might want to consider time onset vaccination
20 which I don't see here, and the other issue is
21 that in the case definition are you going to

1 stick with these ICD codes as cases or are you
2 going to deconstructed them into actual clinical
3 issues that led to the diagnosis such as the
4 ejection fraction?

5 LIEUTENANT COLONEL WELLS: We're
6 going to stick with the ICD-9 codes, that was
7 our plan. And the time from onset, I'm sorry,
8 from vaccination to diagnosis is very important.

9 DR. GRAY: You won't have the
10 clinical records of the cases or will you?

11 LIEUTENANT COLONEL WELLS: We will
12 not, no.

13 DR. GRAY: That's truly
14 unfortunate because then you could characterize
15 severity and the strength of the diagnosis
16 and...

17 LIEUTENANT COLONEL WELLS: We
18 might be able to work with some of the other
19 individuals to get that information.

20 DR. LeMASTERS: Just a couple of
21 comments. In terms of your methodology using

1 telephone interviews that may be a problem that
2 you'd want to think about unless you have cell
3 phone numbers for your active duty folks. I
4 assume that you have phone numbers for
5 everybody, is that correct?

6 LIEUTENANT COLONEL WELLS:
7 Correct. When we do the postal enrollment what
8 we'll do is we'll ask individuals the best time
9 to call them and what number we should call so
10 that hopefully when we do the postal enrollment
11 will have that information.

12 DR. LeMASTERS: And, I assume
13 you'll send a letter asking them to respond?

14 LIEUTENANT COLONEL WELLS:
15 Correct.

16 DR. LeMASTERS: And, then if they
17 don't respond.

18 LIEUTENANT COLONEL WELLS: We'll
19 then use a modified technique or basically if
20 they don't respond we'll make three attempts to
21 contact them.

1 DR. LeMASTERS: By telephone?

2 LIEUTENANT COLONEL WELLS: By
3 mail.

4 DR. LeMASTERS: By mail. So
5 you're planning to do a telephone and a — a
6 telephone call or a mail interview, is that
7 right?

8 LIEUTENANT COLONEL WELLS: It will
9 be to enroll them by mail, interview them by
10 telephone.

11 DR. LeMASTERS: Having just
12 finished a study myself of about 4000 folks I
13 find that by telephone I could only get less
14 than 40% with the interview, but when I added a
15 mail survey to the ones that didn't do the
16 telephone I got another whole larger — than had
17 I just been telephoning alone and then I also
18 got a percent when I did an internet. Then I
19 did a complete interview by internet, mail or
20 telephone gave me a lot larger completion range.
21 So I'll just throw that out to you. You may not

1 want to do just one mode, because you may get a
2 biased group one mode.

3 The other issue was limiting to
4 males. In the world of NIH we would never be
5 allowed to limit it males. So I'm wondering
6 what the rationale is for that.

7 LIEUTENANT COLONEL WELLS: In the
8 cases that have been identified so far, the 59
9 cases we're going — so that was our intent
10 there.

11 DR. LeMASTERS: That would be hard
12 ...

13 (Laughter)

14 PRESIDENT OSTROFF: I must confess
15 I'm slightly confused, maybe it's just the time
16 of day or something like that, but when we just
17 heard these previous presentations where there
18 were seventy-some individuals that have already
19 been evaluated. We understand the clinical
20 presentation, we understand the time frame
21 associated with smallpox associated

1 myopericarditis, and yet you seem to be using
2 completely different methodology to potentially
3 identify the cases.

4 How do we know that the cases that
5 you're identifying in your methodology are the
6 same ones that have been so well characterized?
7 Are you claiming theoretically looking at a
8 completely unrelated group of individuals so
9 that doing this case control study is going to
10 look at risk factors for myocarditis that not
11 necessarily risk factors for myocarditis
12 associated with smallpox vaccination?

13 LIEUTENANT COLONEL WELLS: I can
14 tell you that we also have the roster of the
15 individuals that vaccine health care center has
16 diagnosed and worked up and so as an
17 epidemiologist who's sort of a doubting Thomas
18 you want to try to ascertain all the cases that
19 you can, so I wanted to go to the electronic
20 data and see what I could find initially outside
21 of what they have already identified.

1 And, I can tell you that among the
2 individuals that we've identified to date
3 approximately two-thirds of them are on the
4 listing of those that have been worked up. So
5 there could be some differences. Some of the
6 things that we worry about using the electronic
7 data naturally is misclassification.

8 So are these individuals that are
9 recognized that are in the vaccine health care
10 system, are they actually misclassified as
11 myopericarditis or could they possibly be
12 individuals that have been missed by that
13 system.

14 PRESIDENT OSTROFF: So how are you
15 going to document whether or not they're real
16 cases unless you do some sort of evaluation of
17 their records?

18 It's easy for somebody to make a
19 clinical diagnosis of it being pericarditis and
20 put that on the record as a diagnosis when they
21 don't really have it.

1 LIEUTENANT COLONEL WELLS: Yeah,
2 that's a problem that we commonly have using
3 electronic data. It's one that's difficult to
4 over come unless you actually do some type of a
5 thorough evaluation.

6 Our intent is to get to
7 approximately eighty cases and we have
8 approximately that number now, but my intent was
9 I wanted to make sure that we didn't have some
10 type of ascertainment bias in the vaccine health
11 care system and so I think we've been able to
12 look at that and I don't think there is one.

13 PRESIDENT OSTROFF: I'm not so
14 worried about an ascertainment bias as a
15 misclassification bias, because you'll ruin your
16 case control study if you have cases that don't
17 have the disease. I mean that's my bigger
18 concern rather than there being some large
19 cohort of individuals out there that we missed
20 through the Dare (sic) system, et cetera. Do
21 others share that concern?

1 COLONEL ENGLER: I just wanted to
2 comment that in the formulation of this we're
3 talking about, we have twenty-three cases that
4 do not meet the case definition. The case
5 definition is a logic case definition and not a
6 clinical case definition and to some degree they
7 were excluded because they didn't happen to get
8 worked up, so data was missing. But there still
9 was a clinical suspicion. We had a case, you
10 know, following Anthrax vaccine, just one case,
11 so I think the value of this study is something
12 we were certainly interested in — is your
13 sources for getting the non-BHC cardiologists
14 don't take immunization histories. So that we
15 are missing people who may get the syndrome as
16 (inaudible) and even other vaccines, but the
17 health care system doesn't ask the questions.

18 So from our perspective I think
19 that that is the value of doing this, but I
20 agree that we're trying to explore ways how we
21 can synchronize our efforts and think that all

1 will be kosher with all the rules that we face.

2 LIEUTENANT COLONEL WELLS: I think
3 it's important to emphasize and I don't want to
4 get into a debate here that what we're really
5 trying to figure out here is the risk factors
6 for myopericarditis after getting smallpox
7 vaccination and so it's really, really critical
8 that you not have non-cases in your series.
9 When we seem to have such clearly identified
10 cohorted cases that I'm trying to figure out
11 what you're trying to accomplish by potentially
12 misclassifying other individuals as being cases
13 of this particular syndrome.

14 At the very least I would hope
15 there is some way in the analysis that those
16 individuals in which you don't have clear
17 documentation that they really have
18 myopericarditis are analyzed somewhat
19 separately, so they really can try to phase
20 these specific risk factors that are associated
21 with this complication.

1 So possibly these will be
2 individuals that have been referred to them and
3 maybe they'll have either more information on
4 them or they may want to have a look at them as
5 potential cases. Are you at least going to
6 include some criterion for how long after they
7 got the vaccine they had their myopericarditis?

8 LIEUTENANT COLONEL WELLS: It's
9 within the 30 days from vaccination.

10 (EVERYONE TALKING AT ONCE)

11 MEMBER ... because then you get
12 the Bell shaped curves that's really an
13 association, because otherwise it's going to be
14 scattered. So it's hard to understand why you
15 collect all this data and not look at it in the
16 fine detail that it would be available to you
17 because it may help...

18 MR. PARKINSON: Mike Parkinson. I
19 agree in general that the case ascertained — my
20 point is I understand the general purpose of
21 case-control study, but do we have a hypothesis?

1 I mean what, given the current state of
2 understanding of these factors, and if not
3 wouldn't we try to link in something as serum
4 market from the serum database or something like
5 that? My concern is having been down this road
6 with (inaudible) syndrome this will become a
7 sample study. Once it is out there in one form
8 or another. And, if you have the resources to
9 do some degree of case verification and/or look
10 at something like serum markers with general
11 formation or something like that now rather than
12 trying to get back at it a year from now that
13 have been sitting on the table with a study that
14 has a lot of factors in it but not necessarily a
15 true hypothesis. Can we ease up a little bit
16 with things like that based on more of a risk
17 factor in general?

18 LIEUTENANT COLONEL WELLS: We have
19 the capability of accessing the serum repository
20 if we alter our protocol. The primary
21 hypothesis was that one of the outcomes, I'm

1 sorry, one of the provariance that we're looking
2 at will be a significant difference between the
3 cases and controls. But we do not, right now we
4 don't have serum markers rolled in. We could
5 potentially could though. It's just a matter of
6 money and setting up the agreements and working
7 out the relationship between a vaccination and
8 getting the serum and how long you want to look
9 at that difference in between the two, if
10 anybody has comments on that I'm sure we would
11 look at it.

12 PRESIDENT OSTROFF: one other
13 question. I realize you're about to embark on
14 the actual case-control study. Is it possible
15 for us to take a look at the questionnaire
16 that's being used to see what's actually being
17 asked?

18 LIEUTENANT COLONEL WELLS: Yes, I
19 did not bring it with me, but I can get it to
20 Colonel Gibson.

21 PRESIDENT OSTROFF: Other comments

1 or questions? Thanks very much. Oh, I'm
2 sorry...

3 MEMBER: I wonder whether reading
4 the questionnaire we might be reading protocol
5 and give some suggestions for the protocol.

6 PRESIDENT OSTROFF: Well, I assume
7 the protocols have already been approved by the
8 higher be's, so they certainly can be changed if
9 we think that they're — if we think that's
10 necessary it will cause some delays. But I
11 think, you know, I agree with Dr. Parkinson
12 there's critical information that mya come out
13 of this, we certainly like to make sure and
14 perhaps be some assistance to you making sure
15 that we have that study...

16 LIEUTENANT COLONEL

17 WELLS: Appreciate it.

18 DR. KILPATRICK: Thanks very much.
19 Why don't we move on to the last presentation
20 and it's good to see an old friend that wasn't
21 able to attend the last couple of meetings, so

1 welcome back, Commander Ryan.

2 COMMANDER RYAN: Thank you. Good
3 afternoon. This is a different topic. It's
4 actually the one that rivals the cardiac issues
5 in the smallpox vaccine world. So we're going
6 to talk about smallpox vaccine and reproductive
7 health outcomes. From the perspective of
8 smallpox vaccine and pregnancy registry there's
9 more we can say about reproductive health
10 outcomes but there's a particular registry
11 that's with CDC and DoD to look at those women
12 who were inadvertently vaccinated in pregnancy.

13 This a group of people that have
14 been working on the registry. The top part of
15 the people out in San Diego is my group. Now,
16 we don't actually (audience noise) for a
17 smallpox vaccine and pregnancy registry. This
18 actually was a lot of work, but we do it as part
19 of our charge with the DoD birth and infant
20 health registry. So that's the team out there
21 that works with me on the project since 1998.

1 And, there are several other
2 important to Department of Defense
3 professionals, some of which are here in the
4 room, particularly Colonel Engler and
5 importantly the CDC professionals. They are
6 importantly from the national organization
7 program and importantly from the National Center
8 for Birth Defects and Developmental
9 Disabilities.

10 As a brief review smallpox vaccine
11 is categorized as Pregnancy Category C and this
12 is the actual excerpt from this packet insert
13 right now. It states "animal reproduction
14 studies have not been conducted, should not be
15 given to pregnant women in non-emergency
16 conditions. It does mentioned the rare
17 possibility of of fetal vaccinia which is
18 infection of the fetus with the vaccine virus.
19 That usually results in a very poor outcome.
20 And, it also says that it is not known to cause
21 congenital malformations. And, the three

1 bullets at the bottom there about what's in the
2 literature about that.

3 Nothing in the package insert
4 talks about pregnancy loss and there is some
5 literature that argues that smallpox vaccine and
6 pregnancy does result in an increased rate of
7 pregnancy loss, stillbirth. It's very hard to
8 determine that urologically. Much have been
9 even much harder in the 1940's when most
10 smallpox vaccine were given before. But there's
11 a little bit of suggestion of concern in the
12 literature about pregnancy loss.

13 We only have one report that
14 suggests pre-fetal malformations, particularly
15 club foot in one study. It's really been
16 contradicted by the larger studies of coverts,
17 particularly large covert in New York City in
18 the late 1940's. There's some known and not
19 known about what a vaccine pregnancy should do.
20 But what we do know is that rarely vaccination
21 in pregnancy results in fetal vaccinia or

1 infection of the fetus.

2 Estimated that one in 10,000
3 pregnancies and there were no cases reported in
4 that big New York City outbreak in 1947. But
5 perhaps as many as 173,000 pregnant women were
6 vaccinated intentionally because of the
7 emergency situation.

8 When fetal vaccinia is reported
9 and there's about fifty or so reports in the
10 literature it usually results in a very bad
11 outcome. The baby on the right there is
12 actually quite healthy, but with significant
13 scarring that sort of an exception to the rule
14 of fetal vaccinia resulting in fetal death.

15 So why develop a registry at this
16 point? The registry is developed because we
17 anticipated inadvertent exposures to pregnant
18 women when a large number, military and civilian
19 women, were planned to be vaccinated in early
20 2003. And, it's justified because not all
21 effects of smallpox vaccine during pregnancy are

1 well known or quantified. Basically working off
2 the reports from the 1940's.

3 Like the registry that was
4 developed for rubella and varicella vaccines,
5 we would actively follow all exposed women all
6 of which were exposed during pregnancy. And
7 that is a definition of exposure there, actually
8 pre-dates conception because it's a live virus
9 prior to make up and exposure pre-dates
10 conception in the case until delivery.

11 So what we know to date since the
12 registry has been set up. 236 woman are now
13 actively being followed. We know of 14 others
14 that we have enrolled in the registry. The data
15 here is before 20 weeks estimate gestational
16 age, so it's not fair to talk about their early
17 pregnancy outcomes yet.

18 There are at least 50 others and
19 perhaps as many as 70 others who might be
20 enrolled soon, as we get more data on them. It's
21 really quite an active process. And even though

1 there may not be large numbers of women getting
2 vaccinated this month in the Department of
3 Defense, we do find sort of hypothesis
4 previously in reported women from commands where
5 we're actively still enrolled. And, then
6 medivacs home from Operation Iraqi Freedom and
7 (inaudible) Freedom are also people that we
8 always explore whether or not they should or
9 should not be in the registry if they're
10 medivaced home for pregnancy.

11 Among all those women 10 were
12 vaccinated as civilian healthcare system and
13 actually followed by that CDC team and 226 are
14 being followed by my group out in San Diego.

15 All of them are primary exposed.
16 They are not — women are eligible to be in the
17 registry if they have secondary exposure. But
18 all of these were vaccinated. We do have a very
19 small number who had exposure to vaccinee and by
20 definition are eligible to be in the registry.

21 Only one of those cases had

1 lesions that were laboratory confirmed to
2 vaccinia on her skin, on her secondary exposure
3 to her husband. But close contact was a hotly
4 debated issue about whether it qualifies for the
5 registry and determined that it does. There's a
6 small number of those cases as well.

7 Most of these women were
8 vaccinated before a standard pregnancy test
9 would have been positive. That's really maybe a
10 topic for a different date, but again most were
11 vaccinated before their pregnancy test could
12 have been positive. Really right around
13 conception.

14 We'll take demographics that are
15 not expected. These are young adult women that
16 age range from 18 to 41. Most — this is their
17 first smallpox vaccination, but 15 had prior
18 smallpox vaccination. And for the most, 60%,
19 this is their first pregnancy.

20 Among the military women, as you
21 see is the military demographics for this

1 particular entry, there again I expected young
2 adults, most of them mid-enlisted ranks, most
3 Army received the vaccine as well. 22% are
4 reservists. 16% were vaccinated outside the
5 Continental United States or OCONUS. And,
6 importantly perhaps 66% not unexpected to us
7 received other vaccine or vaccines during this
8 pregnancy. So in the military, of course, we
9 give many vaccines at once.

10 So what have we seen in pregnancy
11 outcomes to date. As of this month 184
12 delivered, including one set of twins, when you
13 look at the deliveries you'll see 185 infants.
14 14 are still pregnant, but past that 20 weeks
15 gestation so we can talk about early pregnancy
16 outcomes in those 14. But not — I've excluded
17 the others that are not yet past 20 weeks
18 gestation age.

19 And, these are the losses among
20 the 236 women. 2 ectopic pregnancies; 11
21 elective abortions; 23 spontaneous abortions

1 before 20 weeks; 2 stillbirths after 20 weeks of
2 gestation age.

3 More on the losses. Observed rate
4 of ectopic of 0.8% and expected 1 to 2%. So
5 we're really not seeing anything dramatic with
6 ectopic pregnancy. Spontaneous losses, there's
7 much in the literature about spontaneous loss.
8 This is difficult to do well, because it depends
9 on how closely you follow the cohort of women
10 whether or not you'll find a high or low rate of
11 miscarriage. But the extent we observed is from
12 9 to 30%. 30% is a little high for observed
13 pregnancies, probably it's closer to 20% for
14 well observed pregnancies and what we're seeing
15 is in the low end of that range. It's not
16 remarkably different than what's expected for
17 miscarriage rate.

18 Just a little more on the
19 miscarriages. 8 of the women's registry had
20 histories of risk factors including SAB, which
21 is spontaneous abortion. 3 had other

1 infections, bacterial infections and/or
2 chorioamnionitis and 1 had incompetent cervix.
3 The two stillbirths are of course interesting
4 because they're very tragic, unexpected losses
5 so late in pregnancy. One had spontaneous
6 rupture at 21 weeks with subsequent infection
7 and the other had a severe compressed nuchal
8 cord, the umbilical cord around the baby's neck
9 at 34 weeks and subsequent fetal loss. Now 4 of
10 the losses we were able to get products of
11 conception tested for vaccinia. Of those 4 all
12 were negative. So we didn't find any vaccinia
13 in the losses that we could test with laboratory
14 testing.

15 This slide is just trying to
16 graphically represent a few things that I've
17 already said. On the chart is gestational age
18 and this is the number of women vaccinated at
19 each gestational age of pregnancy. That one
20 there, that's estimated conception is like last
21 menstrual period estimated conception. As for

1 clinical a positive pregnancy test that is two
2 weeks after conception. You can see most women
3 are vaccinated right there around conception and
4 a bit before. You might argue our case
5 definition is generous to include these women
6 way out here and we considered whether or not
7 they should be in the final analysis, but this
8 is the prime time. Then there are a few that
9 were vaccinated well into their pregnancy. But
10 we created this slide to look at the losses by
11 gestational age just in case we're missing
12 something by looking at the losses altogether.

13 In the little bit of literature on
14 losses after smallpox vaccination in pregnancy
15 it suggests that there's a window that's of high
16 risk for exposure to the pregnancy. We wanted
17 to make sure that we weren't perhaps missing a
18 window right in there that was higher risk than
19 the rest of the time. And, although this rate
20 of miscarriage right in there is higher than say
21 the rate of miscarriage and here it's not

1 statistically — but it's certainly worth
2 watching. And, the overall rate of miscarriage
3 then is not high, but it's important to look at
4 all of the data that's there and the elective
5 losses are in here, because there is a way to
6 adjust for elective losses in viewing the
7 spontaneous loss rate. There's some nice
8 literature on that. Because we can either
9 assume that they would have gone to full term or
10 assume that there would have been losses.
11 There's actually statistical adjustment that's
12 suggested to be made about them. I just showed
13 it graphically here so that in your mind picture
14 that they could go either way.

15 So just to talk about other
16 adverse outcomes. We did have one maternal
17 death tragically in the group we were following.
18 It was a 31 year old woman who delivered an
19 uncomplicated delivery 37 weeks by Cesarean
20 section and unfortunately developed post-
21 operative complication of pulmonary embolus 2

1 weeks after delivery. It was considered by the
2 OBGYN investigation it was considered a surgical
3 complication that was unlikely related to the
4 previous vaccination. The child did well.

5 Other outcomes, the infant outcome
6 there is gender ratio, because that's
7 interesting as we talk about things like birth
8 defects. But approximately 50/50, but a little
9 bit more female babies born in this covert so
10 far. 175 full term infants, and ten pre-term
11 which is defined as 36 weeks after gestational
12 age. The rate of pre-term births has not been
13 harmful so far in the covert, 5%.

14 The adverse outcomes you see 5
15 cases of major potential anomalies of birth
16 defects among the babies born so far. These are
17 the five babies. One ASD atrial septal defect;
18 1 ventricular septal defect; 1 isolated
19 gastroschisis which is the abdominal wall to
20 (inaudible) about 10 weeks gestation; 1 isolated
21 omphalocele, which is the failure of the

1 abdominal wall formation that's expected to be
2 about very early in gestational age. 1 One
3 Beckwith-Weidermann Syndrome, which is a
4 (inaudible) disorder and the total observed
5 prevalence of birth defects is just under 3%
6 with an expected prevalence of 3 to 4%.

7 The is where our work — the Birth
8 Pregnancy Registry used to be called the Birth
9 Defects Registry. We work closely with that
10 national center of birth defects in development
11 of this ability to sort of define, have a look
12 at these birth defects, whether they should be
13 grouped, whether they should be separated,
14 whether we should cluster the abdominal wall
15 defects together or not, and there's a lot of
16 folks with a lot of experience here that we've
17 really valued in looking into it.

18 Now, we've got the National
19 Centers of our Birth Defects consultants who
20 said these are actually all isolated things, not
21 really there when we look to cluster the AFC and

1 BFC. It's not really fair to cluster
2 gastroschisis and omphalocete, interesting that
3 they are coded the same. But CDC has spent
4 about a decade trying to separate them because
5 embryo-wise they're quite different. So it's
6 not really fair to group the gastroschisis and
7 omphalocele and also by the National Center for
8 Birth Defects standards it's not fair to put the
9 Beckwith-Weidemann syndrome in with the
10 omphaloceles who is a different disorder.
11 However, if you put it in with the omphalocele
12 you'd have certainly a higher prevalence of
13 omphalocele. All of these are higher than
14 expected, but they're all a simulator of 1 at
15 this point. So certainly worth watching, but we
16 haven't seen any clustering of defects so far.

17 Other adverse outcomes we've had 2
18 cases of sudden infant death syndrome.
19 Tragically two full term healthy babies who died
20 at 7 weeks and 9 weeks of life and that's also
21 much higher than the expected rate of SIDS,

1 those two cases. We have had postmortem tests
2 for vaccinia for both cases, because they had
3 autopsy specimens and all of that testing was
4 negative at three different laboratories by
5 different techniques.

6 We also had fortunately, in
7 Southern California, Dr. Krauss, Henry Krauss,
8 who's probably with Dr. Beckwith one of the most
9 published people on SIDS. Commented
10 specifically on our cases and reviewed them and
11 there's a lot to learn about SIDS for us.
12 There's actually a soft diagnosis for SIDS and
13 hard diagnosis for SIDS and we could spend time
14 talking about it. Both these babies had risk
15 factors for SIDS. The risk factor for SIDS
16 basically is sleep prone on soft pillows and
17 those sort of things that's not recommended to
18 be done with infants of that age who don't have
19 the ability to control their heads and so SIDS
20 is actually the correct postmortem diagnosis
21 because a diagnosis of exclusion you can't

1 absolutely say it's asphyxia, but it's a
2 troubling history in trying to sort out the
3 ideology of SIDS without those risk factors.

4 This is the last slide on adverse
5 outcomes and perhaps the most challenging to us
6 right now. So of course originally the first
7 thing we look for is fetal vaccinia and we
8 haven't seen fetal vaccinia. So I told you
9 about 16 incidents had laboratory testing, 4
10 miscarriages and 2 SIDS babies all tested
11 negative. What I haven't told you is we've been
12 in close contact in this followup with records
13 and talking to doctors on all these 250 cases
14 and looked at all the births and documented
15 every mole and birthmark and swordfight and
16 Angel kiss and all the other things that are
17 skin lesions on little babies.

18 And, it's documented very well
19 that none of this is concerning even that a
20 clinician has wanted to do anything like touch
21 the fetal vaccinia even when that's offered in

1 any of the babies with little skin findings to
2 date.

3 However, we were actually
4 challenged by ACIT and SED working group
5 particularly about why not test some biologic
6 sample on the healthy babies? Which is
7 certainly easier said than done. But there is
8 potentially the option of testing cord blood,
9 placenta and other tissues on healthy babies for
10 vaccinia because there was an internal exposure
11 to vaccinia. So we really struggling with this
12 question about whether or not to test healthy
13 babies for vaccinia. And, we were challenged
14 that it was a once in a — opportunity and we
15 don't know enough about vaccinia and we should
16 try to test healthy babies with vaccinia.

17 Well, we succeeded or will succeed
18 in 5 which are babies born at the medical
19 centers where we have close relationships with
20 the obstetrician been able to give him a
21 protocol and get cord blood basically or

1 placenta for vaccinia testing. And, just last
2 week, to make things more complicated, one came
3 back positive. This is a healthy baby who was
4 born to a mom, Mom was vaccinated two weeks
5 estimated gestational, actually right after
6 conception. She delivered at 38 weeks,
7 uncomplicated vaginal delivery, this was her
8 second baby, her and baby did well, baby has no
9 skin lesions, no swordbites, nothing, the baby
10 looks great and remains well. Actually it was
11 week before last that it was delivered, but the
12 testing came back last week as positive for
13 vaccinia, a TCR on the cord blood at the
14 hospital where the baby was delivered. And, of
15 course we sent all samples to other labs to
16 relook and in our lab, cultures have been
17 negative. At the CDC lab the first run so far
18 is that they've found nothing positive for
19 vaccinia. The positive controls were also
20 negative in that first run. It's not quite
21 reassuring yet that it's negative. We've got at

1 least at this point too early to draw a final
2 conclusion on what's happened with this case,
3 but we've got these cord lab results between
4 laboratories and although final testing and no
5 cultures positive to date and again baby remains
6 well, this is a critical challenge and a
7 challenge to the registry about what we do about
8 this positive test. And of course we did think
9 about this when we offered testing to healthy
10 babies, instead of staying completely naive to
11 that, that we could have these positive results
12 and what we do with it. And, that's why we only
13 engaged with the hospitals like this is at the
14 Army Medical Center where the OB doctors are
15 very well engaged and prepared to talk to the
16 mom and explain what this might mean or what
17 might not mean if results came back positive.

18 They're just following this baby
19 closely. Certainly not trying to treat with an
20 anti-viral or anything with just that one
21 positive TCR at this point.

1 Baby is getting, I imagine they do
2 a two week heel stick on well babies and we'll
3 be testing that as well. Fortunately we did not
4 have to do an extra stick on the baby but it is
5 done in two weeks so it should have been done
6 Friday.

7 So, the registry remains active,
8 we're still enrolling new cases weekly. Not to
9 the degree we were last spring but still in a
10 steady pace. We've seen so far no observed
11 increase in pregnancy losses. We have seen some
12 adverse events including the one maternal death,
13 5 cases of birth defects and 2 SIDS cases, but I
14 would say our interpretation is limited by the
15 small numbers of those cases. We've had no
16 confirmed fetal vaccinia or fetal infection,
17 that should be infections with the asterisk
18 there on that one last case in health babies.

19 Now, the case definition of
20 developed fetal vaccinia with CBC includes skin
21 lesions as part of the case definition, so even

1 if when all said and done this laboratory
2 testing is decided to be positive, by the
3 current case definition this would not be fetal
4 vaccinia without some clinical pathology. It
5 would be vaccinia infection.

6 And, perhaps this represents some
7 spectrum of the disease of what happens in
8 pregnancy, when women are vaccinated in pregnancy
9 it's not been really well defined before, so
10 that's one of the little bullets I put there.
11 We will continue to follow this registry closely
12 and if we confirm that vaccinia in the placenta
13 and cord blood in a health infant we'll have
14 trouble with that interpretation, whether it
15 represents the spectrum about an infection and
16 importantly for us whether it justifies my offer
17 to that, to you as well we're looking for
18 comments on that, whether this justifies more or
19 less testing on healthy infants and we do accept
20 certainly that there's arguments.

21 We have got plan follow up for all

1 the babies and moms in this registry through
2 infants first birthday and we have a
3 questionnaire, a brief questionnaire to be
4 administered after the first birthday mark,
5 right after the twelve month birthday which
6 includes a set of developmental questions and
7 we're working with the National Center for
8 Births and actually the American Academy of
9 Pediatrics does a nice job with a very brief
10 through screening for developmental issues that
11 would prompt actually more questions if there
12 were anything concerning them.

13 And, again another question about
14 the registry, will our findings prompt even
15 longer followup. We know that you really are
16 concerned about developmental issues, we're
17 opening a whole different spectrum. We won't
18 get it at the first birthday. You really want
19 to talk about developmental issues some might
20 argue that you have to go to age 5 or age 7.

21 I think that's it. I have a

1 little bit of stuff and information on the
2 slides. I'll be happy to take questions at this
3 time.

4 PRESIDENT OSTROFF: Thanks very
5 much. That was just a marvelous presentation,
6 as always, great work. I'm ready to open it up
7 with questions or comments. I saw several over
8 here, Dr. Gray and then Dr. Herbold.

9 DR. GRAY: This is Greg Gray. I
10 wonder if you could review with us how you
11 determined who was eligible to be in your
12 registry? I thought you did some original
13 things.

14 COMMANDER RYAN: I was trying for
15 originality and have them conform with past
16 registries. But in finding cases do you mean,
17 sir, or do you mean in the definition of who
18 belongs?

19 DR. GRAY: Right, finding cases?

20 COMMANDER RYAN: The process will
21 original to the DoD. The case definition of who

1 belongs in the registry we tried to standardized
2 based on other registries. So that window of
3 six weeks prior to conception, which is four
4 weeks prior to LNP, the window exposure up to
5 delivery or pregnancy loss.

6 But in terms of finding who
7 belongs in the registry we reached out — we let
8 CDC figure out what to do with civilian
9 vaccinees and they quickly determined there
10 weren't too many to worry about.

11 But in the military world we
12 reached out to the military hospitals that
13 deliver babies and which is a finite number,
14 because not all of our hospitals will deliver
15 babies. That was relatively easy to do. The
16 funny part is that a lot of these women are
17 reservists, a lot are having their babies
18 outside the the military system and the Tri-Care
19 system. In fact the supplementary data about
20 40% followed at civilian facilities. Then of
21 course there's elective terminations that we

1 would not otherwise get unless we were hearing
2 people before they present to OB care.

3 So we identified each providers by
4 reaching out to vaccine providers as well as OB
5 providers and also looking at the databases like
6 the women medivaced home from Iraqi Freedom.
7 It's really anybody medivaced home from Iraqi
8 Freedom probably belongs in the registry. She
9 conceived over there or she conceived right
10 before going, but she conceived when nobody
11 thought she had conceived which means she may
12 have been vaccinated and nobody thought she was
13 pregnant.

14 DR. HERBOLD: Could you review the
15 questions that are asked pre-vaccination? Are
16 you pregnant or are you having unprotected
17 intercourse?

18 COMMANDER RYAN: Not the latter,
19 but the former with a little more. So, is there
20 any chance you could be pregnant, what is the
21 date of your last menstrual period and then

1 there's this, I'm sorry, it's too small to see.
2 This is the DoD form, so there's this little
3 question right at the top about pregnancy, any
4 chance of being pregnant, any chance of being
5 exposed to someone who is pregnant, close
6 contact thing. When is your last menstrual
7 period and then down here it says something like
8 smallpox vaccine can cause problems in
9 pregnancy, including fetal vaccinia. If you
10 have any concerns write them in the box. This
11 is one of three ways to try to get at it.

12 DR. HERBOLD: I guess my concern
13 is you never told us out of how many these 226
14 pregnant vaccinated women derived, so I don't
15 know whether it's a great failure rate of your
16 screening program or a small screening rate.
17 But there is something profoundly worrisome
18 about this. While it will provide interesting
19 information about abnormalities in women who are
20 vaccinated. It raises the questions whether
21 everything is being done to not vaccinate

1 potentially pregnant women because we know
2 because of the interpart of vaccinia that that
3 is not a very, it is a clear contraindication.

4 So it is, and I do mention it, it
5 is the question that wasn't addressed here. But
6 it does raise, I think, profound IRB questions
7 about doing this kind of a study if one could
8 have prevented the vaccination of the pregnant
9 subjects to be begin with. Because otherwise
10 we're vaccinating pregnant subjects and waiting
11 to see what the outcome is and we all kind of,
12 you know, have a little cold chill about that.

13 COMMANDER RYAN: We certainly
14 agree that all of these are inadvertently
15 vaccinated and unintentionally vaccinated. In
16 supplementary slides it gives you a little bit
17 of these data. They've been presented to HJIT
18 before. There's about 75,000 women in the
19 military and two hundred and some odd vaccinees
20 were vaccinated while pregnant, among that
21 75,000.

1 With CDC we estimated rate of
2 vaccinating pregnant women with no screening
3 program in place and CDC suggested that we were
4 about 11 times lower than expected based on this
5 screening program. Between eight and 11 times
6 lower than expected. So certainly the screening
7 program does something.

8 I would agree with you that we
9 want to vaccinate zero. But I would also say in
10 the experience of vaccinating women who are
11 young and healthy, that despite the very, very
12 best efforts we will always vaccinate a few
13 pregnant women because of the window of negative
14 pregnancy tests early at conception and right
15 before.

16 DR. NEWBOLD: Would that not be
17 for a study which would instead of kind of being
18 the last question, it might be the up front
19 question of are you sexually active and not
20 using precaution and if the answer were yes,
21 that doesn't seem to me that it's rational to

1 immunize that woman.

2 COLONEL UNDERWOOD: This is
3 Colonel Underwood. I just wanted to add you
4 probably perhaps don't know this, but we're also
5 testing all women for pregnancy in deployment,
6 before deployment. So this is another aspect of
7 trying to get out of not vaccinating pregnant
8 women.

9 DR. HERBOLD: Although we know
10 that that leaves a window of two to three weeks
11 where there is no test, so essentially you have
12 to ask about exposure which is unprotected
13 intercourse.

14 COMMANDER RYAN: I think it's
15 challenging. We've struggled with this in
16 recruit setting, we don't want to begin recruit
17 training with pregnant and occasionally we will
18 because we'll be in that window. We don't want
19 to deploy pregnant women we occasionally will,
20 we don't want to vaccinate pregnant women. But
21 when women form up with a unit and the unit is

1 ready to go and we say, are you sexually active
2 and not using birth control, well I've got to
3 wait two weeks before you can pass go, the rest
4 of your unit will go ahead of you and you go two
5 weeks later, it is just operationally difficult.

6 DR. KILPATRICK: I'll point out
7 this is a whole issue with — for those of us
8 who lived through the issue related to the
9 Anthrax vaccine, et cetera, we explored this
10 particular issue in so many different ways
11 looking at whether or not there are
12 opportunities to reduce the possibility of this
13 happening, but your point is one that's very
14 well taken and there are many different ways to
15 try to address the issue.

16 DR. GIBSON: I just wanted to add
17 on top of that there's a committee, a
18 subcommittee of the AFEB that's linked with the
19 subcommittee of ACIP that have gone over this
20 time and time again as well. Maybe on a monthly
21 basis to discuss these types of findings and

1 others. As far as that screening questionnaire
2 down at the bottom which gives you an
3 opportunity to write. It also says you don't
4 have to fill that in you can just self-identify
5 and walk over. You don't even have to write it
6 down. You can come forward to verbally discuss
7 it as well. So there's a fourth...

8 COMMANDER RYAN: The other thing
9 that was added to the extended screening
10 program, both military and civilian, is this
11 mandatory module, training module that the
12 vaccine recipient must see, either look at the
13 slides, read the thing in front of them or get
14 the lecture that includes a fair amount of
15 information on both the skin condition
16 contraindications, the exposure
17 contraindications and the pregnancy issues.

18 SPEAKER: I just want to add that
19 we've talked about this quality assurance survey
20 and across the board service members do not want
21 to be asked with their sergeant or their chief

1 standing by are you sexually active. That's far
2 more horrendous to them then potentially being
3 pregnant. And, we agonized with the screening
4 questionnaire and the teaching slides which we
5 make available again to folks and said you don't
6 have to talk to anyone. If you want a pregnancy
7 test the door is open. We've trained the
8 vaccinees to be very sensitive to know barriers
9 to pregnancy testing and no requirement to
10 expose behavior in any kind of setting where
11 their privacy is potentially compromised which
12 in massive immunization is an issue.

13 I think we worked very hard, based
14 on experience and feedback to construct this in
15 such a way so that we could optimalize the use
16 of pregnancy testing with no barriers and
17 protective response despite massive
18 immunization.

19 PRESIDENT OSTROFF: Let me ask a
20 slightly different question, but gets to some of
21 the same issues. I have always been disturbed

1 when I see that epicurve of when the vaccination
2 occurred and look at that small tail of women
3 that seem to have been vaccinated relatively
4 well into their pregnancy and I wonder if you
5 could enlighten us a little bit about what some
6 of the potential problems were and whether or
7 not there is any ability to correct that from
8 happening and then my second question is in
9 regard to elective abortions. Do you have any
10 information to suggest that any of these
11 occurred because the women were informed of the
12 potential to have been exposed to vaccinia.

13 COMMANDER RYAN: Thank you. I'm
14 going to try the latter one first. We've asked
15 all the women, because we've got a history of
16 elective abortions from interviewees, there's no
17 other way to do that in the military, and we
18 specifically asked that question. And, none
19 have said that the reason for the elective
20 abortion was their smallpox vaccine. All of
21 them was because the pregnancy was not planned

1 and not desired.

2 Now, this is a harder question. I
3 could probably just tell you a story about each
4 one. I'll tell you the story about the hardest
5 one, because this woman was vaccinated at what
6 seems to be eight months pregnant.

7 It was a little hard for me to
8 believe. She's a reservist and she was
9 vaccinated with her reserve unit in Tennessee.
10 She was in vaccinated in preparation for
11 possible deployment but she didn't deploy. So
12 she was vaccinated on one of her drill weekends
13 and went back to her regular life. Now when she
14 was vaccinated she was asked is there any chance
15 you could be pregnant and she said no, no chance
16 at all. Now, she doesn't get regular periods
17 which is also by the way the story of most of
18 the people on this side of the curve, they do
19 not get regular periods so asking them do you
20 think you could be pregnant is a difficult
21 question. You need to ask the last date of your

1 menstrual period and then that helps the
2 provider to say wait a second, your period was
3 six months ago. But if the woman honestly
4 denies there's any chance she would be pregnant
5 and there's nothing wrong with her periods and
6 everything is prefaced for whatever reason,
7 she's actually at the very end of registry, so I
8 don't think she was asked the date of her
9 period. She was just asked if there was a
10 chance she could be pregnant and she said no.

11 Apparently she didn't appear
12 pregnant and she didn't know she was pregnant
13 and she was like you hear stories about high
14 school kids who go into labor and they didn't
15 know they were pregnant. That was her story.
16 So she went into labor not knowing what was
17 going on with her and delivered a baby that they
18 determined to be a full term baby, a nearly
19 seven pound healthy baby boy.

20 We learned of this case from the
21 adopted mom. The adopted mom. So she put her

1 baby up for adoption and a family friend, who
2 happened to be a pediatrician, adopted that baby
3 and called us and said this woman had a bunch of
4 vaccines last month, she didn't know she was
5 pregnant, she delivered, we're worried.

6 So we talked to her at length and
7 have been in close contact with that baby.
8 That's the most extreme case.

9 So they all have a story that
10 makes some clinical sense. It's very
11 unfortunate and they missed knowing they were
12 pregnant.

13 DR. LeMASTERS: Grace LeMasters.
14 I just wondered on the baby with the birth
15 defects. Did you look at the estimated
16 gestational age at the time of vaccination and
17 were there any patterns among either the heart
18 or the GIs?

19 COMMANDER RYAN: Yes, thank you.
20 We did look at that just like I looked at the
21 spontaneous losses and we couldn't see any

1 discernible pattern. In fact on one of the
2 gastroschisis is a little bit later in the first
3 trimester and omphalocele which is supposed to
4 be very early in gestation that that, if you
5 will, the insult were to happen, on one of the
6 cases I was involved in, I forgot this is a
7 syndrome of the other one, was vaccinated after
8 you would think the insult might have occurred.
9 I can't say very much about the timing. There's
10 no pattern of the timing that we can see in
11 those 5.

12 DR. KILPATRICK: Are there other
13 comments?

14 DR. SHAMPOO: At what level the
15 decision was made that we will not vaccinate
16 pregnant women, period? Because what if she was
17 pregnant and she said, "yeah, I weigh the risks
18 and I'm willing to take the vaccine."

19 PRESIDENT OSTROFF: That's the
20 currently DoD policy regarding vaccinating
21 pregnant women?

1 COMMANDER RYAN: I don't want to
2 speak for more than I know, but I believe the
3 current policy is if the woman's pregnancy she
4 cannot opt to get vaccine just like she cannot
5 opt to get deployed. So in the military that's
6 not an option right now in a non-emergency
7 condition. I couldn't answer that if the world
8 changed and I couldn't answer it for civilians
9 who might have a different setting.

10 DR. GIBSON: This is Roger Gibson.
11 I don't want to go too far out on the limb
12 either here, because I've only been tangentially
13 involved with this process for the last little
14 while. We thought with the package insert and
15 the package insert is do not use on pregnant
16 women. So since that's the case if they are
17 pregnant and we know they're pregnant we do not
18 immunize them. We don't offer it.

19 COMMANDER RYAN: In New York City
20 when they intentionally vaccinated the pregnant
21 during the outbreak, and it was known at that

1 time that it could cause fetal vaccinia in
2 infants, so is there an emergency condition that
3 the risk outweighs the benefit. So, yes, even
4 if that insert kind of puts that little caveat
5 on it, but I think we have to all agree that
6 there was a really eminent exposure to real
7 smallpox.

8 MEMBER: There's one more piece to
9 that. If these women are pregnant they're not
10 eligible to deploy. If they're not eligible
11 we're not vaccinating non-deployed individuals
12 except for very special first responder groups.

13 PRESIDENT OSTROFF: I'd like to
14 make one other comment and I wonder if any of
15 the other board members would like to comment
16 about the issue of the healthy babies and
17 testing the healthy babies and I laud you for
18 trying to get as much information as you
19 possibly can related to this particular issue.
20 But I have a little bit of concern especially
21 knowing that the reliability of some of the

1 diagnostics that you're potentially end up with
2 exactly the dilemma that you ended up in because
3 I don't know what to make of that result.

4 And, I personally find it a little
5 difficult to believe and I think that if at
6 least from my perspective I wouldn't do too much
7 of that and I don't know if anybody else has any
8 comments about that.

9 DR. POLAND: Greg Poland and I
10 would concur unless you have an assay that's
11 100% sensitive and specific that you will
12 inherently end up in this terrible gray zone.
13 And I wonder if John had a sort of intellectual
14 interest in that in having done 5 of them I'm
15 not sure it's worth doing any more.

16 COMMANDER RYAN: I'm really value
17 this discussion because we're right now
18 struggling with whether or not to — we have a
19 few engaged providers that would be very willing
20 to talk to their patients to try to get a really
21 good of informed consent and to talk to one

1 about testing healthy babies cord blood, but I
2 don't know whether again if we're adding to our
3 knowledge of vaccinia or we're confusing
4 ourselves more than we need to.

5 So ACIT is very interested in this
6 data and going to look at it in June at their
7 meeting with John (inaudible) who is the one who
8 challenged us with trying to get that. CDC —
9 what do my CDC colleagues say, because we want
10 to do what is right, we certainly don't want to
11 do something just because we can, we're in the
12 military and we'll just go out there and...

13 MR. PARKINSON: Mike Parkinson.
14 As a general rule I always put on my white coat
15 again which I haven't done in a little while,
16 but when you do a test it is different whether
17 it comes out positive or negative. So I ask
18 myself this and I can't get beyond it. The
19 second question I wrote down here as you were
20 presenting was case definition — anytime we get
21 in the middle of a study and we start doing

1 things we didn't think of at the very beginning
2 it is another just potential — as I look back
3 on both counts in my own little world it just
4 raises a few flags that if you can trace in a
5 (inaudible)

6 PRESIDENT OSTROFF: Thanks very
7 much. I think what we'll do at this point is
8 close this session. I'd like to really
9 compliment Commander Ryan.

10 (APPLAUSE)

11 PRESIDENT OSTROFF: From my
12 perspective, again it's just my perspective I'm
13 relatively satisfied that the department is
14 doing everything they possibly can to minimize
15 the number of pregnancies that are inadvertently
16 vaccinated and this is a very different type of
17 presentation than we heard a couple of years ago
18 when we had lots of concerns about women being
19 vaccinated. So I'd like to congratulate all the
20 services in their sincere efforts in the
21 screening.

1 What we'll do at this point is why
2 don't we take — it's a long afternoon. Why
3 don't we take a 20 minute break and then we'll
4 close the open part of the meeting and then
5 after the break the board members and then the
6 medicine liaisons will come back and then we'll
7 have a closed session where we have some open
8 discussion.

9 So I thank everyone for their
10 attention and let's try to be back at twenty-
11 five after four.

12 MR. KILPATRICK: Meeting starts
13 tomorrow at 8:00 right here in this room.

14 (Whereupon, meeting adjourned at
15 4:25 p.m.)

16
17
18
19
20

1
2
3
4
5
6
7
8
9

CERTIFICATION OF COURT REPORTER

I, Donna Kay Evans, the court reporter,
do hereby certify that the testimony appearing
in the foregoing was transcribed by me, and that
said is a true record of the testimony given to
the best of my ability.

Donna Evan