U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE

BLOOD SAFETY AND AVAILABILITY

TWENTY-EIGHTH MEETING

VOLUME I

Thursday, January 5, 2006

9:05 a.m.

Salon I and II
Marriott Crystal Gateway
1700 Jeff Davis Highway
Arlington, Virginia 22202

P A R T I C I P A N T S

COMMITTEE MEMBERS PRESENT:

Arthur Bracey, M.D., Chairman

Judy Angelbeck, Ph.D.
Julie Birkhofer
M. Gregg Bloche, M.D., J.D.
William Duffell, Jr.
Karen Lipton, J.D.
David Matyas, J.D.
Glenn Pierce, M.D., Ph.D.
Glenn Ramsey, M.D.
Susan Roseff, M.D.
G. Gerald Sandler, M.D.
Merlyn H. Sayers, M.D., Ph.D.
Linda Thomas
John Walsh
Wing Yen Wong, M.D.

Jerry A. Holmberg, Ph.D., Executive Secretary

James S. Bowman, III, M.D., CMS
Jay S. Epstein, M.D., FDA
Matthew Kuehnert, M.D., CDC
CDR Michael Libby, Department of Defense

COMMITTEE MEMBERS ABSENT:

Harvey Klein, M.D., NIH
John McGuire
Gargi Pahuja, J.D., M.P.H.
Pearl Toy, M.D.

C O N T E N T S

C O N T E N T S (cont.)

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P R O C E E D I N G S

DR. HOLMBERG: We're still missing some of our committee members and they should be here shortly. I do want to welcome everyone to the Twenty-Eighth Meeting of the Advisory Committee for Blood Safety and Availability. This is the Secretary's Advisory Committee. This is the 28th meeting of this committee, and I do apologize to some of our commuters. I was told that this was the Pentagon City Metro stop, and it is not the Pentagon City Metro stop, so I apologize for that. This is the Crystal City Metro stop, and if you notice, there are two Marriotts. Crystal City is on the left and Gateway is on the right.

So hopefully we will not have this confusion next time because we will be meeting here for the next two meetings, and I would appreciate some comments as far as the accommodations and how you feel this works out for availability around the city.

I would like to call the meeting to order. We have a lot to discuss today, and we've made some

great headway over the last year or couple years, actually since the inception of this committee, and for some of the new committee members who I will be introducing in a few minutes, I would like to encourage them to look into this history of this committee.

The committee was established as the result of an IOM report, IOM report on the Introduction of HIV Into the Blood Supply, and how could we ensure the safety and availability of our blood and blood products.

Just a little housekeeping for today. The restrooms are off to the, as you go out the door, they're off the right. Also, if you're speaking, please speak into the microphone; make sure your microphone is on. There can only be three microphones on at one time, so when you're finished talking, if you'll please push the button and turn your microphone off.

There are some comments that I would like to make as far as the conflict of interest. All of you will be going through ethics training, and I am

the bearer of bad news, that tomorrow morning, the meeting will start at eight o'clock and that will be for our annual ethics meeting.

So we will not open the doors to the public until nine o'clock, but we do need to have our one hour annual ethics briefing. Some of us in the government have this done more than just a one hour session, and we've gone through quite extensive, but as people realize with a lot of the information in the news the last couple of days, ethics are very important.

I also want to encourage each member of the committee to really take their position very seriously. These are comments/issues that are being brought to you because of the Secretary and the Assistant Secretary's interest and trying to know or get a feel for the recommendations, what direction the Department of Health and Human Services should go in certain areas, and so I ask you to very carefully listen to the speakers and also to be very diligent in the recommendations that you make.

I also have to mention that we do have a cross section of academic people. We have clinical users, transfusion medicine, blood centers represented here. We also have the patient community represented here, and we have been able to increase the seats in the patient community by one this year. We've also been able to increase the representation of ethics on to the committee, and so I think that we have a very well-balanced committee that we have put together that the Secretary has put together.

Saying that, I think that it's very important to be able to come to the table with your background in place and to take that background and to be able to make intelligent comments, to ask questions that will stimulate other conversation, all in the scope of your background.

Saying that, I also--just a word of caution--that your position on the committee is not only of being a lobby. It is one of thinking and for the Secretary and coming up with recommendations. So I put that caveat out there

that all of us come to the table with a broad background of experiences, but when we look at the issues, we're looking at the issues with the public health in mind and the direction that we think is the best for the public health and the direction that the Secretary should go.

I would like to introduce our members, our new members, before I do a roll call. The newly appointed members are really newly appointed. As you just witnessed, the new members were just sworn in, and many of them got their letters yesterday overnight express. So I can tell you that the ink was barely dry when they received their letters.

This year, as far as the next few years that he has remaining on the committee, we are very privileged to have Dr. Art Bracey as our chairperson, and Art Bracey was appointed to the committee in fiscal year '05 and is scheduled to rotate off the committee at the end of fiscal year '07.

Dr. Bracey is the Medical Director of Transfusion Service at the St. Luke's Episcopal

Hospital in Houston, Texas. He obtained his medical degree from Georgetown University in 1976 and completed internal medical and anatomical pathology postgraduate training at Georgetown University Hospital.

In addition, he has postgraduate training in transfusion medicine from the National Institutes of Health. He is currently clinical associate professor of pathology at the University of Texas Medical School in Houston, and by the way, he was very pleased last night with the result of the game.

[Laughter.]

DR. HOLMBERG: He has over 30 publications and numerous abstracts. So welcome. Would you like to say a few words?

CHAIRMAN BRACEY: Well, certainly that I'm honored to begin a new level of services as chair of this august group. Around the table, there are mentors, respected colleagues, advocates of the patients that receive these components that we are charged with shepherding.

Over the course of my tenure on the committee, there is one thing that I've certainly begun to greatly appreciate, and that is the importance, as I think we've already heard, of the diverse input of all of the members of this august group.

I would be remiss if I did not acknowledge the important contributions of my predecessor, Dr. Mark Brecher. There's no question that Mark has served as a lightning rod in terms of moving the industry forward. Throughout this nation, many patients are having safer transfusions today because of his efforts, particularly, as many of you know, with respect to bacterial contamination issues.

So certainly I want to thank Mark and let him know out there that I may be seeking some counsel from him in the future, but I'd also like to thank the members of the public. It's very important to really hear the input of those individuals that are dedicated and vigilant and willing to come to participate in these sessions

and I look forward to hearing and engaging those members as well.

And then lastly, to thank our expert leadership here in terms of our staff that in essence serve as the engine that allow us to drive us in the directions that we move, so thank you.

DR. HOLMBERG: Thank you. I'm going to go down the list here. This is not in any order other than the grouping as far as their background. And from the academic community, we have Gregg Bloche, who is a lawyer and an M.D. Dr. Bloche right there.

Dr. Bloche is a professor of law at Georgetown University Law Center and Co-Director of the Georgetown-Johns Hopkins Joint Degree Program in Law and Public Health.

Dr. Bloche is a highly recognized leader in the arena of medical ethics. He is widely published on topics ranging from ethnic disparity in health care to end of life issues to obesity. He has published in both legal and medical peer-reviewed journals such as the Journal of American

Medical Association, New England Journal of Medicine and Yale Law Journal.

He has served on the Advisory Board, the ABA-AMA Joint Conference on Professionalism, and as a review consultant for NIH, AHCPR, the MacArthur Foundation, and the Annals of Internal Medicine among others. His particular view of the interrelation between medicine and ethics certainly qualifies him to serve on this committee.

Dr. Bloche, would you care to comment?

DR. BLOCHE: Just thank you very much for--first I have to learn to press the button; right?

DR. HOLMBERG: Exactly.

DR. BLOCHE: Thank you very much for the opportunity to serve and I look forward to doing the best that I can to be of help and to listen to members of the public as well as all those concerned with the issues that this committee will address.

DR. HOLMBERG: Okay. Dr. Bloche, would you just care to comment what you're doing in this period of time with the Brookings Institute?

DR. BLOCHE: I'm a visiting fellow at the Brookings Institution supported by a Guggenheim fellowship to work on a book project looking at the public purposes of medicine, working title "Hippocrates Myth," looking at the conflict that doctors and society face as we expect more and more by way public health functions, resource allocation functions, and even national security functions from the medical community, and the tensions between these various functions and the traditional notion of undivided loyalty to patients.

I'll also be working with the Brookings Institution's Health Policy Initiative. It's a new project that's getting off the ground looking at some of the health care financing dilemmas facing our country.

DR. HOLMBERG: Thank you. The next person I'd like to introduce is Dr. Glenn Ramsey, and Dr. Ramsey on my left here is Medical Director, Children's Memorial Hospital, Chicago, Illinois. Dr. Ramsey is a board certified pathologist who has devoted his entire career to transfusion medicine.

He was Chief Resident of Clinical Pathology at the University of Rochester in New York and fellow in blood banking at the University of Pittsburgh's Department of Pathology.

He is currently an associate professor of Pathology at the Northwestern University in Chicago. He has over 80 publications in peer review journals and will be a valuable asset to the committee.

Dr. Ramsey.

DR. RAMSEY: Good morning and thanks for the nice introduction. I'm also at Northwestern Memorial Hospital, just to interject that as well, and actually spend most of my time at Northwestern Memorial as well as Children's Memorial in Chicago, but anyway thanks very much, and I'm very much looking forward to working with members of the committee. I appreciate the invitation to participate. It's been a very important forum for many years as you know for our community and I'm pleased to be able to help a little bit as much as I can.

Thanks.

DR. HOLMBERG: Thank you. I'd like to introduce now David Matyas, a lawyer. He is a member of the law firm of Epstein, Becker and Green in the health care and life sciences practices in the Washington, D.C. office. He practices in the firm's third-party payment practice group which specializes in the legal and regulatory matters arising under Medicare, Medicaid and other third-party payment programs.

Mr. Matyas has served as an adjunct professor of law at the American University's Washington School of Law. He has spoken and published numerous articles on the subject of health care fraud, corporate compliance programs, the Stark law, mergers and acquisitions in the health care industry and other health-related topics.

Mr. Matyas is also a co-author of a book sponsored by the American Health Lawyers Association entitled Legal Issues in Health Care Fraud and Abuse: Navigating the Uncertainties.

Mr. Matyas.

MR. MATYAS: Actually it's Matyas.

DR. HOLMBERG: Oh, sorry.

MR. MATYAS: That's okay. I go by "hey you" as well. Thank you for including me. As a health lawyer concentrating just in health care representing a whole array of clients relevant to my experiences here are representation of drug manufacturers, distributors, pharmacies, patient advocacy groups, especially in the areas of hemophilia, IVIG, as well as other blood disorders and the like, so I'm very much looking forward to participation and being part of this.

DR. HOLMBERG: Very good. Thank you. Now for the consumer group, first, I would like to introduce Mrs. Linda Thomas. Linda is the wife of Mr. Mark Thomas, who was appointed to the committee last year, and unfortunately he passed away, but I'm sure that he's smiling down today very pleased with his wife carrying on the torch.

Ms. Thomas represents the Sickle Cell Association of Austin, which is also referred to as

the Mark Thomas Chapter. Ms. Thomas is the widow of a sickle cell victim and has a vivid and personal awareness of the effects of the disease. She is currently involved in promoting the awareness and understanding of sickle cell disease and coordinating summer camps for children and teens with sickle cell disease.

Mrs. Thomas.

MS. THOMAS: Thank you. Good morning. It is an honor to serve on such a worthy committee and I'm just grateful for the invitation to serve in the place of my husband. Thank you.

DR. HOLMBERG: Thank you. Now to the industry. The next person really does not need introduction, but I will introduce her anyway, Dr. Judy Angelbeck. Dr. Angelbeck is currently a member of the committee representing the leukoreduction filter industry per the charter. She is employed by the Pall Medical and as a Senior Vice President for New Business Development in Cell Therapy.

Dr. Angelbeck has been reappointed to

serve an extension of one year to the committee.

Dr. Angelbeck.

DR. ANGELBECK: Thank you, Jerry. I'm happy to be back and looking forward to, I hope, a productive year. Reflecting, it has been a very interesting time period to have served on the committee and add whatever I can to its work.

Thank you.

DR. HOLMBERG: Thank you, Judy. The next person, Ms. Julie Birkhofer, is the Executive Director, North American Plasma Protein Therapeutic Association in Annapolis, Maryland. Ms. Birkhofer is the individual nominated to fill the industry's representative chair designated to the Plasma Protein Therapeutic Association.

She works to assure that the plasma patients in the United States have access and full choice to all therapies on the market and is responsible for health policy agendas regarding the plasma protein therapeutic industry before Congress.

She has a long history working in

government affairs and will definitely be an asset to the committee.

Ms. Birkhofer.

MS. BIRKHOFER: Thanks, Dr. Holmberg, for your kind words. It's a pleasure to serve on such a distinguished committee. I look forward to making contributions on behalf of the public health as a member of this important committee that has played such a pivotal role over the years in assuring consumer access to life-saving blood and blood products including plasma protein therapies.

Thank you. It's a pleasure to be here.

DR. HOLMBERG: Thank you, Julie. The next person I would like to introduce is Dr. William Duffell. He's an individual nominated to the trade equipment representative's seat per the charter. Mr. Duffell, Dr. Duffell is the Director of Government Affairs and Quality Systems for Gambro BCT in Lakewood, Colorado, has over 20 years of experience in regulatory issues related to medical devices.

Dr. Duffell.

DR. DUFFELL: Thank you, Dr. Holmberg. It's a pleasure and privilege to have been appointed to the committee. I look forward to getting to know the committee members and working with you in the next three years ahead.

DR. HOLMBERG: Very good. Thank you, Bill. The next person on my list is not here today, and I understand he's very busy at the present time, so I don't know what his continuing status will be, but the Secretary has nominated or has appointed Mr. John McGuire from the American Red Cross, the Executive Vice President, Biomedical Services.

As many of you know, he is currently in an acting position leading the American Red Cross and more to come later.

The last person I'd like to introduce really does not need an introduction. He's probably one of the most colorful people on the committee and--I can say that, can't I--

[Laughter.]

DR. HOLMBERG: That's Dr. Jerry Sandler.

He is being reappointed to serve an extension of two years. He is a current member of the committee representing the American Hospital Association and is renominated by the trade association.

Dr. Sandler is Medical Director of Transfusion Service at the Georgetown University Hospital.

Dr. Sandler.

DR. SANDLER: I don't get a light.

DR. HOLMBERG: I made you speechless?

DR. SANDLER: The good news is that there's been some wonderful advancements in blood safety during the time of tenure of this committee. The bad news is that reimbursement to hospitals hasn't kept pace with the advancements in the costs. The gap means that hospitals like mine have paid for the increases in blood safety.

I represent the American Hospital Association on this committee and one of my goals is to see that that gap is as narrow as possible. Thank you, Mr. Chairman.

DR. HOLMBERG: Okay. Well, welcome aboard

and--oh, Glenn. How did I overlook--thank you. I apologize. I was going down the list and I think the last time that I did something like this, I blamed it on one contact. I recently got another contact and sometimes with the lights, it really does a halo effect on me, and I apologize.

Another representative of the consumer group is Dr. Glenn Pierce who holds an M.D. and a Ph.D. Dr. Pierce was nominated by the National Hemophilia Foundation. He's the medical researcher who also has a bleeding disorder and related complications associated with hemophilia.

He obtained his Ph.D. and M.D. at Case Western Reserve University. Dr. Pierce has served on the National Hemophilia Foundation Medical and Scientific Advisory Committee and the Blood Safety Working Group. He's published over 65 peer-reviewed publications and we're pleased to have you join us.

Would you care to say something?

DR. PIERCE: Thank you, Dr. Holmberg. I really appreciate the invitation to join the

committee. I was very involved as the president of the NHF when the IOM report was called for over ten years ago, and have watched the genesis of this committee as well as other improvements in the blood supply that make it safer for all individuals in this country to use blood products and am honored to serve over the next couple of years on this committee.

Thank you.

DR. HOLMBERG: Thank you, Dr. Pierce. Now, I'll do a roll call. Dr. Angelbeck?

DR. ANGELBECK: Here.

DR. HOLMBERG: Ms. Birkhofer.

MS. BIRKHOFER: Present.

DR. HOLMBERG: Dr. Bracey.

CHAIRMAN BRACEY: Present.

DR. HOLMBERG: Dr. Bloche.

DR. BLOCHE: Present.

DR. HOLMBERG: Jack McGuire is absent. Karen Shoos Lipton.

MS. LIPTON: Present.

DR. HOLMBERG: Mr. Matyas.

MR. MATYAS: Present.

DR. HOLMBERG: Dr. Ramsey.

DR. RAMSEY: Here.

DR. HOLMBERG: Dr. Roseff?

DR. ROSEFF: Here.

DR. HOLMBERG: Dr. Sandler.

DR. SANDLER: Present.

DR. HOLMBERG: Dr. Sayers.

DR. SAYERS: Here.

DR. HOLMBERG: Ms. Gargi Pahuja is absent. Dr. Pierce.

DR. PIERCE: Here.

DR. HOLMBERG: Ms. Thomas.

MS. THOMAS: Present.

DR. HOLMBERG: Dr. Toy was not able to join us. Mr. Walsh.

MR. WALSH: Here.

DR. HOLMBERG: Dr. Wong.

DR. WONG: Here.

DR. HOLMBERG: Dr. Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Where is that voice? Okay.

Dr. Epstein.

DR. EPSTEIN: Here.

DR. HOLMBERG: Dr. Klein could not join us. Dr. Kuehnert.

DR. KUEHNERT: Here.

DR. HOLMBERG: And Commander Libby.

CDR LIBBY: Here.

DR. HOLMBERG: Very good. I would like to take the opportunity now to go through a little bit of what the committee has addressed over the last year, sort of as an introduction to some of our discussions today, and hopefully shortly thereafter we will have Dr. Beato joining us for a few words.

So excuse me for a minute as I go to the podium. As some of you who have been on the committee for a period of time can reflect over the last year or last couple of years, we really have addressed numerous issues, especially with the bacterial contamination or the bacterial detection in platelets, and in January of last year, the committee recommended that HHS Secretary request the cooperation of appropriate agencies with blood

organizations and transfusion facilities to establish an ongoing program to monitor residual bacterial contamination risks and generate summary reports, provide resources for surveillance of transfusion associated sepsis, and make such additional recommendations as may be needed to maintain recipient safety.

As far as nuts and bolts, what has happened out of this recommendation, it really has been the result of some stimulus of further discussions in later meetings, and I would have to say that although we have nothing tangible at the present time as far as a surveillance system and reports, there is some definite progress being made as far as what was our strategic plan for the upcoming years as far as surveillance is concerned, and we will continue to monitor and to report back on the progress of this recommendation.

Also in January of last year, there was quite an extensive recommendation that went forward on the reimbursement of plasma-derived products and their recombinant analogues. The committee

endorses the following principles to guide such efforts:

Plasma-derived products and their recombinant analogues should be reimbursed at rates consistent with true costs including costs of distribution and administration.

Reimbursement should be sufficient to ensure an adequate supply of these therapies.

Individual products within product classes should be recognized as therapeutically unique.

Equivalent reimbursement should be provided in different care settings.

The life-long cost of treatment to individual patients should be addressed in any pricing structure including the extraordinary impact of copays.

The committee urges the Secretary of Health and Human Services to support any proposed policies and/or legislation to address the extraordinary financial burden of these patients.

Once again, I can't directly say that there is something tangible other than we have made

our voice known to the agency of the Centers for Medicare and Medicaid Services, and I think that one of the advances that really took place was the addition of add-on costs for this next year, although some people may argue whether that is sufficient enough.

However, there are certain things that the Department is under constraint, and that is basically the MMA mandated by Congress, but we can continue to work on this, and when Dr. Beato arrives, I'm sure she'll say a few more things about the reimbursement issues.

In the May meeting, the recommendation was that since our prior recommendation of January 2005, there is a worsening crisis in the availability of access to IGIV products that is affecting and placing patients' lives at risk. Changes in reimbursement of IGIV products under MMA since January of 2005 have resulted in shortfalls in the reimbursement of IGIV products and their administration. Intermediate interventions are needed to protect patients' lives and health.

The committee recommended that the Secretary declare a public health emergency so as to enable CMS to apply alternate mechanisms for determination of their reimbursement schedules for IGIV products and otherwise to assist CMS to identify effective short and long-term solutions to the problems of availability of and access to IGIV products in all settings.

As far as something to report to you today, I would like to hold off on Dr. Beato's comments, that she will express later, as far as some of the results of our efforts within the department and working with the agencies, but once again I think that the biggest issue with the reimbursement of IGIV has been the understanding of the complexity of the problem and I think we are making some headway there and looking at some of the ways that additional add-on charges can be reimbursed.

In September, a strategic plan was put together or principles of a strategic plan for increasing safety and availability of blood

products and their analogues. This plan should include a review of the process of policy and decision-making for blood issues and its integration into the broader public health policymaking.

Such a plan should encompass structured process for policy and decision-making, integration of the blood system within the public health infrastructure, surveillance of adverse events related to blood donations and transfusion, risk communication, error prevention in blood collection centers, transfusion services and clinical transfusion settings, donor recruitment and retention, clinical practice standards for transfusion, strategic research agendas, disease planning, stable and sustainable reimbursement, funding for promising new technologies.

Within the department we are working on this. As far as strategic plan, I am in hopes that in May, we will be able to bring you a little bit clearer report. We are working right now, as far as trying to get working groups together within the

agencies, to put a plan together on these various issues and what you recommended in September is really the framework in which we are assembling the working group and how would we put together this strategic plan.

In September also, there was a recommendation to the Secretary to take immediate steps to increase reimbursement for non-hospital IGIV therapy to a level consistent with current market pricing, to reconsider reclassification of the IGIV as a biological response modifier, consider declaring a public health emergency to address the short-term problem, modify the current plan to challenge hospital outpatient reimbursement to ASP plus eight percent in January 2006 in such a way as to prevent any sudden or large decrease in reimbursement, to reexamine whether the current IGIV supplies are meeting patient needs, to work with Congress to establish a long-term stable and sustainable reimbursement structure.

Since these are recommendations from the September meeting, once again I just want to

present these to you. I think that when Dr. Beato gets here, she will address these in much more detail and give you an explanation of some of the activities that have taken place.

To let you know, we have, just very briefly, we have contacted each one of the manufacturers. The manufacturers have established emergency inventory levels, and also the manufacturers have established 800 numbers. We have an 800 number established at the Medicare number. The Medicare 1-800 number has a script. We constantly have to go back and refine that script based on some of the complaints with it, but we are continuing to work on that.

I have to say that the last three months other than the month of November, there was a green status for the availability of the product, but what we're also uncovering as we do more and more evaluation of the problem is that there are still multiple levels that we are identifying such as the distributors and the group purchasing organizations and the allocations that they have put on the

various hospitals and how changing some of those allocations affects the individual hospitals.

Also, some of the reimbursement of the special needs areas have also been identified. All of this to say that one of the biggest things that has taken place at the present time is that there is an IG evaluation report that is going back to Congress. They are surveying. They have surveyed and talked to the manufacturers. They have various steps in process of their further evaluation and looking at some of the problems associated with the current structure.

Once these are put out in a report, we're in hopes that this will be the evidence, the data, to be able to support any decision that Congress may make.

That's basically an overview of what we have done in the last year. I'm pleased to say that I think the results of the previous year--we're starting to see the ripple effects as far as the bacterial contamination of platelets or the bacterial detection in platelets, and we have seen

a movement towards the various companies' willingness to be able to go forward with seven day platelet product. And so there is some great progress there, but I think the emphasis primarily last year was where are we going in the future, what we need to do as far as our total overall surveillance and looking at the emerging infectious diseases or adverse clinical outcomes of transfusion and even as far as it relates to transplantation.

Just with that comment of transplantation, I have invited as special guests to the meeting today Dr. Whitten from CBER. Dr. Whitten, if you'd like to stand up, and would you like to go to the mike and introduce yourself and what your office does? Yes.

DR. WHITTEN: Okay. I'm Dr. Celia Whitten. I'm the Office Director for the Office of Cell, Gene and Tissue Therapy at the Center for Biologic Evaluation and Research, and our office is charged with implementing the tissue program for safety of human tissues.

DR. HOLMBERG: Thank you and thank you for joining us. And I also invited HRSA to be with us, Dr. Burdick and Dr. St. Martin, but I don't see them here at the present time. Is there anybody representing that office in HRSA? They will probably be here a little bit later.

What I do want to do is go through a little bit as far as the agenda for the next couple days. As I said, Dr. Beato is expected to join us very soon, and as you can see here, my slide still reflects that she is Acting Assistant Secretary for Health. Her title today is the Principal Deputy Assistant Secretary for Health. Dr. Agwunobi was sworn in yesterday morning, and so the agendas do not reflect that change.

Later on, we will have discussion on the global epidemic and pandemic surveillance. We'll be looking at some of the transmission and clinical detection of pandemic flu and vaccine preparation by Dr. Goodman and also pandemic vaccine and antiviral strategies and also the HHS strategic plan by Dr. Schwartz. And then we'll also have in

the afternoon discussion on state and local preparedness for an influenza pandemic.

CHAIRMAN BRACEY: Excuse me, Jerry. There was a request if we could have a brief question or two on your presentation?

DR. HOLMBERG: Sure, sure. Let me just finish this up and then I'll go back to the questions.

We're going to also be looking at the risk communication and then also the gaps in our knowledge of pandemic influenza, and then on the second day we will be looking at the blood community's preparedness and also some studies that are currently in process for influenza viremia in blood donors, and then also looking at the various models that are potential for us to look at the potential effects of the pandemic influenza in the blood community.

I'll stop right there before I go through the questions of what I would like the committee to consider over the next couple of days and go back to some of the questions that people may have.

CHAIRMAN BRACEY: I believe that Merlyn has a question.

DR. SAYERS: Dr. Bracey, thanks. Dr. Holmberg, as far as the recommendations are concerned, those of us that have been on the committee for some time know that they reflect an earnest effort and diligent attention to detail. I mean some of them even survived the wordsmithing of the "colorful" Dr. Sandler.

I'm just wondering, they risk atrophy if they're not revisited, and what are the opportunities for us to reflect on where they might have led and request a review of what the outcomes might have been, what the obstacles to progress remain?

DR. HOLMBERG: Well, we can do that, and this is one of the reasons why I wanted to present them today was for you to be able to reflect on the last year's activities. One of the things that is difficult within government is to see progress, and you know sometimes progress is extremely slow, but I think that it is good and I think it is very

beneficial for us to be able to go back and to reevaluate the recommendations and the progress that were made on these.

If there is a suggestion as far as how you would like to do that, I'm open to hear that.

DR. SAYERS: Well, could we possibly get a report on outcomes?

DR. HOLMBERG: Yes. And that's basically I was waiting for Dr. Beato to give her presentation, her talk to you this morning, for some of that report, but definitely at the next meeting, I will have for you the breakdown as far as the progress that we have made and some of the gaps.

CHAIRMAN BRACEY: Question and comment from Karen.

MS. LIPTON: Yes, Jerry. One of the questions I have specifically relates to the strategic plan, and I understand that something that will be brought back to this committee in May, but one of the issues that I think we deliberated the last time was really making sure that there

were some sort of public, an ability for the public to be involved in that, and also that there was some role for this committee in developing the strategic plan.

And I don't know if it's premature to ask, but it concerns me a little bit that suddenly this activity is going on, but we as a committee aren't involved in it or don't know how this is going to progress.

Is there something you can tell us about that?

DR. HOLMBERG: Yes. Along with the agencies working on the various committees, the working committees, it is the intent to be able to bring in various people, special government employees, that are sitting around the table, to be part of that working group, to bring in the knowledge and to bring something back to the overall committee.

So it is the intent to have the actual committee members be part of the working groups. What we also have is that we will have a steering

committee that will be at a higher level to look at the various, where the overall project is going, and I anticipate that the new chair will be part of that steering committee along with the various directors of the various agencies or their designees.

CHAIRMAN BRACEY: As chair, one thing I think that would be important, getting back to what Merlyn commented upon, would be to develop a tracking mechanism so that we can monitor the progress and that progress will be revisited at each meeting of this committee. So I will work with the staff on that.

DR. HOLMBERG: Are there any other comments? Well, let me go forward on some of the issues and questions that I would like you to consider over the next couple of days. And again, these are not carved in stone, but they are just basically to get you to think, and if there are other questions that arise, I would greatly appreciate hearing those questions and having some discussion revolve around those questions.

As you know, the primary emphasis of today's meeting is the pandemic influenza, the potential pandemic influenza, and what effect that might have on the blood and blood product community as well as transplantation of blood organ tissues, progenitor cells, and where we need to go as a department.

So I would like you to look at, and you do have a copy of this. The copy that you have is really of the e-mail that I sent you ahead of time.

What strategies should be considered by the Department of Health and Human Services to help prepare the blood system for a possible flu pandemic? Approach to immunization of blood center staff; encouraging immunization of regular repeat donors; supply monitoring and managing during an outbreak.

Also, how can DHHS help to resolve the present scientific uncertainties underlying a potential need for donor deferrals?

Some of the issues there are characterization of viremia during infection with

influenza; the value of deferral for clinical exposure and/or of the use of Tamiflu or any of the antivirals; and the potential for a falsely positive donor screening test following either influenza infection or vaccination.

What new approaches to communication between public health and the blood, organ and tissue communities would be helpful in order to enhance preparedness?

What would be the most efficient interface with global and domestic influenza surveillance data? The communication links between collection centers, transfusion facilities and local/state public health. And also the possibility of communication between blood, organ and tissue communities.

What surveillance methods are needed for blood and plasma recipients in order to detect transfusion-associated transmission of pandemic influenza?

The need for enhanced adverse reaction reporting; testing/evaluation of frequently

transfused patients; and surveillance, evaluation of vaccines or antiviral prophylaxis.

So over the next couple days, you'll have those questions in front of you. I would like you to consider those as we have the presentations and I think that with the way that the meeting has been set up, that there will be ample time to have deliberation on these issues.

Dr. Beato still hasn't arrived yet, so if we can, I'll just move on to our first speaker, Dr. Chu.

CHAIRMAN BRACEY: I will introduce Dr. Chu to the group. Dr. Chu is a health scientist with the Centers for Disease Control and Prevention. She obtained her degree in microbiology and public health from Michigan State University and a Ph.D. in biomedical sciences at the John A. Burns School of Medicine at the University of Hawaii at Manoa.

Dr. Chu is currently assigned as Technical Officer, Emerging and Dangerous Pathogens Alert and Response Operations for the Department of Communicable Disease Surveillance and Response at

the WHO Headquarters in Geneva, and she's just come in from a long flight and is brightly alert and awake.

The topic of her talk will be "Global Epidemic and Pandemic Surveillance and Response System."

Thank you.

DR. CHU: Thank you for the introduction and I thank you for the invitation to speak with you. I'm going to be going over a fairly global view of issues being handled at the World Health Organization, and it is good afternoon, isn't it, for me?

But let's hope that this generates some thoughts and some questions, and I'll be happy to answer them after this.

At the World Health Organization, and many of you know of the World Health Organization's operations, I just thought I'd give you a little background as to what we do and what we are governed by at this time, and this is the briefing, and it is prepared by what we call the Epidemic and

Pandemic Alert and Response Operations.

This is actually a new name for us, changed recently in August of 2005. And this is a quick view. I know it's very busy so those of you in the back don't worry, I just want to kind of give you an overview of what it is that is at WHO and this is the building in Geneva and we're led by a Director General. Under the Director General, there are 12 different clusters, and under this cluster comes Communicable Diseases, which is where we work in for Alert and Response Operations.

And the blood banking and other efforts are actually under Health Technical and Pharmaceutical. So we're actually two different clusters, but what we do is we hope that we have good links and communication.

And this is again a very busy slide. I don't want you to get too worried about it. This is from October 2005. Reorganization happens at every institution at every level. Our Cluster Director is Dr. Margaret Chan, and she heads the various activities for surveillance in communicable

diseases and response.

She's also designated as a Special Representative to the Director General for Pandemic Flu Preparedness.

If you would just kind of stretch your eye down to this site here, this is where the Epidemic and Pandemic Alert Response is, and it is headed by Dr. Mark Ryan. Some of you may know him. He's a fiery Irishman, and a wonderful person to work with, and underneath that, we have the National Preparedness programs, and we have the--sorry--I think I'm just going a little too fast here--looking for the arrow--and the Global Influenza Program is actually that little box that you might see here, and then underneath that, on the far left side, is Alert Response Operations.

The group that I actually work in is called Emerging and Dangerous Pathogens, and it's just sort of a name, and the reorganization is coming, and this is a new reorganization for the Epidemic and Pandemic Alert Response, and that we have the office in which we have a platform here in

this box, and this is actually just a platform that allows us to go out anywhere in the world within 24 hours when a decision is made, and that goes with the airplanes, trains, and whatever else you might need.

And underneath that, then, is the group we're in that soon is reorganized into Dangerous Pathogens and Bio-risk Reduction, and we're horizontally organized with the Global Influenza Program, which I'll talk about a little bit more.

And within the Global Influenza Program, we've recently been enhanced in services because of pandemic issues by Dr. Kaji Fukuda and Dr. Mike Perdue, both from CDC, and so we are fairly well imbedded into the system there.

What I want to go over quickly is a few slides on the international health regulations because that impacts how we operate at the global level. The WHO Assembly is the board of directors, if you will, and it consists of the 192 countries' ministries of health, and that is the Secretary Mike Leavitt is the representative for the U.S.,

and they meet once a year and decide.

WHO is essentially authority that has no teeth and essentially does everything by voluntary subscription and guidelines. The regulations is the only thing we have that has some legal status for us to operate from. And what it is is that this is revised from 1999 when only plague, cholera and yellow fever were to be notified.

It is now fairly enhanced in scope, in focal points and obligations and recommendations. For instance, the 1999--sorry, I'm misspeaking--it's the 1969 regulations previously would not have allowed us to identify SARS, pandemic flu or any of the other diseases because it was only three disease specific.

And so with the time frame that was adopted in 2005, there's actually five years before the full capacity of the regulations will be enforced, and that is probably too long in advance for pandemic flu.

In 2007, countries are supposed to begin to voluntarily comply with the IHR, and in between

this time, countries may select to join and enforce the rules, but it is very difficult because it's very resource demanding.

And what we have now is in the May 2005 version adopted by the World Health Assembly is that there is Annex 1 that defines national core capacity for surveillance. 192 countries. The variation is great. Annex 2 gives you a decision-tree as to what to call a public health emergency of international concern, and that is where pandemic flu will fall in and where some of the outbreaks will fall in. And the two years to prepare for this is going to be a challenging one for WHO at this time.

The third red bullet I want to talk about is that each of the member states under the new IHR has to designate a focal point, and that focal point is the entree into the country legally to find information about outbreaks. This has impact on how we detect internationally cases of pandemic flu. It is very critical at this point that this is not yet operational. So we're sort of in a gray

zone at this time.

Following that, the bottom four bullets just explains a little bit about how the expert panels and review panels and internationally emergency periods are identified and codified in these regulations which were not done before and also allows the intervention of WHO at the request of other member states who are concerned of international spread of disease, and they can activate these panels for asking countries to provide correct information, which also WHO did not have the capacity to do before.

So for epidemic and pandemic control then requires really very strong national public health systems and capacity. It requires that we have very specific preparedness plans as you are doing today and tomorrow to look at particular issues, and that for the global view is that the international system has to be a partnership, has to be coordinated, and has to be an advocacy role rather than a punitive role.

Just to remind you briefly is that the

annual influenza outbreaks alone take about half a million deaths worldwide--sorry--in developed countries alone. And in developing countries, that number is much greater; we actually don't know because we lack the surveillance and the capacity to do so in developing countries. So the impact of pandemic flu, if it happens worldwide, is great. And at the moment, it is almost very tough problem to get your hands around.

So the implications of influenza pandemic is that we certainly believe that it will affect medical services and essential disease control functions, and we will also feel that equally other public sectors in the community, the continuance of operations will be affected, that the social and political disruption will be great.

You know, equitabilty of Tamiflu distribution, who gets vaccines, is an issue. I think you'll be discussing some of the blood banking and transfusion issues, and then also the economic loss is great, and that probably is what hits home with most of the countries and member

states throughout the world and the health consequences of controlling this and confidence in the public health system is very, very important to consider.

Some of the slides I'm showing are already outdated. This is from November 2005. At that time, there were already 12 countries affected with avian influenza. Mind you right, we have avian influenza, not pandemic flu, but the avian influenza has the possibility of becoming adapted to a pandemic, but at the moment, this has not happened. But the fact is that the H5N1 is of high concern because the fatality rate of persons who have been infected with H5N1 is high, and the virus causes a very disseminated disease, this H5N1, in multiple organ system failure, and it's more than--I believe it's around 54 percent fatality rate at this time, and most of the cases occur in non-previously suspected influenza high-susceptible groups, and that is they're in healthy individuals, children and young adults.

And that H5 has not circulated widely

among humans, so therefore the cohort immunity against this virus is very low in the world.

This is as of December 30, and you see on the far right side on the red, and let me just show you the red bars on the far right side over here, this includes what's happening in China at this time. And China is, as many of you know, is usually where virus strains appear, and it is a large country. It's diverse; it's complex. And the information from there comes in in a way that sometimes is difficult to verify till long after. So for us early detection just means that events happen, but we want to try to intervene as early as possible, and sometimes that is after the fact.

So it's not just--so those are issues that we are trying to handle as far as communications go, and that there are 137 cases with 70 deaths. Now, as of this morning, there are some reported cases in Turkey and that is being verified right now in London at the WHO Collaborating Center, but it certainly does look like that there is a small cluster of cases in Turkey that needs to be

verified.

The World Health Organization then has a--this is a box down here. I'm sorry it's not large enough. I should have made it larger, but the box with the circle is that in the pandemic plan there are different phases that we take a look at, and right now the phase is at what is circled there on sort of the bottom right hand side, and that is really in the pandemic alert phase, and that is no or very limited human-to-human transmission is occurring, and this is the stage.

And as clusters break out and events happen in a more larger and potential spread situation, that we will start going through the various different stages. I think some of you have seen similar types of things like this for bioterrorism alertness and others, but that is we're at the Pandemic Level 3.

So what is the capacity at WHO to do some of this work? We have a daily morning intelligence and verification meeting every morning at nine o'clock. Every epidemic report and rumor is looked

at, and the team takes a look and asks various questions. We have a network of WHO regional and country offices who also provide information, and there is a group called the Global Outbreak and Response Network, called GOARN, and this is a voluntary 120 institutions around the world, many of them--12 of them are located in the United States, for instance--who provide expertise.

WHO is an administrative secretariat. We don't have laboratories; we don't have facilities. So depend on these partners to help us, and that we have very specific disease networks called the collaborating centers, and these work, for instance, for SARS, influenza, and they make guidelines and manuals and the operate in an interactive way, and that about to launch is the Global Laboratory Network Directory so that people can understand where the assets are for these things.

Every morning then we have this event management process. On the right-hand side, you will see that it's called informal and that is the

Global Outbreak Response Network, media, news and other things; information comes in that way.

Then we have the formal reports from countries and regional offices. In initial screening everyday, our officers screen several thousand bits of information, and then we would do the event verification, risk assessment as to whether this poses a risk for response, and then we develop a strategy, and below that, the boxes you see are all the elements that go into the response strategy. It is not just getting out to the field. It's getting all the elements in place of which there are many.

If you can see from the back, there's lots of little dots all over the place, mostly centered in Africa, sub-Saharan Africa. These are the events we've responded to that is outbreak response since 2001, about 900. You see that it is distributed and concentrated really in resource-poor areas of the world, and so there is a disparity, and knowledge and information tends to be very challenging to get to those sites.

And that the Global Surveillance System for human influenza consists of four international WHO collaborating centers in Melbourne, in Tokyo, in London and in Atlanta, and these are the four international reference centers for which they set the standards for global human influenza and verification. They also do animal influenza verification, but in a less concerted way because they partner up with the Department of Agriculture.

As you see, there's a National Influenza Center Network throughout the world, the light blue. I think it shows up as gray, so maybe I'll have to show you that in countries of importance like China and other places, we actually only have one national center. In sub-Saharan Africa and Africa there's hardly any, and then within the United States, there's a national network. Throughout Europe and Russia, there's national networks, and in Australia the national networks.

So the information comes in, as I say, sometimes in a challenging way, but the annual output of this group, essentially they look at

something like 250,000 samples a year. They look at 40,000 isolates and they characterize up to about 10,000 viruses looking for--I think perhaps the next speaker will describe a little bit--for mutations and genetic changes and pathogenicity.

So the key strategies for us is really at this time is somewhat operational. You have to reduce the human exposure to H5N1 because it's not common in humans. We have to strengthen the early warning system. I've pointed out some of the issues. We have to intensify rapid containment operations and that is put teams on the ground as soon as an outbreak is happening.

For instance, at the moment, there are teams mobilized to go to Turkey to investigate this reported outbreak, and then build the capacity within countries to deal with the pandemic and to coordinate the global science and research and to accelerate vaccine development and expansion of production because that's always an issue.

And so these are some of the things that we want to do. The national-regional-global system

has to have very sensitive detection systems, rapid laboratory confirmation, because so much depends on that. We have to have real time risk assessment and immediate communications, and that the rapid field investigation and contact, tracing, monitoring, I think will be discussed a little bit later.

Develop stringent infection control in hospitals and places where people are exposed and to intervene using international stockpile. If we can get some agreements to that, and that the capacity to build has to be up front, which means a lot of money and time, and that the coordination needs to be done properly.

So these are some of the things that we've been doing there, and on the very bottom there is called the Strategic Health Operation Center. It's called a SHOC, and that is really where most of the information comes in and gets triaged, and that the WHO uses quite a bit its regional offices, those at the hubs in the bright blue, and then they have sub-offices throughout the region in the red,

smaller red dots, and those are really the people who are the front-line information and fighters for various outbreaks, and that there are National Pandemic Preparedness Plans published by WHO which is available on the Web.

And that what we have to do is to really make sure that the information coming in is decent information and have good risk assessment and rapid response and tracking.

The main thing right now in Europe and in the areas where H5N1 in human is crossing the line between animals and humans is to look at all these areas and try to block the transmission. That is really the best effort. It's really a fire-fighting effort, but if it goes global, it would be very difficult to contain that fire.

And so, again, the key strategic actions we're considering is reducing the human exposure, strengthen early warning systems, rapid containment capacity and to coordinate the development of good science-based products to use to mitigate the impact of pandemic influenza, and with that, thank

you very much, and I'll take some questions if you have them.

CHAIRMAN BRACEY: Dr. Sayers.

DR. SAYERS: Thanks. As far as H5N1 is concerned, that 70 deaths and 137 cases sounds just awful, but is there any likelihood that there are individuals who are being infected with H5N1 who recover and who escape reporting?

DR. CHU: At the moment, that's a difficult question to answer because we really simply don't know. We know where H5N1 in human cases are found at this time, and it's mostly Southeast Asia and in Asia, and in those places, there are very rigorous systems put in to look for cases, but we don't really know if there is a way to capture what you're just describing, that is persons who may have been infected and recovered, and right now I would say that if you look at serology of these affected communities, we don't see apparent infections and recovery.

We see--it's at the acute stage where patients are very, very ill clinically, very ill,

and most of them require some intensive medical attention at the moment, but if and when H5N1 adapts, as many of you probably have heard, this, of course, will change the clinical picture because there is some adaptation going on, and that we cannot predict at this time what will happen.

CHAIRMAN BRACEY: Question from Dr. Bloche.

DR. BLOCHE: I have two related questions. One is is there any valid basis for estimating what the difference, if any, in the death rate might be if disease of this same severity were treated in accordance with so-called "first world" medical standards?

And then the second question is what if anything can be said validly, or at least by way of perhaps even stating an error range, with respect to the possibility that there be attenuation of disease severity once we reach the stage of person-to-person transmission since, of course, the virus has to evolve? The virus doesn't want to kill all its hosts or it can't transmit.

DR. CHU: Well, let me answer the second question first. Right now it's still avian influenza strain H5N1, and at this moment it is very easily transmitted among the birds of migratory birds and domestic birds. Humans tend to be end-stage at this time and we have one or two person-to-person transmission that's unsubstantiated scientifically, that is by laboratory tests. But we feel that that can happen.

So at this point, it's sort of a limited infection in humans. If it becomes adapted as a more human-friendly strain, we can't really predict how it's going to go. We don't know how fast it will mutate, and we don't know how--and it depends on sort of the cohort immunity, too. For those who have been immunized with the current seasonal flu, there's likely chance of mixing flu strains or being doubly infected, so that probably is reduced if you take your flu shots.

In countries where there isn't such servers available, there may be adaptation and

mixing of various strains so that the human receptors become adapted to the H5N1 virus and then that might go very quickly and very acutely.

DR. BLOCHE: But what's the implication of that? What's the implication of that for the severity of the disease? Does that--

DR. CHU: At the moment, it looks quite severe. It's more so than before, but I think overall rates will probably be like any other flu. It's just that its ability to spread will be much faster, and so in developed countries I think we'll treat the patients fine, survival will be better, but it's hard to say how that will be as well.

CHAIRMAN BRACEY: Dr. Epstein.

DR. EPSTEIN: Yes, thank you. Dr. Chu, you mentioned that there is no human exposure historically to the H5 viruses, and presumably that's a factor in the potential severity of a pandemic, and it raises the question whether there is any feasibility to H5 immunize the human population before there's ever a pandemic so as to reduce susceptibility in the human population. So

what is the thinking and how feasible is that?

DR. CHU: That's a very good question. I think that has been discussed quite a bit and especially at NIAID, there is a H5N1 virus that's going to go into field--I think going to phase one and phase two trial very shortly, and I think maybe Dr. Goodman or somebody else might answer that better as to the prognosis.

The thought is that if we have a H5N1 vaccine that can be used as a preemptive strike, it can be used, but used in a proper way where if there is outbreaks, to really cover them much like the smallpox vaccine strategy, to cover that cohort cover so that it doesn't spread beyond that, and for those who may be front-line at risk of being exposed, the health care workers and others, may want to be immunized with that vaccine.

CHAIRMAN BRACEY: One of the key principles in terms of the safety net is the development of robust core surveillance, which requires resources. I noted in some of the reading of the materials that we sent, there's a certain

economic figure associated with that.

The question is have adequate resources been applied to the necessary areas where we need to develop that core surveillance? Is it a pipe dream or more a reality?

DR. CHU: Well, we'll always say we never have enough money no matter how much you get. I think that question actually is that--I think people are alert and aware, which is great, for pandemic flu preparation. The coordination and guidance of the funding needs to be much more strategically put together because I think folks are looking at various different ways and I think has to be multifaceted, and so at WHO, we really depend on the generosity of member states for money and resources, and I think at the moment that there has been several of these conferences for donors, that is funding donors, not blood donors, and there is a big one in January in Beijing.

It's, I think, next week, and they are going to look at exactly that balancing funds available and what needs to be done. But I think

we always say it's never enough.

CHAIRMAN BRACEY: Thank you.

DR. KUEHNERT: Just had a question along the same lines about coordination of surveillance, and you mentioned there being--a requirement being put into place as far as core surveillance and reporting, and I'd expect that different countries have slightly or maybe not so slightly different ways of doing things, and I'm just wondering how you integrate all this information that comes in different formats or do you ask that they present you the data in the same format, and then also how you feed that back to the countries?

DR. CHU: Okay. The information provided by countries officially belong to the countries, and it is only released at their permission. So within the daily updates in intelligence and verification, all the information is kept confidential within the people that need to know to work it out.

And there is no specific format for information to come in because you can well

understand how diverse that is. We take everything because if you ask people to do it in certain ways, which formally you can through the collaborating centers and regional offices, the formal route, you can get that information in a prepackaged way so it's easy to abstract, but in general it's a mixture of all those things that really happens with us.

So I didn't go over it, but we have what we call an event management system that actually DHHS has kindly funded WHO to develop and that, in essence, captures those thousands of pieces of information that I'm talking about and it parses it in, but it also requires the eyes and ears and attention of desk officer to verify everyday. So that's about as harmonized as we've gotten.

DR. KUEHNERT: Okay. And my other question was just internally you mentioned about there being where you are communicable diseases group and then the health technology group which contains the blood safety folks. I'm just wondering how you interact? Is it informal? Do

you have a working group where there overlapping relevant topics or how does that work internally?

DR. CHU: It's really informal in-house communications. Whenever an incident or a topic of cross-cutting concern happens, then they are called in to come into what I call the SHOC room, and we will sit down and discuss how we can do that. It is on an hoc basis.

CHAIRMAN BRACEY: Question for Dr. Pierce.

DR. PIERCE: You had mentioned that it was primarily previously healthy individuals who were infected, who got disease. Are there any host susceptibility factors that have been identified?

DR. CHU: I think that's part of the research that needs to be looked at very clearly, and some of the strains that are held at the WHO collaborating centers like in Atlanta, in Tokyo, in various places, those eventually are going to be looked at for those susceptibility factors, but at the moment, I think our attention is not going that way yet, but the plans are in place to look at those as research factors.

CHAIRMAN BRACEY: Dr. Ramsey.

DR. RAMSEY: I'd like to ask a little bit about the clinical features of these patients. In the 1918 pandemic, as I understand it, many of these patients had very prominent hemorrhagic manifestations from what I've read.

And I was wondering about--that's not something we think of today in the usual flu that we're mostly aware of. So I'm wondering what you know about these patients that might impact the need for blood products in their care in terms of their clinical features?

DR. CHU: Actually I'm not prepared to answer that question in detail with you because we have so few cases to look at. By and large, it's been multi-organ system failure. By and large when we have been informed of these cases, the patients, they were fatal cases and very little pathology is available at this time.

So that's another area that needs to be coordinated better. I think Anna probably, Anna after me, the next speaker, will probably talk a

little more about the clinical features.

CHAIRMAN BRACEY: Thank you. Dr. Angelbeck, yes.

DR. ANGELBECK: I have two questions actually. One is what is the trigger that identifies that the pandemic is here? Obviously, it's some observation of the efficient human-to-human transmission.

DR. CHU: Uh-huh.

DR. ANGELBECK: But is that five cases; is it ten; what is that?

DR. CHU: I think at the moment is any efficient transmission among a cluster that have a common exposure is important, so it could be two cases, brother to sister, mother to child, you know, in very close quarters.

DR. ANGELBECK: Right.

DR. CHU: And the second trigger would be simultaneous reports of activity within a geographic disparate region. And so there is no particular trigger as every case counts at this time.

DR. ANGELBECK: I have a second question. Could you just give a little more detail on when these cases appear, such as in Turkey that you just identified, what are the immediate elements of your rapid containment plan?

DR. CHU: Okay. As in Turkey, there's a reported cluster. It's not confirmed by the WHO collaborating centers so it is suspicious, and immediately what happens is the ministry of health is called and they're asked to invite us in. And much like what CDC does with EIS for the investigations, and a team will go in consisting of medical, epidemiologists, clinicians, field people and others, and there are rapid response teams available of that skill set, and they will be going in very rapidly along with the ministry of health counterparts to investigate together, and that we help the ministry of health investigate, and the ministry then makes the report available.

CHAIRMAN BRACEY: Could you comment on another element of the response, would be the control of the population, that is birds that are

affected? And obviously from the news, et cetera, it seemed that in certain areas, there is great activity. What really is the extent of the response among the many nations where this is a problem?

DR. CHU: At the moment, compliance is very high because everybody understands the potential of a pandemic and its spread. I think SARs was a great lesson, and most of the governments are very active in controlling the environmental contamination and the animal side of it, and then the ministries of health are very active in monitoring and tracing those persons who are closest exposure to those animals.

It is really event-based at this time, and there is a lot of work going on in China and what they're planning to do is immunize every domestic fowl for the next year, and you're talking about 250 million immunizations every month. And they're trying to put that in place. So there is some concerted effort to doing that.

CHAIRMAN BRACEY: Thank you. In the

interest of time, I think we're at a point for our first break. We'll reconvene in 15 minutes.

[Recess.]

CHAIRMAN BRACEY: We'd like to reconvene the committee. Our next topic will be delivered by Dr. Anna Likos. Dr. Likos is from the Epidemiology Section of the Influenza Branch at CDC and her topic will be "Pandemic Surveillance at the Grass Roots Level: Transmission and Clinical Detection."

Thank you.

DR. LIKOS: Thank you. I have to say I have not heard the words "grass roots" and "CDC" in the same sentence very often before. Grass roots level surveillance to me means clinicians who are aware. So I'll be talking mainly about clinical aspects of influenza including its transmission and clinical features.

By way of introduction, I'd like to just say that I was an internist initially, practiced for a couple of years as a hospitalist, before I saw the light and entered public health by doing a second residency in preventive medicine.

I just joined the Influenza Branch last July so I'm relatively new to the field of influenza which is my way of saying I realize I don't know everything there is to know about influenza, but I'm working on it.

I'm really happy to be here, though, for a different reason and that is because in a prior life, before medical school, I was actually a blood banker. I worked in a small community hospital in Dodge City, Kansas as a registered medical technologist, did everything, and I have memories of being up all night long, cross-matching units, scrounging additional units from hospitals in neighboring towns and worrying about that, so I have a very real appreciation for the importance of a national blood supply that is both safe and available.

Today, I'm going to be talking about influenza, both the virus and the disease, and what I thought I would do is really start with common influenza and review the virus itself, the disease including transmission of influenza and infection

in the host, clinical course, complications and address some of the non-pulmonary considerations that would be of concern to a group like you.

I'll then back up and review the same kind of issues briefly in terms of what we know about the clinical features of H5N1 infection.

To begin with, I think we need to realize that the term "influenza" refers to both an illness and a virus. The illness is a contagious disease which is caused by a virus which is an RNA virus and it poses a global infectious disease threat as well as annual public health problem.

It primarily affects the respiratory tract, causing severe illness and leading to life-threatening complications such as pneumonia in many people. Now, there are lots of influenza viruses out there in the world, lots of them, and they naturally infect several animal species including birds as well as mammalian species including humans.

In general, certain strains of influenza viruses tend to infect certain animal species so

there are horse influenza viruses that infect horses and pig influenza viruses that infect pigs and humans are usually infected only by human viruses.

Now, people who do genetic sequence analysis and phylogenetics, much smarter than I, have looked at lots of different influenza viruses and determined that all the known A types of virus--they're two that I'll be talking about shortly--but all of the known A subtypes are present and circulate in wild birds. Wild birds can pass these viruses to domesticated birds and ultimately serve as a source of all viral genes and viruses that infect other animal species as well.

This is a schematic drawing of the influenza virus itself. As I mentioned, it is an RNA virus. It has a genome that consists of eight segments of single stranded negative sense RNA. This is covered by a protein and lipid coat on the surface of which are two different proteins represented by the spikes, which are hemagglutinin, a protein that appears to be involved in entry of

the virus into the host cell, and then those button or mushroom shaped proteins called neuraminidase, which are involved in exit of progeny virus from the cell as well.

There are 16 different types of hemagglutinin and nine types of neuraminidase, and these can combine in a wide variety of combinations resulting in different subtypes of influenza A such as noted there as H3N2.

Every strain of virus is given a descriptive name as you see there-- A/Beijing/32/92(H3N2). This is kind of its pedigree. It tells the virus type, the geographic location where that virus was isolated, the strain number, the year of isolation, as well as the virus subtype.

So by looking at this name, I know that I'm dealing with a type A influenza that's H3N2. It was the 32nd strain isolated in Beijing in the year 1992.

As I mentioned there are two main types of influenza, Type A and Type B. Type A is the one we

are concerned about the most. It causes not only epidemics but pandemics. It infects, as I mentioned, animals and humans including humans of all ages.

Type B affects only humans, and it tends to cause only epidemics, though we do find them in the U.S. on a yearly basis. It primarily infects children.

Now this slide graphically depicts the most common means of transmitting influenza virus, and that's by degeneration of respiratory droplets or droplet nuclei.

Essentially, any process that can move infected respiratory secretions from an infected person to a susceptible person will result in influenza infection. These transfer mechanisms include coughing, sneezing and even talking as well as hand contact.

Now, this refers to the fact that influenza A has been shown to be relatively stable in dry cool environments especially. This means that in some cases, at least on stainless steel

surfaces, the virus can persist and remain infectious for up to 48 hours. So someone coughs. Respiratory droplets are fairly large size and of good mass. They fall out of the air fairly easily on to oneself, one's clothing, the table. You come along, you touch that table, unknowing that there is virus present, you touch your mucus membranes and infect yourself.

Of course, the obvious way to prevent this--I am a preventive medicine doc--is by good cough hygiene as well as frequent handwashing.

Once the virus enters the new host, it attaches to columnar epithelial cells located in the respiratory tract. These are typically found in the large airways such as the nasopharynx, the throat, the trachea and the bronchi although the virus can infect anywhere within the respiratory tract itself.

Using cell culture studies, a replication cycle takes about four to six hours, and the host, as progeny virus are produced, the respiratory epithelial cells die, and the virus is actually

released at the apical side of the epithelium or towards the lumen of the airway.

This facilitates not only infection of nearby and neighboring cells, but also places the virus in the airway so that it can be expelled from that infected host and make its way to a new susceptible host, again by coughing, sneezing or talking.

Once the individual has been exposed and infected, symptoms will appear one to five days after exposure, and these symptoms, which many of us are familiar with, include fever, headache, cough, sore throat, myalgia or severe body aches, nasal congestion or runny nose, weakness and loss of appetite.

Now, these symptoms have been shown to be due to a combination of affects of the virus. There are direct effects of viral replication in the respiratory tract which can result in the scratchy throat or sore throat. In addition, the virus is a foreign object, and it will trigger cells that initiate a reflex that results in a

cough or a sneeze and attempt of the body to rid the virus from the body.

Systemic symptoms such as fever and myalgia are thought to be due to the production of pro-inflammatory cytokines and lymphokines such as IL-6 and tumor necrosis factor alpha. In the uncomplicated case of influenza, full recovery will take about two to three weeks, usually a week for the systemic symptoms to resolve, but the cough itself may persist for an additional one to two weeks.

The most serious effects of influenza, however, are really in the complications which can be either pulmonary or non-pulmonary. Most frequently, pulmonary complications occur. The least common but most serious is probably primary influenza viral pneumonia, where the virus actually infects cells that are deep within the lung tissue itself resulting in a pneumonia.

Bacterial pneumonia also occur as a secondary invading pathogen. Very frequently it's streptococcus pneumonia and actually secondary

bacterial pneumonia can account for up to 25 percent of influenza associated deaths.

The non-pulmonary complications are those that are perhaps of interest to this group. They include myositis, myo/pericarditis, encephalopathy and encephalitis. Myositis is a severe inflammation of muscle tissue, typically in the lower extremities. Although severe myalgia is a common feature of influenza, myositis itself is fairly rare. It's noted by very boggy sore muscles that are present.

The pathogenesis of myositis is not understood. However, a paper published in the '70s gave evidence that influenza virus can be found in infected muscle tissue.

Myocarditis and pericarditis or inflammations around the heart and of the heart muscle itself have been described, especially in the 1918 pandemic, less frequently since then. However, reports have been made, as we'll see, of influenza virus being isolated from heart tissue in post-mortem specimens.

Encephalitis has been reported occasionally and the influenza virus has been isolated and cultured from cerebral spinal fluid in some of these individuals.

So the question then becomes how does the virus get to these nonpulmonary sites and the obvious answer is going to be, of course, through the blood stream.

However, the generally accepted influenza dogma is that there is no viremia within influenza infections. Now, one of the benefits, I think, of being a new person to the field of influenza is that I frequently do literature searches before I learn the dogma. It kind of takes up some time, but I learn a lot, and I'd like to present for you some of the historical literature concerning this question.

The studies cited here are all observational studies of community acquired influenza. In 1962, Minuse and their colleagues followed seven Michigan State patients who were admitted to hospital with influenza like illness.

As early as 22 hours after the onset of symptoms, they collected both blood and throat washes and then collected serial specimens lasting up to about 78 hours after the onset of symptoms.

Six out of the seven individuals had virus present in the throat washes and they were able to culture that out. None of the blood specimens, however, showed any evidence of virus.

A year later, however, Naficy published a case report of a case of influenza in a 40-year male whose publication was in the New England Journal. This 40-year old male presented with fever up to 104 on the second day of illness and on the third day following fever, a blood specimen was taken, and influenza virus was isolated from this blood specimen.

In addition, again, virus has been shown to be present in non-pulmonary organs. Kaji, et al, did a survey of 33 individuals who had died of influenza-like illness and on autopsy, he was able to isolate influenza from at least one organ in 17 of these individuals.

Collectively, the organs included tonsils, lymph node, spleen, kidney, liver and heart. The last two papers that are cited there, that of Yan and colleagues, as well as McGregor and colleagues, report the isolation of influenza vira from amniotic fluid indicating the potential for influenza virus to infect a fetus from the pregnant mother.

There's been one study, however, which is of concern for an asymptomatic viremia. Again, I want to reiterate that all of the studies on the previous slide were from studies that took samples after the onset of symptoms. Hopefully, if those patients presented to donate blood today, they would be declined the opportunity to give blood.

Khakpour and his colleagues in 1969, however, investigated an outbreak of influenza in a prison in Tehran. There were 21 individuals who became ill during the course of a week with influenza-like illness. Within 24 hours of the onset of symptoms in each case, throat washes and blood specimens were collected.

12 of those individuals did have influenza virus as cultured from the throat wash. However, none had virus present in their blood stream. At the same time, the researchers investigated 29 asymptomatic contacts or fellow inmates of these individuals, collecting blood and throat washes at a time when all individuals were reporting good health.

One individual had virus present in both his throat wash as well as in his blood specimen, and 12 hours later, this individual had the onset of influenza-like illness. Subsequent blood specimens were drawn at 12 and 24 hours following the onset of symptoms, but no virus could be isolated from these.

So, in general, then influenza is a serious illness. Estimates are that there are 36,000 annual deaths per year from influenza and its complications and we expect that there are greater than 200,000 hospitalizations per year. People who are at greatest risk for influenza complications include people who are 65 years and

older, persons with chronic diseases, especially lung and heart disease as well as diabetes, infants, pregnant women and nursing home residents.

It's important to realize, however, that there are variations in the manifestation of influenza infection. H7N7 is an avian influenza virus that is highly pathogenic in birds and in 2003, it caused a fairly large outbreak in commercial poultry farms in the Netherlands.

Because there were at least four anecdotal or four independent anecdotal reports of increased cases of conjunctivitis in people around these farms, the Dutch Ministry of Health initiated an investigation. They examined over 400 people, taking specimens from all, and found 86 cases of laboratory confirmed H7N7 infection in these people.

78 of these 86 cases, or 91 percent, were actually conjunctival swabs only. These people only had complaints of a conjunctivitis and had absolutely no respiratory symptoms. Now, in the past few years, there have been a number of strains

of avian influenza that have infected human beings including H5N1 in 1997 in Hong Kong, two cases of H9N2 infection in humans, again in Hong Kong in 1999, the previously mentioned H7N7 infection in 2003 and, of course, the current situation in Southeast Asia where H5N1 infects a number of humans.

None of these instances, however, have sustained human-to-human transmission which would be an essential feature of pandemic influenza. However, they have served to increase the concern of public health officials about the inevitability of another influenza pandemic, inevitable because the influenza virus changes. It changes more often than other respiratory viruses.

Typically these changes are very small, minor changes in both the hemagglutinin and neuraminidase proteins, which over time accumulate, so an H3N2 virus as it replicates, it changes a little bit at a time. At a second point in time, you can look at that virus and realize that it is now very different from the virus when it started.

Because of this, our immune system no longer recognizes this new drifted virus and we have to have a new vaccine, and that's why our vaccines are updated each year.

Very rarely, radical changes occur, so that we have a new, a completely new "N" or hemagglutinin and neuraminidase protein on the surface of the cell, to which people have absolutely no immunity. This is an essential but not sufficient feature for pandemics to occur.

Now, this slide depicts the major antigenic shifts, these major changes in the H and N genes that have occurred in the past century. The 1918 pandemic, or the Spanish flu, began with an H1. We know that this was replaced in 1957 with an H2, which itself was replaced in 1968, the third major pandemic of this century, by H3.

Interestingly, H1 reappeared in 1977, a small little blip that was referred to as Russian influenza. The interesting thing is that at that time, the people that were most susceptible to it were young people, those born after 1957 because

they had never seen the H1 protein before and had no immunity.

Now, the H7H5 and H9 viruses are avian influenza viruses that circulate globally and each have had the potential to mutate to form a pandemic virus or one that's capable of infecting human beings.

Of course, the major concern at this time, as stated, is the H5 virus, because of its continued infection or transmission from birds to humans.

So what do we know about H5N1? Transmission of H5N1 differs in two features. First of all, it's from birds. There is no human to human transmission that we know of to date of H5N1 virus.

Second, it requires close or direct contact with the bird itself. So people really believe that most likely the virus is transmitted by touching the bird and then touching their own mucus membranes.

The replication of H5N1 may occur in a

different site than our regular influenza. It appears not to replicate as well in the nasopharynx but rather it chooses sites lower down, deep in the lungs.

There's at least one report from a Thai case that indicates that it may replicate in type II pneumocytes, which are actual cells found within the deep alveoli of the lungs itself.

In addition, the incubation period may be longer, eight days or even up to ten days in some cases following exposure.

Prominent features of H5N1 illness still include fever and cough or shortness of breath. However, there have been reports of cases that had no respiratory symptomology at all.

Gastrointestinal complaints, especially diarrhea, are frequently reported, much more frequently than with regular influenza. And in some cases, the diarrhea actually precedes respiratory symptomology.

Lower respiratory tract symptoms occur and develop fairly early in the course of the disease,

clinically suggestive of primary viral pneumonia. These include shortness of breath, tachypnea as well as inspiratory crackles. At presentation, X-rays are abnormal, usually with a multi-focal consolidation in at least two segments, and these chest X-rays rapidly worsen.

Again, the signs are that of a primary viral pneumonia. Mechanical ventilation can be required and this is a bad prognostic sign. Multi-organ failure has been noted including both renal and cardiac dysfunction.

In terms of extrapulmonary H5N1, there have been two reports that are of concern. The first was in a six-year Thai male where viral RNA was isolated from post-mortem specimens in lung, intestine and spleen tissues. Now, the type that was isolated was messenger RNA only in the intestine and lung. This is a positive sense RNA and would tend to implicate replication of the virus in those tissues.

In the spleen, no such MRNA was found, suggesting that viral replication did not take

place in this organ.

Of concern also is a nine-year-old Vietnamese female who died. She presented initially with diarrhea and it was followed by coma, so the differential diagnosis initially was that of encephalitis.

Cerebral spinal fluid was collected and placed on cell culture in the lab, looking for the causative agent. Initially, they were expecting to find herpes simplex virus. Certain features of the cell culture were suggestive of H5N1, however, and subsequent testing revealed that it was indeed the H5N1 virus.

They pulled out ante-mortem specimens of serum as well as throat and rectal swabs and were able to isolate virus from each of these specimens. Now, I wanted to finish up by putting our knowledge of pandemic influenza into some kind of frame of reference.

As you recall, there were three major pandemics in the past century. The 1918 pandemic actually occurred 15 years before we had isolated

the etiologic agent of influenza.

In 1941, a reaction known as hemagglutination whereby the virus can clump together red blood cells was described, and we still use this particular feature of influenza virus to subtype strains as well as identify the presence of antibodies in suspect patients.

Our first influenza vaccine was licensed in 1945. Now, during this time, we've also developed laboratory techniques for identifying and isolating influenza virus. However, many of them require a specialized laboratory capacity. It wasn't until the early 2000s that rapid flu tests, kits that were amenable to a busy clinician's practice, became available.

In terms of blood banking, it was 18 years before the pandemic, the 1918 pandemic, that Karl Landsteiner described the ABO blood groups. And two to three years before the pandemic is when citrated anticoagulants were described, obviously a development important for the storage of blood, and the subsequent development of blood banks, the

first being established in 1932 in Leningrad.

It was in 1947 that the American Association of Blood Banks were formed. Now, today we have a couple of important tools that will assist us greatly in both identifying and responding to an outbreak of influenza that has pandemic potential.

These include the laboratory technique of PCR, or polymerase chain reaction, as well as the Internet. These have become to be of great use only in the late 1980s and early 1990s, ten to 20 years after the last pandemic occurred in 1968.

I think it's important to note that during this history where our knowledge of blood banking as well as influenza virology has increased, that there has never been a report of influenza associated with transfusions. The caveat to that statement, however, is that we may not have recognized it.

Influenza virus transmitted by blood may have different clinical features and it may not even have features of respiratory disease at all,

which makes the statement before you today in 2006 a good one, and that is can influenza be transmitted by transfusion? We have the techniques to evaluate this question today better than we ever have in the history of either influenza virology or blood banking.

Finally, I'd like to thank my many CDC colleagues who have helped me in preparing for this talk, especially Matt Kuehnert, who gave direction as well as advice on slides. These people have also participated and stimulated me with a lot of very interesting discussions about this topic.

Thank you.

CHAIRMAN BRACEY: Okay. We'll take questions now. If I may, could I ask one question initially, and that is are you aware of any trials now that are looking at spiked samples and the onset of clinical disease related to influenza?

DR. LIKOS: Yes. I believe one of the speakers later on today will probably address that. Several trials have been suggested, and we hoe to collaborate with people as well. And rather than

steal their thunder, I think I'll let them describe that.

CHAIRMAN BRACEY: All right. Dr. Epstein.

DR. EPSTEIN: Yes, thank you. You know the best chance to find out if there are asymptomatic viremic individuals is to look at the case contacts and that's what was shown in the Khakpour study. So I wondered if you could specifically comment on how much effort there really is right now trying to look for viremia in case contacts?

DR. LIKOS: In H5N1?

DR. EPSTEIN: Yes. Presumably in Asia.

DR. LIKOS: Yeah. I've not been able to participate very much in the studies that are being done over there. I do know that contacts are followed very closely for onset of symptoms and in some cases, at least nasal or throat swabs have been taken. I'm not aware that blood specimens have been tested in the contacts.

CHAIRMAN BRACEY: Dr. Wong.

DR. WONG: In the Vietnamese case for the

13-year-old girl and her mother who died, how do yu rule out human-to-human transmission even though one is Tamiflu resistant and one is not, that the mutation didn't occur human to human?

DR. LIKOS: Yeah. The report, the publication that was made actually in the New England Journal about that case suggests that human-to-human transmission did occur. It's difficult to tell. The aunt was present at the same place where the girl was living, had actually killed the chickens when they were ill, and came down with influenza I think 17 days after that last exposure to chickens.

There have been some reports of possible human-to-human transmission, but they have not been sustained and have not gone beyond that. I don't think it's possible to completely rule out the possibility that it was still bird-to-human.

CHAIRMAN BRACEY: Dr. Holmberg.

DR. HOLMBERG: Yes. Dr. Likos, how reliable are the data from China to be able to detect the human-to-human?

DR. LIKOS: Not being at WHO and the recipient of those data, I really would defer to May Chu actually in answering that question.

DR. CHU: I think the answer to that is we trust that we're getting as accurate information as possible. The WHO office in Beijing works very actively with the Ministry of Health and every case is being investigated with a field team that comprises of WHO specialists as well as the Ministry of Health. Some of those reports are still being finalized.

So what we would feel is that for the cases that have been noticed and reported, we are looking into every case. But I think the avian infection, the infection of the domestic poultry is quite extensive in China and so there are likely other cases that may have escaped finding. In fact, one of the questions asked earlier was are we getting to every case, and I think at the moment, we're really looking at event-based after the infection.

So it's an incomplete answer, but I think

what we're trying to do is putting a lot of effort into it with CDC and a lot of partners.

CHAIRMAN BRACEY: Follow up?

DR. HOLMBERG: Yes. May I ask both of you what is the general consensus as far as the trigger for when it is recognized as a pandemic? Is it one case of human-to-human? Is it multiple cases of human-to-human? Is it human-to-human outside the family? Just what is the latest thinking on this?

DR. CHU: I think at the moment, we're able to look at, as far as we know, every case, and every case is investigated, and every case is sort of a mini-trigger, and until we find really efficient human-to-human transmission, we won't-- that is really the key. And it could be found in any situation.

CHAIRMAN BRACEY: Dr. Ramsey.

DR. RAMSEY: With influenza as we know it, what would be the value or what is the value of prophylactic therapy in advance of exposure? I'm thinking of the possibility of treating transfusion recipients before their transfusion.

DR. LIKOS: It's my knowledge that with Tamiflu especially that actually it's better prophylactically than it is as a treatment for influenza.

CHAIRMAN BRACEY: Dr. Sandler.

DR. SANDLER: As you observed, a lot of folks in the United States get blood and we don't spread influenza, common influenza, by a blood transfusion. From your reading and the information that's available to you, is there anything about the biology of this bird flu that would cause you to think that the current mechanism of taking someone's temperature and doing other things won't work if this virus comes here compared to common flu?

DR. LIKOS: Basically you're asking if asymptomatic viremia with H5N1 is possible or likely, and I have absolutely no idea to answer that question. I think, I think it is of value to look at regular influenza to see what the capability of the virus in general is, but I think in general, as I tried to point out with H7N7 as

well as H5N1, that each influenza virus can be a whole new ball game.

CHAIRMAN BRACEY: Follow-up?

DR. SANDLER: Yeah. That wasn't entirely what I had in mind.

DR. LIKOS: I'm sorry.

DR. SANDLER: A person with syphilis, and who has spirochetemia could donate a bag of blood, but the recipient isn't going to get it because what we do in the process makes it non-infective, and I was just wondering if there is any difference in the biology between the various viruses that would cause you to think that whatever we're doing today and we don't see people getting flu from a blood transfusion would cause you to worry about that what we're doing today wouldn't work if the new virus were present?

DR. LIKOS: I really don't know. I don't have--I feel very unprepared to answer that question. I don't know all of the processes that a unit of blood goes through as it goes from the arm of the donor to the blood bank refrigerator. So I

think there would potentially be, you know, processes that would remove virus or kill virus that might be present. However, no information on that whatsoever.

CHAIRMAN BRACEY: Question from Dr. Bloche.

DR. BLOCHE: Thank you. I'd like to ask you the same questions that I asked Dr. Chu. One, do you have any science-based sense of what if any might be different about the death rate for disease of the same severity as has been reported on bird-to-human transmission? What might be different about the death rate with U.S. level or first world medical care?

And then the second question is any science-based sense for the extent to which symptoms or severity might be attenuated if we went to human-to-human transmission and the inevitable evolution of the virus for its own benefit to keep its host alive?

DR. LIKOS: Yeah. In terms of the first question, I get the impression you're asking about

clinical capability here in the United States as compared to Southeast Asia.

DR. BLOCHE: And the implications of that difference for survivability?

DR. LIKOS: For survival.

DR. BLOCHE: Yeah.

DR. LIKOS: And I honestly could not tell you. I've been in several hospitals in Vietnam and have seen extremely capable clinicians there with good equipment to work with, and other places not as good equipment and they're trying to build up their capacity and I think that will be an interesting thing to watch as we go along.

The U.S. has such a remarkable health care system, it's entirely impossible to predict what the effect of that would be on the mortality rate in the U.S. I wouldn't even want to venture a guess at that.

In terms of the second question, whether or not the virus itself, if it became a pandemic virus, would be less virulent is also impossible to predict. We were talking during the break, Dr. Chu

and I, about a mutation versus reassortment. The segmented genome of the influenza virus is significant for the generation of these new strains in that two different strains of influenza virus could infect the same host cell.

And in the process of replicating, the different segments could be reassembled in a new combination, getting part of them from one strain and part from the other, and this would result in an entirely new virus.

Now, it is tempting to think then that the virulence of the H5N1 virus, as we see it today, would be diluted out. Do we know that that would happen for sure? I don't. And I think that you would run a risk as well, difficult to quantify, that it could become even more virulent. Mutation was shown to be the predominant reason, single mutation, not reassortment, that moved the 1918 virus from an avian influenza virus to causing the pandemic.

If that's the case, if that's what happens with H5N1, then it's possible that it would remain

as virulent as it is today.

DR. BLOCHE: But is there an overall propensity with these viruses for those kinds of mutations to push them in the less virulent direction, not as absolute truth but as trend?

DR. LIKOS: Yeah, I think that's a lot of theory and maybe--I just don't know the data that well to be able to say that with impunity.

DR. BLOCHE: Thank you.

CHAIRMAN BRACEY: Thank you, doctor. We will move on to--actually Dr. Wong.

DR. WONG: Coming from Los Angeles, I'm just concerned about the recognition of clinicians at entry, port entry sites from Southeast Asia and thereabouts, in recognizing the difference in, you know, the H5N1 versus regular flu and whether the usual mechanisms of detection would pick up these carriers, so to speak?

DR. LIKOS: In Southeast Asia?

DR. WONG: Flying into the States?

DR. LIKOS: Do you have any--I think, yeah, I'll let you address this.

DR. BRESEE: I'm Joe Bresee from CDC. I think the answer is, yeah, there were case definitions that are made for travelers which include, that are being used right now by quarantine stations. There's lots of education now ongoing with quarantine officers and physicians that work with these groups. So I think there's a growing level of recognition and sensitivity to the system for detection of new cases. It will evolve and I think as we train people, it will become better and better, but we've actually learned a lot from the system over the last year and will continue to learn a lot more I think over the next few years.

DR. LIKOS: Yeah. CDC has opened 23 new quarantine stations at airports and cities around the U.S. and part of their training is in looking at avian influenza.

CHAIRMAN BRACEY: Follow-up question.

DR. WONG: However, I think the physicians in children's hospitals of which I am one are not trained that way. I can tell you that we are not

given information, and if somebody slips through and shows up at these hospitals, I think just beside the quarantine stations, if somebody slips through the net, you got to be able to catch that, too.

DR. LIKOS: I would say we get a number of questions throughout the summer months. We get calls from physicians all over the country, though, that have a patient presenting with influenza like illness. They've recently traveled in China and can this be H5N1, and we investigate those as best we can.

CHAIRMAN BRACEY: Thank you, Dr. Likos.

DR. LIKOS: Thank you.

CHAIRMAN BRACEY: Our next speaker will be Dr. Goodman, Jesse Goodman. Dr. Goodman has been the Director of Food and Drug Administration's Center for Biologics and Evaluation since January of 2003. CBER is, of course, the FDA center that's responsible for regulating blood, vaccines, and many different types of tissues and transplantations.

Dr. Goodman is a practicing physician and researcher specializing in infectious diseases and he will speak to us on vaccine preparation and process in influenza pandemic.

Thank you.

DR. GOODMAN: Okay. I'd like to thank Jerry and also the committee for taking on this issue and Jerry mostly asked me to talk about what are some of the efforts we and other components of the government and industry are making to on the vaccine front to have us be better prepared so I'm mostly going to talk about that which is somewhat peripheral to your interests, but given my involvement, as many of you know, also in the blood system, I just wanted to make a little overall plug when I start to sort of keep all of this in perspective.

You know I think that the issue of disruption of the health care system, the issue of blood supply is very big. I think keeping the--I think we can't be sure there isn't going to be in an evolved or drifted virus or even in current ones

small periods of viremia in asymptomatic individuals, but I think we need to keep the issues about the potential burden or problems from that in perspective with the disease that would cause massive social and economic disruption and probably infect a third of the population through natural route.

So I think we just have to keep that in perspective as we discuss--I have an infectious disease, too, right now.

[Laughter.]

DR. GOODMAN: So forgive me for occasional coughs. But anyhow I do want to mention that the FDA has, it's not just in our center dealing with vaccines and blood, but in the FDA as a whole that we are taking this quite seriously. We have a task force for the entire FDA dealing with pandemic issues. Obviously, there are issues in antivirals and diagnostics that I think are obvious to all of you, but there are also issues with respect to food supply, veterinary medicine, et cetera.

So we do have a cross-agency task force

which several of our people serve on which helps participate with the president, White House level strategy, as well as HHS strategy and plans. This involves 14 centers and offices of FDA and is focused not so much on specific products, but as policy development, planning, et cetera, and I'll just leave it at that, given time.

Now, I'd also like to point out that influenza is not something that we or HHS have handled as business as usual, and speaking particularly for our center, and we've interacted with many of the people in this room in some of these issues since September 11, I view this as another extraordinary challenge just like what we've dealt with in bioterrorism.

And since then we've adapted to those kinds of urgent public health challenges through similarly urgent and I think creative efforts, and some of these include things like meeting with sponsors to actually encourage development of new products rather than just waiting until they're developed, early and intensive interactions then,

rapid turnaround on critical product reviews, trips to inspect facilities as manufacturing is developed and brought up to speed.

We work with our colleagues in the Department of Health and Human Services as well as with people in industry on many product development teams, and this would, for example, an important priority, bioterrorism area, this is what helped get our country to the point where we have smallpox vaccine preparedness now for the nation.

And then to target and prioritize our research to some of the more critical areas in getting these products developed. An example, a very mundane example I'll mention more about, is, you know, assay development for--and reagent development that allows products to be more rapidly evaluated and developed.

And we used a lot of these outreach approaches in dealing with the shortage in 2004 and it is good feeling to be here towards the end of the flu season in 2005 and have achieved, you know, near normal production of influenza vaccine again

in this country after a year ago losing 50 percent of our supply. So I think that shows you that working with multiple partners, both in the government and industry, we can accomplish a lot.

And I think for pandemic, we have to use some more approaches. They're very resource intensive, I will say that. And this has been recognized and we are receiving additional support for the pandemic activities.

Now, what are some of the things that we're doing? We're working to increase manufacturing diversity and capacity. That's something that happens in industry, but we can help make it easier, and we can help make it higher quality.

We're developing pathways and regulatory processes that can get us vaccines more quickly both now and in the event of a pandemic. We can facilitate the actual manufacturing process itself. I think FDA is, you know, sort of gold standard role and a very important one, not to forget about, and I'll talk a little bit more about this, is

assuring that the vaccines we produce are appropriately safe, and maintaining public confidence because vaccination isn't just about flu. We have a healthy population that relies on confidence in vaccination to maintain that health.

Considering pathways to prevent a pandemic, I'm very engaged in that and very concerned can we treat this as something other than an emergency, but as more routine kind of problem, I'll talk a little bit about that and then working globally.

Obviously, both on an epidemiologic viewpoint, but also increasingly on a product development, manufacturing availability viewpoint. We live in a global village.

And because this is a serious challenge, it may or may not be H5N1 that becomes our next pandemic, but it could be, and I think one of my worries is that we sure don't want this to happen in the next year or two because preparedness is not optimized, but I'd had to see it be forgotten about like so many threats de jour if that doesn't occur.

I'd like to be in a place where in five years or ten years, we can all say we have a system in place that can help face this challenge. The other thing is realistic expectations in all this. You know we live in a society where people feel there can be, that if somebody gets a disease, that's a complete failure. Well, for those who have gotten them, it is. It's something we should do everything we can to avoid, but the history of pandemics of infectious disease I think tells us we need to be somewhat realistic about our ability to either prevent transmission of disease or to always intervene successfully medically.

But fortunately in this case we do have potential interventions like vaccine antivirals or even public health measures and we need to use those optimally.

Now, talking--I'll go through each of these briefly, but talking about increasing manufacturing diversity and capacity, very important and everybody in blood is very familiar with this, but that it's markets that are main

driver. People are not going to invest--I sometimes say nobody is going to produce three billion doses of vaccine once every 50 years and build the infrastructure to do that for the world. I mean for the United States if it was 300 million, let alone for the world which might be six billion.

So we need to keep this in mind and this is why I think the administration rightfully has said we're going to invest in producing some incentives for influenza vaccine manufacturing both for annual vaccine and for pandemic vaccine.

In the last few years, a good thing is working with CDC and others, the health care community and the public have increased their demand for flu vaccination because it is beneficial on a public health level and that has stimulated the market and interest of manufacturers and there is nothing like good shortage also to stimulate interest.

And in dealing with that shortage, we've had a lot of helpful interactions, for example, with global manufacturers from all over the world

and all continents who worked with us to assure potential access to additional vaccine, not licensed in the USA, if it had been needed in 2004 to 2005.

We sent inspectors out to multiple places. Australia, Europe, et cetera, to look at facilities and manufacturers were very cooperative with us in making it possible that if we needed more vaccine, we could bring it here. And I will say as a result of that, several companies with whom we'd already been interacting are now on--and I think also because of pandemic are now on a faster track to work with us to seek U.S. licensure.

And one pathway we used to speed availability is what we have in our legal armamentarian which is accelerated approval and basically if we consider there to be a short supply of a product for a serious and life-threatening illness, and we believe we have a likely surrogate market of clinical efficacy--in this case, we believe that antibody levels against the hemagglutinin are a likely surrogate, we can

approve the vaccine based on the host immune response to the vaccine with a post-approval study to show its clinical effectiveness.

So you don't have to wait for an influenza season and then a year after that to analyze all the data, but you could do this in real time, and we've made manufacturers aware of this, and one of the reasons that we're in better shape this year than we might have been, for example, is that GlaxoSmithKline working collaboratively with us and the National Institutes of Health very rapidly generated and reviewed data--we reviewed, they generated data--in a 900 person study to establish the immunogenecity of their vaccine.

This study actually of this number of people was planned and fully enrolled within one month. This indicates that with preparation and resources, substantive needed data can be obtained now and potentially even in an evolving pandemic situation.

And we have stated that we'll consider similar approaches for most of the pandemic

vaccines and I'll get to some of the other technologies in a minute.

One of the other things we've done to speed the process is we've said that a pandemic strain comes along and a licensed manufacturer using a licensed vaccine process, we would view this like we view an annual strain change in the vaccine, and again this accelerates greatly the regulatory process and reduces the burden. I won't go into this in a long way.

But I'll also say we also believe that a virus made by reverse genetics, which is a useful technology, that gets us a little more quickly to a new manufacturing stock in many cases--for example, the European regulatory system views this as a genetically engineered organism requiring a variety of--raising containment issues or somewhat different issues from a regulatory point of view--we view this as just an effective tool to make an influenza strain when it's properly characterized and carried out.

These things make it faster. Now, I

didn't have the slide in the talk, but I realized when I was talking to the blood community that live vaccines are an issue that the blood community is always interested in, and I do want to mention both because of that and because of its potential use and some issues about it, the live attenuated vaccine. We currently have one approved live attenuated vaccine that's called FluMist. About three million doses a year have been used. It's very effective in children.

The efficacy in other populations is still under study. One of the nice things about this is that it is like many live vaccines, it's a live vaccine, so you're exposed to an infection. The immune system is stimulated in a more similar way than using a purified single antigen and particularly to a broader array of antigens. So in theory, there's the possibility of inducing immunity that might be broader as strains drift, for example, or potentially more rapidly.

Now, this remains to be seen. A study with H9, one potential pandemic threat,

hemagglutinin has actually been enrolled. Data is being collected and analyzed, and a study with the H5 strain is planned. I'll mention those in a second.

Given adequate clinical and immune data, again we could handle these as a strain change to a licensed vaccine, too.

Now there are some issues here. As you can imagine, if you have a live virus carrying this H5 hemagglutinin, there is concern that if people are there in the community with that virus, that H5 could reassort with a wild type virus and essentially let the H5 gene into the population. The risk of this is probably quite low, but it's unknown. In addition, this concern makes clinical studies have to be performed in confinement or containment right now which you can imagine that's a real challenge for performing clinical studies of these vaccines.

But nonetheless, those studies are going ahead, but I think for these reasons, even if this vaccine technology works for pandemic strains, it's

something unlikely to be used before a pandemic but that could potentially be mobilized during a pandemic.

On the blood banking side, I'm not aware that viremia is an issue with this highly attenuated vaccine, but I have not personally reviewed the literature or what the manufacturer may have.

Some patients do persistently shed virus for periods of time, but in general there is not significant systemic illness.

Well, we're doing a number of other things to strengthen the supply of vaccine. I mentioned globalization. We've put in place a lot of information sharing agreements, and this is important not just in how we assess new vaccines, but how we monitor the safety of vaccines during use, I've always encouraged vaccine--you know the economics are different than this, but I think we're very supportive of the idea of coordinated global vaccine development plans.

We're now performing annual inspections of

flu manufacturers and this, I think actually for a pandemic puts us in a better position, because may be able to be preventive in terms of identifying issues or preventing them. And we're also paying a lot of attention to vaccine manufacturing issues and working actually collaboratively with manufacturers.

We have a roundtable now with PhRMA to discuss some of these issues and quality issues in vaccine manufacturing.

Now what could we do ahead of time and what are we doing? We can prepare qualified seed strains and high growth reassortants. Every year we generally prepare strains for manufacturers' use in their influenza vaccines. This is a very unusual degree of interaction with the government where the government in our case, or WHO in the case of many other countries, actually provides the high growth seed strains to the companies for these vaccines.

So for a pandemic, we can try to be as prepared as possible ahead of time and our

colleagues at CDC and NIH are also participating in this effort.

I won't go into this in detail because of time, but we also provide reagents needed to calibrate how much virus is in vaccine, et cetera, to manufacturers, and we can prepare many of those ahead of time, again for representative strains.

It may turn out as a strain shifts or drifts that we don't have the right thing, but maybe we will.

I mentioned assay development. You heard before that these vaccines were developed more than 50 years ago. Well, a lot of the technologies involved in assays of antibody, assays of antigen, were developed around then or not that recently, and there hasn't been a lot of incentive to apply what I would describe as modern technologies to what is not a simple problem.

There are a number of very complex laboratory problems here, but with some of the support we've received, we're going to look at some of these assays that are involved, both in

manufacturing and then in our ultimate quality control lot release of these vaccines to see if they can be improved or sped up.

But the fact, as all of you have heard, that even with these kinds of efforts, even with increasing the number of manufacturers, capacity of vaccine production is still very unlikely to be adequate for widespread pandemic in the U.S. and certainly for global needs.

Now another thing I want to point out, I have a time line slide, but I didn't get it into here, is that flu vaccine manufacturing is not a simple thing. You don't turn on a switch and then you get flu vaccine a week or a month later. Typically it takes even under a very rapid fire process about a month to go from a virus isolate to a strain, and this is with very heroic efforts, that is qualified to be safe for manufacturing.

And then you have to have the reagents, et cetera, and then for the first vaccine to then come off the line and be tested as sterile, et cetera, is something like a three month process, so even at

the compressed end, you're talking about four months or so before, from when you get the virus, you know, to having a vaccine in a vial.

And then, of course, the capacity is such that to make enough for the number of people, it depends on the dose, but we're talking many, many months to potentially years at the current levels.

We also have preliminary data many of you have heard about from H5 that suggests that very high doses of antigen may be needed and if that's the case that's a huge problem. So technologies to spare antigen, to be able to use less in a dose, need to be developed and evaluated now before a pandemic.

Now, I'll just mention where we are on a couple of these. With adjuvants, this is generally nonspecific stimulants of immune response, some recent clinical results are promising, although some are sobering. There's reported--in the newspaper only--there's one study saying that, well, it took 30 micrograms which is twice the dose of a single antigen in our normal flu vaccine.

There's three antigens in our normal flu vaccine, 15 micrograms each. Well, there's a report in the newspaper study suggesting that with 30 micrograms and an adjuvant, you could get an immune response, but that's not a huge difference and it's still more than with a normal vaccine.

There is a history, though, of also negative studies with adjuvant in the past. So adjuvants may increase the immune response, and another nice thing about them is in some cases they may increase cross-protective antibodies. In other words, not just the level of the antibody response but the diversity of the antibody response.

But they may also increase adverse events for some of the same reasons, although it's important to say that many of our childhood vaccines are adjuvanted with alum and are extremely safe and well tolerated.

It does require changes in manufacturing that really essentially make a new product. We've seen products where their stability is affected by adding to an adjuvant, but again if this is a minor

addition on a known manufacturing process, we look at that in a certain way.

We can use accelerated approval for adjuvanted vaccines. A very important thing is there are proof of concept studies going on in various places and also being initiated by NIH shortly, and if these are favorable, we really feel that's great and let's do some larger studies to try to get these evaluated very quickly.

What about new delivery approaches? There's limited past data that suggests that intradermal delivery might reduce the amount of vaccine needed. A couple of pilot studies were reported in the New England Journal last year. However, I would also caution they're also is a study, for example, from about 30 years ago that didn't show a benefit with flu vaccine.

So again that study is sort of in the can through the NIH and we're waiting to see some of the data on that.

Again, from the FDA point of view, we see this as pretty straightforward and we could

evaluate this as a supplement in the case of licensed vaccines.

What about new technologies? This egg technology--again, I didn't go into it, but I'm sure most of you have heard, you know, basically you use millions of embryonated live hens' eggs every year and it's not a sterile environment. It requires very interesting and antique manufacturing processes, many of which have been updated incidentally, but it's tremendously challenging.

In theory, there's the vulnerability of the flocks to an avian virus, although these flocks are carefully isolated.

So could this be grown in cell culture? There's been a lot of interest in this for several years. There's no reason it can't be. I mean the answer is it can be. However, there have been issues with yield, economies of scale. I mean egg is great at producing vaccine. We've licensed many cell culture vaccines. We don't have specific regulatory concerns.

On the other hand, for those of you who

know some of the concerns that have been raised historically, for example, about polio vaccine, about vaccine safety in general, it's very important that cell culture vaccines be well characterized with respect to not having adventitious infectious agents or carcinogenic properties that might raise concerns about safety or actually cause safety problems.

Several are in development. We're having a number of interactions to try to stimulate pathways forward here and make it easier to do this, and I think based on time I won't go into that in detail.

Now, I did want to mention--Dr. Epstein raised a question about earlier immunization, et cetera, and this is something that I've been trying to put on the table a lot. For a pandemic to be a pandemic, a prerequisite is lack of population immunity so could we conceptualize preparedness in a more routine prevention mode?

You know each year, as you heard, we change strains. Could we additional strains

through routine vaccines? Could we consider making these vaccines if there's a true threat strain out there available ahead of time. There's certainly been thought to immunizing high risk individuals ahead of time. Could this even be integrated into our routine public health preparedness?

Now, I think if people look at the whole issue of concern about adverse events with vaccines, concern about the Guillain-Barre syndrome that was seen after the swine flu campaign in 1976, you realize this is a very complex area. It's also an area that if you do this, it's a significant investment in time and resources, but I think it's a good time for us in the public health community to be discussing these issues.

They will be informed and it will be a more intelligent discussion when we know what it will take to immunize people against these pandemic strains.

I mentioned swine flu and I think the blood community is very cognizant about communication issues and I just wanted to--I always

make these points. We always want to learn from history. Communication about the benefits and risks of what we do in health care and public health are really important. That's a lesson from the swine flu campaign.

I think people did the right things. There was a human-to-human transmission. They said we need to get a vaccine ready. This had the potential for a global pandemic. And some of this is not the public health system. The media and the public have a role here to explain to people, well, what really is the risk of a pandemic?

I often say in our country, there's sort of two positions to the switch. It's either on or off, you know. People either don't pay attention to a problem or they're jumping off bridges.

And it's a complex part of human nature and society that hasn't gotten easier. But I think we need to make it clear to people, especially in the pre-pandemic period that, you know, for example, we don't know what the risk of a pandemic may be. We don't know till it happens what the

risk of death may be. We don't know till it happens to some degree what the efficacy of some of the interventions may be, and it's important that we keep being very open about the unknowns.

Another point where FDA comes in, I think, is the public safety and concerns and expectations are highly significant. They're also appropriate. You know when you give things to healthy people, it's appropriate to want to be sure that everything is being done properly. In the case of swine flu, this affected and could even derail a vaccination program.

And as I mentioned before, vaccines are important, but confidence in a whole number of things that we take for granted in protecting our people's health, the government, the public health system, industry, are very important and on the line.

There's also some lessons from when we try to develop products very quickly that we've encountered in counterterrorism efforts to be prepared for something of unknown risk in a very

quick time period. And these include that vaccine production is complex and time consuming and not always predictable.

This is very hard for people to take, especially people who are used to, you know, if you produce an industrial object. I mean even there I'm sure those are challenges, but this is a biologic, made in a living system usually. Shortcuts seldom are. Less expensive often is not.

And then as I said, I think FDA and other global regulatory counterparts--it's not just sort of being--we can help facilitate getting things done right to the degree possible, but I think also when you're in the throes of a high priority national effort with high visibility, it is important to have somebody who can both rapidly but also objectively step back and kind of do their job to evaluate the products and what's going on, and that does help in confidence, too, as well.

Okay. And then I'm going to close just saying something about global regulation and this is not totally foreign to the blood community where

you see a lot of diversity in global practices and sometimes it's not a huge deal, but when you're dealing with certain public health crises and challenges, or economic efficiencies, that can be a problem.

So I've always thought that we should move in general in many areas towards global regulatory convergence. I say that rather than harmonization, by the way, because--or mutual recognition--because a first step is to converge in what you see as the science and the scientific requirements, and many countries have different legal systems and regulatory constructs where their approval under this law may be different from our approval under another law.

But it should be possible to agree upon a science-based data set needed to assess potential pandemic vaccines of various types. This could make development faster and more efficient, make for global resource. It could help assure quality globally. I think, you know, it can bring quality up.

In urgent situations, we could share some of our regulatory resources and know how, and others could share with us. There are experts in other parts of the world to work with us, and so I think this is desirable to try to help in this. We're producing, in essence, many guidances or concept papers to try to explain our thinking in a number of these product and manufacturing areas.

We've also convened with WHO and our colleagues in Health Canada and the European regulators are involved in this as well, plan for two global regulators meetings, the first to occur in quarter one and the second in quarter two of this year.

So just to summarize, you know, we've really been working earnestly with a number of partners to diversify and strengthen manufacturing. There are scientific data needs for evaluating antigen sparing approaches and non-egg based technologies. I mentioned cell culture, but I didn't mention recombinant technologies. They're also some very recombinant, promising recombinant

vaccines that are being evaluated.

Key studies that are still underway. We don't have an answer yet, but I think it's quite promising. I don't think it should have to take ten to 20 years.

Advance preparation and improvement of strains, reagents, and assays, as I mentioned. It's kind of mundane. It's not typical academic research. Industry tends to do what they do and it works, so I think it's an area where we can be helpful.

I mentioned the issue of potential for early intervention and regulatory convergence, and I'll close with that. Thanks very much.

CHAIRMAN BRACEY: Thank you, Dr. Goodman. Question from Karen Lipton.

MS. LIPTON: Thanks, Jesse. That was very interesting and I want to thank you. First, a comment for your observations at the beginning about needing to balance. Really what we're talking about is a much bigger problem than perhaps viremia in blood, and I know as we've gotten into

this--you're going to hear from the task force later--but we think that some of our biggest problems are going to be logistical issues related to donors and the workforce rather than whether there is an asymptomatic viremia period for this influenza.

Two questions I have, though, that are a little bit different. Is the limited number of what I'll call adjuvants that are approved for human use and sort of the proprietary nature of some of those, has that proven to be a barrier to the development of some of the vaccines?

DR. GOODMAN: Well, two things. You know, one is because different adjuvants interact differently with different vaccines, the approach of regulators generally, in FDA in particular, has been to evaluate each vaccine and the adjuvant in the setting of the vaccine. So you don't need to have an approved adjuvant, but you need to have an approved vaccine.

Now that said, the fact that something like alum has been used in hundreds of millions of

doses here and is not associated with known significant problems gives you a certain confidence in looking at a vaccine with that in it or a new one.

There are several other promising adjuvants. Alum has advantages in terms of safety, innocuousness, but there are certain other adjuvants that in both experimental animal and human studies may be more potent or different in their modes of action and some of those are proprietary.

In general, what we've seen in industry as we've talked to them about pandemic is a willingness if their proprietary adjuvant works out to work with others, you know, to try to make--you know, not to say, well--because it's recognized that one company is not going to have capacity to make enough vaccine in a pandemic.

So I think the Secretary and others have sort of encouraged people to be willing to share these technologies if they work. So, now, you know, but sharing, I mean this is a business issue,

and those issues, I think, if we identify something promising will need to be worked out.

Now, on the regulatory and public health end, I will say that I would put the remaining adjuvants that are not in any U.S. licensed vaccines--you mentioned there are a couple of different kinds--there's one, for example, that's used in some European licensed vaccines where there may be a large European experience that could help inform us.

There are others that are in earlier stages of development. So we look at each product on the basis of the scientific information available. But there are some very promising things there.

One other thing I want to tell people because it's an opportunity to proselytize is that what you see with one pandemic strain may not be the same as what you see with another. These viruses may different in how much of an immune response they induce, even in completely naive individuals, and then the other issue that the

speakers mentioned before, for certain viruses there have been cross-reactants. In some cases, not even the same hemagglutinin type, but cross-reacting exposures in the population 20 or 30 years ago.

So, for example, during swine flu, and I should mention--I mentioned how people did a lot of things right then--they did within a year something like 20 controlled clinical trials of those vaccines before they were given to the American people, and despite that, Guillain-Barre syndrome wasn't noted in something like 20 clinical trials.

But just to mention that in the case of swine flu, for example, unexpectedly, older adults seemed to have a memory response to it despite no evidence of that virus having been around before that.

MS. LIPTON: And just a quick question about risk communication because I think this is really a critical issue for us when we deal with vaccines, and I guess I wonder is it your perception that there has been a shift in people's

view towards vaccines? We came off of a pretty negative period with people with experience with DPT and not wanting their kids to get vaccinated, and I'm wondering if you, you know, if you were monitoring that at FDA or thinking about, you know, even a big public education program about vaccines or if you think things are just moving in that direction anyhow?

DR. GOODMAN: Yeah, well, that, you know, we--you know, I would say that is monitored. It's mostly CDC and the National Vaccine Program Office which is this coordinating function in HHS that look at that.

There is still--the way I would put it is although specific concerns have been raised, you know, MMR and autism, or multiple sclerosis/ hepatitis B vaccine, and a number of these things have been studied and evaluated and found not to be safety signals or concerns. So I think some people's concerns have lessened, but there are still people who are very concerned about vaccination.

There is a large amount of concern about preservatives, particularly Thimerosal, that used to be in routinely administered childhood vaccines, is no longer other than in some flu vaccine.

So I think we and others have taken a lot of steps to either investigate safety, possible safety issues that people have raised or try to prevent some of those concerns, but there are still people who, you know, are very much concerned about vaccines, and I think this is still very high profile.

There is, you know, it's a tremendous thing if you think of a parent, particularly with a young child, who has an unintended event, and then you think of the number of vaccines that people are administered, there are circumstances where it seems very clear to people that the vaccine must have caused a problem, you know, when the epidemiologic or other data may not support that.

So it's a very complex area and it requires a lot of vigilance. The other whole issue there is that who has seen measles or polio

recently? So you have these people who don't recognize the potential benefit because they're not seeing the disease.

So I think we still have an important job to do. Our piece at FDA is making sure that these are high quality vaccines, well manufactured and that the studies support their safety. I think it's the public health system who then and the CDC and others who have to more deal with that interface.

CHAIRMAN BRACEY: Question from Dr. Birkhofer--Ms. Birkhofer.

MS. BIRKHOFER: Thank you, Mr. Chairman. Dr. Goodman, I appreciated your presentation. The clarity of it was helpful for me. And also FDA's recognition of the importance and appropriateness of collaboration with industry to assure that the needs of the public health are met with regard to vaccine development.

I was wondering if you could expand upon the internal processes or the criteria that the FDA uses to lead to expedited review and if you could

comment on the adequacy of resources within the agency to move rapidly to bring these vaccines to market?

DR. GOODMAN: Well, you know, I think we live by our laws and regulations and so that in terms of the actual, you know, time frames for approvals and actions, we follow those. When the Secretary or the President of all of us in the public health community identify something as a particular, you know, this is an extremely high priority, then we tend to do some of the kinds of things that I've talked about, you know, more meetings, you know, more visits to sites if they're appropriate.

All of this, as I mentioned, is resource intensive, and we want to also do it in an even-handed manner where for the things of equal importance, we're handling them in similar ways. So we try to be very scrupulous about that.

The budget for--there was a supplemental appropriation approved by the Congress and proposed by the administration, which does provide more

support for us, specifically in the area of pandemic influenza preparedness.

I think that will help. You have to train and bring new people along, build new capacity. So I think it's going to be a building process in this area. We have been very challenged and we're still challenged in many other areas of our activities to do what we can with the limited resources that we have.

It's kind of like the comment made from WHO, you know, we would never say we don't need more resources, but, you know, things have been quite tight, and I mention the not business as usual thing. We have so many things now that are not business as usual and, in particular, our Center has all these sort of urgent public health issues, you know, whether it's bioterrorism or the safety of the blood supply or, you know, things where we can't just say, oh, you know, go do a study and come back and talk to us next year.

I think a lot of the FDA is living in that world now. The expectations are very high and,

frankly, what's exciting to me is helping be part of the solution to many of these problems, and it is intensive and it requires collaboration.

CHAIRMAN BRACEY: In the interest of time, we'll take two more questions and then we'll have to move on to Dr. Schwartz because he has an appointment.

Dr. Bloche.

DR. BLOCHE: This is more of a comment than a question, but I appreciate your thoughts and reactions. The American people expect their vaccines and medications to be, quote-unquote, "safe," but as you've pointed out, part of the essence of this dilemma is that the risk is non-zero that a vaccine is not entirely safe, and politically elected or appointed officials are in a kind of awkward position here, to do--and I would urge a shift in the paradigm from risk communication to risk education--to do effective risk education.

You have to tell people in advance that what you're asking them to do is not entirely safe.

And here a very low risk, but presumably balanced off by the potential benefits if this pandemic developed.

So what are your thoughts and what are the agency's thoughts about how you get proactive and warn people so we don't repeat the swine flu Guillain-Barre fiasco of 25, 30 years ago?

How do you get out proactively and warn people that, yeah, some bad things are going to happen to people that wouldn't happen if you didn't give this vaccine, but those bad things are justified by the much greater potential benefits?

DR. GOODMAN: Well, I think, you know, this is a huge, huge challenge and you can see it even--well, it's very challenging for vaccine that's given to a healthy person or for a blood product that's often given to a healthy person or a person with a chronic disease, et cetera. Look at how even for therapeutic products that are given to people who are suffering acutely and want relief, these kinds of risk balancing issues have been real challenges.

I honestly think the only way is honest and clear communication of what you know and what you don't know in language that people can understand and the scientific and public health communities are not--that's not what we all do for a living. Some people are better at it than others, but, you know, I think we need to look at how public communication is best done. I know CDC is interested in this.

We're certainly interested in this. I totally agree with you. I don't think--you know, the flip side is you don't want to say to people, well, you know, this--I mean you want to express the information as you know it. You want to make clear its deficiencies, that if you've tested something in a few thousand people or maybe less, as it goes broadly out into the population, you may detect rare side effects and that things may occur coincidentally that don't have anything to do with the product.

We need to communicate those. On the other hand, if we think something is a net benefit

to people, you know, we need to express a public health opinion, you know, that, you know--but this is where it gets to like what happened with swine flu. You could say, gee, well, let's say you had an avian flu vaccine and we didn't know how--and an epidemic had just started--you don't know how big it is or you decide to use it for some people before that, I think you have to very transparent.

You know we don't know the risk of this disease to you, but, you know, here's what we know.If you get it, this could be a serious disease, and we know that that pandemic caused this, but, you know, it could be that it doesn't come or it could be that the risk isn't as high as we think, and then you've got to say and here's this vaccine or drug or public health intervention.

We think this will help for the following reasons. Here's what we know about its safety, but as it's used in millions of people, there are other things which could be observed, and treat people as intelligent beings and answer their questions and try to--let them, help them make informed

decisions.

But again I think that doesn't lend itself to the way the Internet, the news cycle and the culture is currently there. So I think we need to look to, you know, how people do public communication effectively in other sectors. For example, the private sector when they want to sell things or--I don't think we should be selling these things, but it's more a matter of effective communication.

I think it's one of the biggest challenges we face in this society right not, you know, and just then--and there's a much bigger thing than that, and that is the notion that you can control everything at all times, and that if anything ever happens, it's something you should have prevented and somebody is to blame. And in some cases, on the other hand, we have to be serious about preventing harm whenever we can.

CHAIRMAN BRACEY: Last question. Dr. Epstein.

DR. EPSTEIN: Yes. Thank you, Jesse, and

first I'd like to echo Julie Birkhofer's comment of appreciation for the clarity of your discussion of the vaccine issue.

My question to you is whether you wish at this point to venture any comments on the core questions for this committee, which are about preparedness of the blood system, addressing the scientific uncertainties surrounding risk from blood and efforts to improve interfaces and surveillance.

I realize that, you know, sort of antedates the general discussion of the committee, but you know you might have some valuable thoughts in this area.

DR. GOODMAN: Well, I think we do welcome the input. I think the paradigm of the task force, the AABB Disaster Preparedness Task Force--I don't know whether it's a group of that to look at the pandemic issue. Is it a subgroup of that or is it a separate group? But I think the notion of the people who really are going to have to operationalize having a working blood system both

from our end and the industry and public health and CDC, et cetera, people working together to explore these issues is the right approach.

I think this is--it's sort of a potential disaster, and you know people who, if you read some of the literature about, you know, the 1918 epidemic, it's quite striking what the stresses on a fairly non-complex health care system, agricultural system, will people have food; will they come to work? If you're caring for a sick relative, will your blood bank worker or health care worker come to work?

And I think the group should look at some of the worse case scenarios even within FDA. We have a group that's talking about, well, how do we do our core critical operations if you could have huge absenteeism rates? And, you know, I would look at some of these models, but I've heard things like 30 percent and this and that.

And we saw with 9/11 issues about availability of assays and diagnostics that you need to do efficient blood screening, and I think

the blood community is much better prepared about a lot of these things than the broader health care community or agricultural communities that are sort of our life support systems.

So I think the blood community, I would say, I know that CDC is working with hospitals and health care systems, but the whole issue of, you know, not only are you going to have to function, but it's going to be to function at a level exceeding your current surge capacity. So I think this whole issue of surge capacity, I think these are very important things, and what can we do to be prepared.

I don't want to totally blow off the viremia issue. I think, you know, I think that's worthy of consideration, but I think this is a, you know, where I would go first.

CHAIRMAN BRACEY: Thank you, Dr. Goodman.

DR. GOODMAN: Thanks very much.

CHAIRMAN BRACEY: We'll move, then, on to our last speaker for this morning or now this afternoon, Dr. Benjamin Schwartz.

Dr. Schwartz is a senior science advisor for the National Vaccine Program Office within the Office of Public Health and Safety, Public Health and Science for HHS. He's been primary author on a number of papers. He serves in a number of excellent and outstanding capacities in the world of vaccine development and antimicrobial therapy.

Thank you, Dr. Schwartz.

DR. SCHWARTZ: Yes, thank you, and because I'm standing in between you and lunch, I'm going to try and go pretty quickly. What I'm going to talk about in this presentation is the Health and Human Services Pandemic Plan and specifically vaccine and antiviral drug targeting as is indicated in that plan but also in subsequent discussions in the Department of Health and Human Services, as well as at the White House level, given that they're developing the National Pandemic Plan right now.

So just a brief chronology. I spoke before this committee in May of last year presenting what an influenza pandemic might look like and what our preparedness activities were at

that time.

Since May, there's been a lot that's gone on. On November 1, the president announced the national strategy for pandemic influenza, and the following day the HHS Pandemic Influenza Strategic Plan was released, and it's available on the Internet.

In December, there was a tabletop exercise that all of the cabinet secretaries participated in, and I highlight that as important for two reasons. One, it indicates the level of concern that pandemic preparedness has raised within the government and, secondly, because leading up to that tabletop, all of the cabinet secretaries had to think about a pandemic and make some decisions and there was a lot of discussion within our department about what some of the pandemic response activities would be.

And then ongoing, there's the development of the National Strategic Plan as well as departmental implementation plans. So in this presentation, what I'd like to do is begin with the

assumptions on the spread and impacts of a pandemic, and I share these assumptions for a couple reasons.

One is because I think they're important for us to understand what a pandemic might look like, what the impacts might be on the blood donors and on the blood community in general, but also because those assumptions form the basis for the recommendations included in the HHS and the National Pandemic Plans.

Then I'm briefly going to talk about pandemic vaccine and antiviral strategies and conclude with a couple comments on next steps and planning.

As we consider what the assumptions are for our pandemic, I think it's important that we first list what the caveats are in making these assumptions. Although there have been ten pandemics that may have occurred over the last 300 years, really we only have substantial information about the three pandemics that occur during the 20th century.

So our experience with pandemics is limited. In addition, each of those pandemics has been very different, so trying to generalize what a pandemic will look like when our historical record is three pandemics that differed greatly is very difficult.

And finally, the impacts that we're seeing with the H5N1 infections in Asia right now are very different from what we've seen in past pandemics.

Now, the virus certainly may change. The virulence may be less than what we're seeing in Asia right now, but I would like to highlight that when I present these assumptions, they do not include this spread of a virus that looks like the current H5N1.

Finally, extrapolations may be incorrect because of changes in medical care and society, and these changes include lower hospitalization rates than we've seen in the past century, improved medical care and the availability of antiviral drugs, as well as increased complexity of networks and global supply chains that are much more likely

to increase the infrastructure impacts of a pandemic compared with those that we've seen in the past.

So what I'm going to do now is to go through pandemic planning assumptions in three different groups. The first of those being illness and transmission.

We assume that the illness rate during the next pandemic in the initial wave will be about 30 percent, and it's interesting. When you look at past pandemics, regardless of the virulence, whether it's 1918, which was a very severe pandemic, or 1968 or '57, which were much less severe, in each of those pandemics, the rate of clinical illness was about 30 percent, with rates of hospitalization and death varying with virulence.

Transmission in a pandemic will occur by contact with respiratory secretions. It has done so in each of the past pandemics as well as with annual influenza. Because children have a higher virus titre as well as a higher infection rate and

closer contact with others, children play a large role in transmission of pandemic as well as annual influenza.

Finally, we assume that the average period between infection and illness will be about two days with viral shedding and some risk of transmission during the last half day of this asymptomatic period. This natural history of seasonal influenza infection is shown schematically on this slide.

So following exposure and infection, there is a two-day average incubation period during which time one is totally asymptomatic. For the first day and a half of that, the virus is latent. In other words, it's not transmissible, but for the last half day of this incubation period, one sheds virus and can transmit infection to others.

After the two day period, about two-thirds of those who are infected will be symptomatic and at higher risk of transmitting infection, whereas one third will remain asymptomatic, though still have the possibility of transmitting infection.

There are a number of important implications of this natural history of disease. First, disease may be spread by asymptomatically infected persons. Secondly, given that there is a two-day interval between infection until symptom onset, most of those who are asymptomatically infected when they board a plane over in Europe or Asia or wherever the pandemic might be coming from will still be asymptomatic when they get off the airplane, meaning that screening of individuals for fever or other symptoms at entry into the United States is not going to keep the pandemic out.

The second set of pandemic planning assumptions involves the impacts in communities and workplace absenteeism. We assume that community outbreaks will last about six to eight weeks, and again this has been a consistent pattern in past pandemics regardless of the virulence of the specific virus strain that has caused those pandemics.

At the peak of the outbreak, we assume that workforce absenteeism may be about 40 percent,

and I have to admit this number is kind of squishy. It includes absences due to illness because of caring for ill family members as well as fear of becoming infected at the workplace.

This peak rate of absenteeism will occur within the peak couple weeks of the outbreak and certainly will be lower before and after that peak. Absenteeism rates are likely to be different based on the severity of the pandemic. In other words, how many people stay out of work because they're scared to go to work as well as the specific occupation.

And public health measures such as closing schools or snow days where people are recommended to stay home in order to decrease transmission of disease obviously will also have an impact on absenteeism.

This slide shows the age-specific illness rates from the pandemics in 1918 and 1957. 1918 is shown in green. 1957 in muddy yellow. And as you can see, the rates of illness are greatest in children, particularly school-age children, peaking

at about 40 percent in those two pandemics, and then decreasing throughout adulthood among the working age population so that in 1918, among working adults, the attack rate of illness ranged between about 12 percent and 32 percent, and in 1957 between about ten percent and 20 percent.

Based on the numbers, from 1957 and 1968, Martin Meltzer at CDC did some modeling, looking at what work loss might be expected at the peak of a pandemic outbreak within a community. His modeling included work loss due to illness, hospitalization and death as well as caring for ill family members, but did not include estimates for how many people might stay home from work because they're scared of becoming ill, and in Martin's modeling, he applied low and high estimates for the number of days off work per episode.

The model suggested that in a pandemic outbreak, in a community, even using the more severe estimates, that only about ten percent of people would be off work because of illness or caring for an ill family member in a pandemic of

similar magnitude to 1957 or 1968. So that while overall somewhere between ten and 20 people may become ill during the entire outbreak, at those two peak weeks of the outbreak, Martin estimated only ten percent would be out.

Now, there are a couple clear limitations of this work loss model. First of all, it's unclear exactly what the duration of work loss would be with pandemic illness. Impacts are likely to vary between communities, industries and work sites, and again Martin's estimates were based on a less severe pandemic based on 1957 and '68 rather than the more severe pandemic of 1918.

So that really the unknown here is how many people will stay home from work because they're scared of becoming ill? And our estimate of 40 percent obviously includes a multiplier of several-fold of people staying home who are not clinically sick.

The final set of pandemic assumptions that I'd like to share have to do with seasonality and disease spread. We assume that the introduction of

disease into the U.S. will be at major travel hubs. That is if the disease doesn't begin in the United States. We assume that multiple areas will be affected simultaneously--and I'll show you data from previous pandemics supporting that point--that over one to two months the entire country will become affected, and that disease waves are most likely to occur in the fall, the winter, and possibly the spring.

This slide shows pandemic spread in September and October during the fall wave of the 1918 pandemic. And you can't read the caption here, but basically it shows a period between mid-September and early October with the darker-shaded areas having infection first.

So that you can see up in the Northeast and California were a couple of the earliest sites affected in the 1918 pandemic fall wave, but then you can see that there are a number of spots around the map of places that were infected early with the entire country being involved in the pandemic within about a month to a month and a half.

This slide shows the mortality of pandemic outbreaks in three cities, in Boston, Washington and San Francisco. And there are a couple points worth highlighting on this slide. First, you can see that the mortality peaks, the outbreaks in these three cities, overlap substantially. So that there isn't disease spread from east to west, west to east, but rather multiple major areas being affected simultaneously.

Second, you can see that the duration of the outbreaks in these communities averages about six weeks, and then, third, you can see after that tall peak occurring in September and October, that there's a smaller peak of disease occurring in January and that represents the winter wave of the 1918-1919 pandemic.

In 1957, the spread of pandemic disease across the U.S. was a little bit different. Pandemic cases first occurred in Asia in the early spring in February and March. Cases were first introduced into the United States by returning military personnel with the first cases coming with

a destroyer fleet that returned from the Far East and docked in Newport, Rhode Island. Cases also, then, were introduced into military bases on the west coast, and this is in June and July of 1957.

There was some spread of disease in closed communities and at specific gatherings like Boy Scout jamborees, but they were no community outbreaks of disease until the middle of August. The first community outbreak occurred in Louisiana when schools went back into session on August 12, but still disease did not spread widely until a fall peak occurred in September and then peaking in mid-October.

So lessons from the spread of prior pandemics suggest that depending on the timing and the season, that community outbreaks may be delayed after the cases are first introduced as they were in 1957.

There's no consistent pattern of spread with urban areas likely to be affected first, and national spread in one to two months, and many areas will have simultaneous outbreaks limiting our

ability to shift personnel and resources.

Well, given that background and given these assumptions on pandemic influenza, we developed the HHS Pandemic Strategic Plan, and as I mentioned the National Plan also is being developed, and I'm going to highlight a number of the issues associated with vaccine and antiviral drugs.

The HHS Pandemic Plan is centered around doctrine and guiding principles. And so the doctrine and guiding principles tell us what we would like to achieve in terms of our pandemic preparedness and response, but then looking more specifically under this big umbrella, we have the assumptions on the characteristics of a pandemic. We have the key pandemic response actions being identified as well as our current pandemic response capabilities, and when you compare the actions and the capabilities, you then identify gaps that need to be addressed for an effective response, and so what I'd like to do in the next few slides is to cover these key response actions, our current

capabilities and to identify the gaps that exist.

With respect to pandemic influenza vaccine, the doctrine is to have sufficient vaccine available for the entire population within a six-month period. If we assume that two doses of vaccine will be needed to protect people, that means we would need to produce 600 million doses of vaccine in six months.

Now, that far exceeds what we're able to do currently. Recognizing that our current vaccine supply is global supply with some of it produced in Europe and some in the United States, in a pandemic we assume that only U.S.-based production would be available to us, and currently there is a single U.S.-based manufacturer. For that manufacturer as well as for others, it may take four to six months for production of the first vaccine doses, and the capacity of this manufacturer depends on the amount of antigen required in each vaccine dose as well as the number of doses needed for protection, and I'll present some assumptions about much vaccine might be available recognizing that these are only

assumptions, and that the antigen content per dose really is the key variable.

HHS is supporting cell-based production and is looking to expand manufacture and production of licensed influenza vaccine in the United States, but licensure of new vaccines and development of new facilities will take at least five years to accomplish.

The National Institutes of Health has completed a clinical trial of H5N1 vaccine, and the results of that trial suggest that two doses of 90 micrograms per dose may be needed of this vaccine to achieve good protection.

Based on the current U.S. production capacity, this means that we could protect about 1.7 million people per month of vaccine production, or less than one percent of the population per month.

The manufacturer is expecting to almost double their capacity over the next year, but even then we would only be able to protect slightly more than one percent of the U.S. population with each

month of vaccine production.

Now, Jesse has mentioned these antigen sparing strategies where with adjuvants or with intradermal injection, you may be able to get a good immune response with less vaccine antigen. But even if we were optimistic and thought that intradermal injection of a tenth of a mil would be similar in immunogenecity to half a mil introduced intramuscularly, we would still be able to protect fewer than three percent of the population per month, only about a third of Americans in an entire year of vaccination.

And this clearly highlights the gap that exists in order for us to reach our doctrine, and the need to establish priority groups for these first vaccine doses that come off the production line.

HHS is also stockpiling what we call pre-pandemic vaccine and this is vaccine against potential pandemic strains with a target of having 20 million doses or the ability to protect 20 million people against strains that may result in a

pandemic.

Currently, there's a stockpile of H5N1 vaccine directed against a 2004 Vietnam isolate that will be sufficient to protect 5.7 million civilians and 1.8 million military personnel with delivery of some of this vaccine in February of this year. But because production is limited to those periods between annual production campaigns, the ability of manufacturers to make this vaccine for us also is limited.

In July of this year, the two advisory committees, the Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee issued recommendations on priority groups for vaccine and antiviral drugs, and these recommendations are included as an appendix to the HHS Pandemic Plan, and again are on the Web site that I showed you earlier.

For vaccine, there are four different tiers that have been defined as priorities for vaccination. Tier one includes essential health care workers and personnel at vaccine and antiviral

manufacturing facilities, those who are at highest risk of severe influenza disease, household contacts of those who cannot be protected with active immunization, as well as key government leaders and pandemic responders.

Other tiers you can see below. Tier two, other high risk people and critical infrastructure groups. Tier three--I don't know why they did this combination--but it's health decision-makers and mortuary personnel.

[Laughter.]

DR. SCHWARTZ: I don't know if it's a comment on the decision-makers. And then finally, healthy people who don't fall within other groups. So these were the recommendations that are listed in the Pandemic Plan.

However, in the thinking that led up to the cabinet tabletop exercise, Secretary Leavitt, who is really personally involved in pandemic planning and preparedness, enunciated several principles that he thinks are important as we consider vaccination.

So Secretary Leavitt believes that pandemic vaccine and pre-pandemic vaccine should be targeted in order to preserve national security, to preserve constitutional government, as well as to preserve critical infrastructures, with states making the decisions on specific priority groups.

A potential allocation scheme that he has suggested is to take about five percent of the vaccine that we have available to preserve constitutional government, another five percent to support federal health care providers such as the VA, the Indian Health Service and the Bureau of Prisons with the remainder being allocated pro rata to the states.

The National Plan, which is being developed under the auspices of the Homeland Security Council adds to the discussion of vaccine priorities by suggesting a couple pivot points for vaccine priority groups. And that is suggesting that the priority groups for pandemic vaccination would depend both on pandemic severity as well as on the available vaccine supply.

So if you look at the situation with relatively low vaccine supply, in a very severe pandemic, that supply should be targeted toward critical infrastructure, which without vaccination might collapse.

However, in a less severe pandemic where the threat to critical infrastructure may be less, a limited vaccine supply might be targeted to those who are at high risk for death or for severe illness, and then if supply is greater, you can obviously expand the number of groups that you might target for vaccination.

Now, what about the blood community? In the ACIP and NVAC discussions, blood center personnel were included as a priority group. They don't appear explicitly in the document, but were certainly looked at as a critical infrastructure. However, other groups that have been discussed by this committee that Jerry asked me about in preparing this presentation such as platelet or stem cell donors were not discussed as part of that process.

In terms of the HHS and national discussions, those have been largely focused on principles, but no specific target groups have been identified, so that is the current situation with targeting for vaccines.

With respect to pandemic antiviral drugs, the doctrine in the HHS plan is that there should be sufficient antiviral drugs in a stockpile for 25 percent of the population as well as some courses available for containment overseas as well as outbreak control for the first U.S. cases.

Translating the 25 percent into an actual number means 75 million treatment courses with about six million being proposed for containment and outbreak control.

Our current assets in the Strategic National Stockpile include about 4.4 million courses of neuraminidase inhibitor primarily oseltamivir, or Tamiflu, but also some zanamivir, or Relenza. In addition, the military and the VA both have their own stockpiles.

For oseltamivir, there are approximately

two million courses at pharmacies and at the manufacturer and distributors before the influenza season as well as a U.S.-based supply chain with a production capacity of about 1.5 million courses per month.

The proposed strategy for expanding the stockpile is for HHS to purchase a total of about 50 million courses with states purchasing the remaining 31 million courses with some federal matching funds to sweeten the pot for them.

And what I'd like to emphasize here is not the specific numbers because I'm sure those are still being discussed, but rather the idea of a federal and state partnership so that some states actually may have more antiviral drugs available whereas states that may decide not to purchase their share would have less antiviral drugs available in a pandemic.

The National Vaccine Advisory Committee went through the same process with antiviral drugs as with vaccines and has recommended priority groups and strategies, and they're shown on this

slide, and again, they're also in the document on the Web site.

The recommended groups are listed here in priority order and begin with patients who are admitted to hospital and include then both patient groups as well as infrastructure groups. The strategy that is primarily recommended is a treatment strategy which is far more efficient in terms of the amount of drug that's used than a prophylactic strategy and modeling suggests prevents far more deaths than could be prevented with prophylaxis given a limited drug supply.

As was done with vaccine, Secretary Leavitt enunciated a number of principles with respect to antiviral drug use and allocation, and they include use of antivirals to help contain an initial outbreak and delay the spread of disease if it's feasible, to reserve the drugs for treatment rather than prophylaxis, and for state decision-making on targeting.

The proposed allocation includes five percent to contain an initial outbreak, five to ten

percent to slow the spread of disease within the U.S., and the same five percent to preserve constitutional government and five percent for federal health care providers with the other 80 percent or so going to the states.

With respect to the blood supply and the blood community, the NVAC discussions again included blood center personnel as a priority group, but other groups were not discussed, and the HHS, the national discussions focused on principles but don't identify specific target groups.

So in conclusion, I would suggest that the HHS doctrine for both pandemic vaccine and antiviral drugs, once the doctrine is met, once the supply goals are met will certainly minimize the need for targeting and for designating priority groups.

However, there is a significant gap that for vaccines will likely remain for more than five years, and for antiviral drugs, we expect that the stockpile purchases will be completed in 2007 so we'll have a gap for a couple of years with respect

to antivirals.

The specificity of federal and HHS guidance on priority groups is really unclear. And as I've suggested, at the HHS and the national level, the focus is primarily on principles with a lot of latitude for state decision-making.

So that I think integrating the blood community into discussions both at national as well as state levels, where the decisions ultimately may be made, would be particularly important.

Thank you.

CHAIRMAN BRACEY: Thank you, Dr. Schwartz. Question from Ms. Birkhofer.

MS. BIRKHOFER: Thank you, Mr. Chairman. Dr. Schwartz, I have two points I'd like to hear your comments on. The first part of your presentation was, I think, learning from the past, and I agree, we can learn a lot from the past and from history, the overview of the 1918 and the 1957 outbreak, and I noted with interest your focus on schools when children returned in August to schools in 1957. I notice also your focus on work loss in

adults, and you know more adults may stay at home, but how much focus is there on children with regard to education and prioritization for vaccine?

So that's my first point. I'd like to hear a little more discussion on children as a vulnerable population.

And then secondly, when you talked about the targeting for vaccines, the ACIP and the NVAC recommendation of the blood center personnel as a priority, I would ask that included in your discussions that the prioritization of plasma collection facility workers as well as plasma fractionation facility employees be on your radar screen.

Clearly, those personnel in the collection centers and the fractionation facilities serve a valuable public health role in terms of their production of life-saving therapies. So we are working--the plasma industry is working with the AABB committee, Disaster Planning Committee, and I would just ask that in addition to the populations you described, stem cell, et cetera, that you take

into consideration the importance of the plasma collection facilities and fractionation.

DR. SCHWARTZ: Great. Let me respond to those two points. First, with respect to vaccinating children, there's a lot of modeling, mathematical modeling, as well as some clinical trials, that suggest that vaccinating kids will prevent disease in adults by decreasing transmission of infection.

And I think that that likely is true. The problem in a pandemic is that given the very limited supply of vaccines, we really don't know how many children would need to be vaccinated in order to really observe this indirect effect and we have such pressing needs in terms of protecting our critical infrastructure that I think the vaccine in a limited supply situation would be targeted directly to those who would support that critical infrastructure, maintain security and constitutional government.

Whereas, in a situation where there is a lot of vaccine, perhaps the one where this doctrine

is met and we can vaccinate everybody within six months, children would be higher on the priority list.

With respect to plasma and platelet donation and all of the other things that encompass what I might call the blood community, and I do express ignorance in what the best terminology to use is, I think that what would really be important is for your committee to communicate directly with Secretary Leavitt and with the folks as high in the department as you're able to speak with. Dr. Agwunobi, the Assistant Secretary, I think would be a good focal point to represent your interests within the department.

But I think it's also really important that you work at state levels and that you participate on the groups that are developing pandemic plans at the state level because, as I indicated, there's going to be some federal guidance but a lot of latitude for the states to make the designation of priority groups at that level.

And so I know it's a lot harder to work in 50 states than with one national government, but I think that work would be well served.

CHAIRMAN BRACEY: Dr. Roseff.

DR. ROSEFF: I have a question about the distribution of Tamiflu and antivirals. We had some of our readings before the meeting about the drugs not being allocated properly and consumers asking for it and stockpiling it themselves. Are there currently mechanisms in place to monitor that or will there be if there's a need for the drug considering the amount that's available?

DR. SCHWARTZ: Yeah, before this influenza season, individuals and organizations were basically purchasing all the Tamiflu that was available, and there was a lot of concern about their not being drug left for people who became ill and really needed the therapy this influenza season.

So for that reason, the manufacturer actually stopped distributing Tamiflu to make sure that supply was available for patients who became

sick this year.

We certainly understand that people want to have a personal home stockpile. There are a number of risks with doing so. The drug certainly may not be stored properly. It may become outdated. It may not be potent at the time a pandemic occurs, and certainly it may lead to mail distribution of drug that's available.

So I think our focus is, first of all, to assure that we have the ability to fill up the national stockpile and that states take seriously their duty and obligation if you will to participate in that stockpiling activity, and then we need to communicate and educate the public about what the risk is and how we think that people can reduce their own risk of developing influenza in ways other having some Tamiflu in their medicine cabinet.

CHAIRMAN BRACEY: Question. In terms of the broad term critical infrastructure, I would assume that the vision currently is that the blood industry is not viewed as a component of the

critical infrastructure in the eyes of HHS currently; is that right?

DR. SCHWARTZ: Well, you know, I talked at this committee in May, and I went back to the ACIP and to NVAC and said here is a group that really is a critical infrastructure and that may not be included in a health care worker priority group because, you know, many blood center donation staff are not considered health care workers, and I think they took that to heart and said this was included in the discussions leading up to recommendations in July of last year.

And so the blood community is considered to be a critical infrastructure, but there is not a lot of specifics in terms of what that designation means, and that's why I think that the active involvement of this committee in the decision-making process at HHS nationally and in the states will be useful.

CHAIRMAN BRACEY: Dr. Katz.

DR. KATZ: Dr. Louie Katz, Mississippi Valley Regional Blood Center. I'm involved in

statewide influenza pandemic planning, and I want to emphasize to the committee--I think you already understand this--that at the level of each state, the planning processes are in different stages of maturity and the medical and political and other considerations, the relative pressures in various jurisdictions are enormously different.

And for the blood community in an individual state to raise the blood community's priority to that of critical infrastructure is going to be highly variable, and I think it is absolutely necessary that this committee make it clear at the level of the Feds that we are, so that the argument doesn't have to occur, so that the blood community can sit at the table and be recognized as part of critical infrastructure and that part of it will be taken care of.

Otherwise, I found it a very difficult sell to my state health department as an individual from a little blood center out in the middle of nowhere.

CHAIRMAN BRACEY: Thank you. Dr. Sandler.

Dr. Sayers. Sorry.

DR. SAYERS: Thanks. Do you know if there are any major differences in the public health strategies here and in Canada towards this threat?

DR. SCHWARTZ: There are not significant differences. We've worked with the Canadians in developing their recommendations and vice versa, and our strategies look very similar.

The strategies of other industrialized countries such as the UK and France also tend to be pretty similar.

CHAIRMAN BRACEY: Thank you for a very informative presentation. Two more questions. Sorry. Dr. Wong.

DR. WONG: Given the vaccine development that time and the stockpiling supply, is there a gradual sort of priority list for saying using amantadine for regular flu, saving Tamiflu for possible pandemics and Relenza for Z-strains?

DR. SCHWARTZ: Amantadine and rimantadine, which are in the same class of drugs, when used for therapy, induced resistance pretty rapidly, and so

I think probably the best course in using those agents is to use them primarily for prophylaxis, for example, among nursing home personnel, and they are used widely in that setting.

In a pandemic, we believe that it's likely that strains would be amantadine and rimantadine resistant such as the H5 strain in Southeast Asia is. And so I don't think we can rely on those drugs in a pandemic.

However, there have been some who have suggested that if the isolate is susceptible to the adamantanes that their use as part of combination therapy with the neuraminidase inhibitors may be useful to decrease the development of neuraminidase inhibitor resistance, and so there is still a lot of discussion on what the best use of those drugs might be.

CHAIRMAN BRACEY: Commander Libby.

CDR LIBBY: In your experience with the vaccine development technologies, would this vaccine always be injectable vis being an oral vaccine? I'm talking about donor deferrals. Would

there be any time in the future that the vaccine could be in a pill or a FluMist and be a live vaccine at all or--

DR. SCHWARTZ: Well, we do have the licensed live attenuated vaccine FluMist that is manufactured by one company. The primary focus of the companies that are making egg-based as well as cell-culture based vaccine is on the inactivated vaccine.

So, you know, I think the live vaccine concept has proven to be successful with the licensure of this product, but, you know, most of the industry is still thinking of the inactivated products.

CHAIRMAN BRACEY: Thank you. One last question. Dr. Angelbeck.

DR. ANGELBECK: Given that we have a five-year gap in the vaccine--

DR. SCHWARTZ: At least.

DR. ANGELBECK: At least.

DR. ANGELBECK: --a two year gap, at least, in the antiviral, that leaves us, it seems

to me with only one strategy which is containment.

DR. SCHWARTZ: Hope. That's the second strategy. I'm sorry.

DR. ANGELBECK: Well, hope and luck. Am I correct?

DR. SCHWARTZ: Well, let me talk about containment if that's where you're going with this.

DR. ANGELBECK: Yes.

DR. SCHWARTZ: And, you know, we've worked with mathematical modelers to look at whether a pandemic could be contained, and so what they did was modeled an initial outbreak occurring in rural Thailand and asked the question how likely is it that containment would be successful and what would we need to do to succeed?

The model suggests that if we identify the outbreak, if we identify person-to-person transmission within about three weeks of when it first occurs, if we can respond effectively by identifying cases, by coming in with antiviral drugs and treating cases and giving geographic prophylaxis, you know, picking five or then

kilometers around the cases and just giving everybody antiviral drugs, and if we can isolate and quarantine and increase social distance by closing schools and workplaces, we have a high probability that we could stamp out the spark and prevent a pandemic.

But there are a lot of if's. I mean if we can identify it early, if we can respond effectively, and so I think there's a lot of interest on the part of our government in contributing as part of a containment effort that would be led by the World Health Organization, but whether it works or not depends on a number of critical variables.

DR. HOLMBERG: Just one additional comment. What are we doing as far as education, especially at the state public health level for hygiene, just the fact of handwashing?

DR. SCHWARTZ: Yeah, and the measures that individuals can take to protect themselves like personal hygiene are important. Mask use by the public is something that has been discussed

recently, so that if you talk about the measures that might be taken, you have individual measures and also community measures like school closing, snow days, et cetera, and all of that is being discussed and modeled as possible.

CHAIRMAN BRACEY: We said we would have one last, but Dr. Bloche, you are the ultimate.

DR. BLOCHE: I'll be brief. If there is a focal outbreak, say in Southeast Asia, of human-to-human, are there the legal mechanisms in place and is there the political will to quickly move our scarce vaccine and Tamiflu resources to that point to try to do containment?

DR. SCHWARTZ: Yes. I'll answer a little less briefly. The World Health Organization has a stockpile of Tamiflu. It's a vendor-managed inventory and when their stockpile is complete, it will include about three million treatment courses which the modelers suggest would be sufficient to contain an outbreak.

In addition, the Secretary, Secretary Leavitt, has indicated that he would commit five

percent of our stockpile for use as part of a containment strategy and he has suggested that that might be forward-deployed to Guam where it could easily get to Southeast Asia in a very short period of time.

DR. BLOCHE: Is that five percent enough based on these models?

DR. SCHWARTZ: In addition to what WHO has available, I think it is, and what other industrialized countries might contribute.

CHAIRMAN BRACEY: Thank you, Dr. Schwartz. We'll--actually Dr. Goodman, a burning question, I see.

DR. GOODMAN: No, this is a comment.

CHAIRMAN BRACEY: Or a comment.

DR. GOODMAN: Since I have to run off at lunch. But just one comment. I have to say I think Ben's projection of five years for a vaccine is reasonable, but, you know, we're proceeding hopefully a little more, proceeding very aggressively, and so we can't rely on anything, I think, but, you know, I'm hopeful that if, for

example, of a particular adjuvant strategy works, some of the cell culture vaccines are in fairly advanced development.

So I think given the resources the government is investing and the way we're going to look at these things, there is hope for something in that area before then, but I think in terms of the time frame for public thinking and expectation, that's reasonable.

The other thing, and I'm only saying this because it was raised, I think, in one of the earlier questions before Ben's talk or maybe in Jerry's commentaries, but very important to know that there are a lot of unknowns about the efficacy of both vaccines and antivirals in a pandemic. The pandemic strains, for example, may drift enough from the vaccines that we produce in the pre-pandemic that protection may be partial or absent, and that's one of the problems with that strategy.

And then with the antivirals, it's very, very important to remember this isn't penicillin for, you know, strep throat, that, you know, really

the benefits even in annual influenza are in terms of a slight reduction in severity and days of illness.

So, again, in our education of ourselves and our strategies, it's important that while they are highly effective in prophylaxis for sensitive strains, their effect in treatment is incremental. And we don't know again with a pandemic strain, what that will actually pan out to be.

DR. SCHWARTZ: I certainly agree, Jesse. I think there emerging data with antiviral drugs that they have an impact on lower respiratory infections, hospitalization, and even mortality in high risk populations, and these are, you know, coming out through metanalyses and through epidemiological studies.

But certainly we need to be cautious on what we predict the impact might be.

CHAIRMAN BRACEY: Thank you, Dr. Schwartz. We'll take a one-hour break and reconvene at ten minutes after two.

[Whereupon, at 1:10 p.m., the Advisory

Committee recessed, to reconvene at 2:15 p.m., this same day.]

A F T E R N O O N S E S S I O N

[2:15 p.m.]

CHAIRMAN BRACEY: Good afternoon. We will resume the presentations. Our next presenter will be Marc Wolfson, and here we are. Mr. Marc Wolfson has been a public affairs officer for 26 of this 31 years with the federal government. Looking at his list of interactions, they've been extensive, including communications of Exxon-Valdez oil spill, Haitian migrant crisis. It goes on and on including some experience with hurricanes, Oklahoma City bombing, et cetera.

He will speak to us today on risk communication in an influenza pandemic, something that we've talked about.

Thank you.

MR. WOLFSON: Good afternoon, ladies and gentlemen. It's a pleasure to be here, and let's get started. You've been focusing on the pandemic influenza all day and to set the stage for the communications end of things, taking a look at some of the things that we would be faced with in trying

to manage an influenza pandemic. Of course, some of the key elements involved initially are surveillance activities, moving right into dealing with the quarantine and isolation issues.

Of course, there will also be some societal interventions that may be necessary such as closing schools or social distancing, limiting large social gatherings.

And then, of course, as some of the earlier presenters discussed, the issues of vaccines and antivirals. One of the most important things in the communications world to think about is the fact that we're dealing with a situation which is basically immune to political boundaries, and a response to a pandemic outbreak is going to rely a lot on how successful we are in communicating, and we're not dealing with something that knows boundaries and therefore we are for the first time actually working with our colleagues in WHO on communication strategies, on an international level.

Last month some of my colleagues from HHS

and CDC met with their counterparts in Geneva from a number of countries to begin for the first time ever planning communication strategies on an international level on how we would deal with an influenza pandemic.

Of course, one of the big differences between the now famous Spanish influenza outbreak of 1918, which has been reported on widely and used as an example, in today's world, we live in a 24-hour news cycle. We can't just say at the end of the workday, it's over until tomorrow morning. The news keeps flowing. CNN and Fox and the other 24-hour news stations continue broadcasting.

The Internet keeps operating. We have bloggers out there. We have podcasts going on, so it just never stops, and the voraciousness for information, especially in a situation like this, is going to be absolutely huge.

Today, just in today's newspaper, you read about the most recent death reported in Turkey. A young boy in Turkey died, and we know about it here in Washington within hours of a confirmation of the

death, so that's the kind of situation we're dealing with.

Secretary Leavitt has taken the forefront on our communications with this, and you may have heard him say this, and I think it's very important. One of our key goals is to inform the public without inflaming them. People have a right to know what's going on. They need to know what the truth is so that they can make informed decisions to protect both themselves and their loved ones.

Now, you've probably already gone over this particular part of my presentation so I won't linger on this too long, but WHO has set up a series of phases dealing with pandemics with the phase one and phase two being where there are no new strains, and we don't really have a threat going on.

Then we move into the pandemic alert period in phase three which is where most experts think that is where we're at right now, is phase three, where human infections with a new subtype,

but there is no human-to-human spread or at most rare instances of spread as a result of close contact.

We may be starting to approach phase four, but I'll leave that to my colleagues who are more expert on that area.

Of course, phase six is when we actually are in a pandemic, and then we move back into the post-pandemic period once it's over.

I think of most concern for all of us in the communications arena is when we find ourselves moving from phase four to phase five, and what I mean by that is phase four is when you have human-to-human transmission in a localized area and phase five is when those localized areas begin to grow, and when that happens, the tactic that's been most discussed among the experts is trying to localize the containment, trying to cut it off there, you know, like if you think of it as a wild fire where you're trying to hold it from spreading further.

Of course, the news media, they report on one or two deaths in Turkey. You can imagine what

would happen if this thing starts to spread a little further. The media has been sensitized to the word "pandemic" so they are immediately going to start saying the pandemic is coming, the pandemic is coming, and there will be an overwhelming need for subject matter experts who can appear on television and be interviewed by reporters, and if the news media can't get their experts from the government, from CDC, or from NIH or any of our other sources, you know very well that there are plenty of sources out there that they will go to to have people speak on the issue.

Our communications objectives, as this begins to spread, of course, number one, we want to communicate the seriousness of human-to-human transmission and start to prepare the U.S. public for the possibility that the virus might indeed spread to the United States.

We need to start talking to them about the tradeoffs involved in sharing some of our stockpiled antivirals and possibly vaccines in order to hold it where it is rather than having it

spread.

And, of course, we're going to have to manage expectations. The likely success of containment overseas is pretty sketchy, so we need people to understand that even if we do use some of our antiviral stockpile overseas, that doesn't guarantee that it's going to stop the spread.

And, of course, all along we're going to be developing and clarifying both our visual and our spoken messages, identifying who our key spokespersons are, who we feel are well-spoken and the public grows to trust so that we have people that we can use.

It's very important in our planning for communications that we realize and that, of course, you realize, you understand that we're not just dealing with the news media, that there are a number of special audiences out there that have important information need.

All of you in the health care community have special information needs and your communities turn to you as experts so it's very important for

all of us at the federal level to make sure that that information gets to you in a way that you can use it quickly and easily, and the emergency communications plans that we have at HHS and CDC actually break us into teams where we have teams that are developing information for all of these specific target audiences.

Some of the key messages that we would be trying to impart during this particular phase would be, number one, making sure that people understand at this point we have not found the virus in the United States yet; that we're working very closely with the WHO and our other international partners to try and contain this where it has begun; and again the American public needs to get used to the idea that this is an international effort, that this is not just the United States, that we're working with the WHO and our international partners.

They need to understand what domestic surveillance is and what we're doing to watch out for the spread of it in the United States, how

we're monitoring passengers coming in from outside the U.S., and what particular preparedness efforts that we are undertaking, and what people can do for preparing for the possible spread.

So how do we do that? Well, one of the key tools that we use now in risk communications is what we call message maps. And what message maps are, they're a risk communications tool that's used to help organize complex information like we would be dealing with in a situation like this, and make it easy to understand in a way that the news media finds it easy to use and the public finds it easy to distill.

The challenge is working with our subject matter experts in these areas. It takes a team of communications folks and subject matter experts in these areas to develop these messages and then distill it down to a level where we're actually pointing to a sixth grade reading level.

To give you an example of how message mapping has been used in the past, one of the biggest successes of message mapping of recent

times was in the wake of the World Trade Center attack and Mayor Rudy Giuliani, and as you know, he's been on the lecture circuit since the attack, and he's made a number of speeches talking about his experiences, and one of the things that he would tell you is that you know that the World Trade Center was initially attacked back in 1993, and shortly after Mayor Giuliani took office, he turned to his team and he said I want to plan, I want to make sure that if we are attacked again, that we know exactly how we're going to handle this, how we're going to communicate, and he brought in some risk communications experts.

One of the foremost leaders in this area, who has been working also with us on these message maps, is a fellow by the name of Dr. Vince Covello. And they actually developed messages that they felt would be appropriate in the event they had a major attack in New York City with large loss of live, and the one particular message that I recall that's kind of burned into my brain and it follows the pattern of these message maps that Mayor Giuliani

used was when he was initially asked at one of the news conferences how many people do you expect have died in this attack?

And I don't know if any of you remember what he said, but what he said was that more than any of us can bear, but he didn't stop there with just "more than any of us can bear." He went on, and he said, but New Yorkers are a strong lot; we're a strong people. And we will learn from this experience and move on. We will get through this.

And that message was written five years before the attack occurred. It was heartfelt. He really meant it when he said it, but he didn't think of that off the top of his head. That was developed ahead of time.

How was it developed? Well, here's how message maps work? What you're looking for are three short phrases that convey three key messages in 30 words. It's kind of easy to remember--3, 3 and 3.

Now, this approach is a scientific approach. It's been developed using surveys, and

it shows that the lead stories, the main stories in both newspapers and broadcasts usually convey three key messages, and in the news, the sound bites are usually around nine seconds, and the main message in a story is usually in those first 30 words of print.

So that's what we're aiming for when we develop these message maps. Mayor Giuliani's "more than we can bear, but New Yorkers are strong and resilient, and we will all get through and be stronger and learn from this afterwards." So that was his message.

Now, let me give you an example of one that we've been working on. Now, we've been working on these message maps for pandemic influenza for about six months now, and we're developing quite a database of them, and I just have one example here to give you an idea of what they're like.

The question what should people do if there's an outbreak of pandemic influenza? Okay. So the first key message that we want people to

know is that they should stay informed about the prevention and control actions. Listen. We want people to listen. Now, when we develop these message maps, the way we work it is for each of those three key messages, we developed three supporting facts.

So what you'll see on this slide here is there are three supporting facts. Now if you're in an interview situation, and you're discussing this with the reporter, obviously you're going to have more time to speak with the reporter in the news conference than nine seconds or 30 words. So this is the backfill information that you can use to support each of your three key messages.

In this case, staying informed. What do we want them to do? Well, public health officials are going to be out there sharing information. The information is going to be shared in a variety of ways. CDC has a hot line. There's a special Web site available, and we also want people to know that they have to be informed and they have to be cooperative in order for public health efforts to

succeed. So those are the three facts that fall under this part of the message.

What's the next part? People should use this information about prevention and control to care for themselves and their loved ones. And again, three supporting facts under that. We're going to provide information on signs and symptoms. People should practice good health habits and they should discuss their health concerns with their health care provider, their health department or other trusted sources. So again three supporting facts.

Finally, people should take common sense actions to keep from spreading germs, and again three supporting facts under that.

So how do those three things fit into a 30 word, nine second sound bite? Well, there's your 30-word, nine second sound bite. People should stay informed. Remember what the question was. What should we do if there's a pandemic influenza outbreak in the United States?

Our first message is people should stay

informed about prevention and control actions, use the information to care for themselves and loved ones and take common sense actions to keep from spreading germs. That's the message. Okay. That's the basic message.

Then you can go back in your interview or your discussion and reinforce these message with those supporting facts that were developed.

Now, as I said, we've been working on message maps like this for hundreds of questions, and we're building a large database. This database is being shared with our partners at the state and local level so that they will all have the information.

When I'm finished, I've brought along some of our initial message maps on a series of different questions, and I've brought them along to share with you so you can take them with you.

So within the federal government in terms of communications, we have three main lead roles. Of course, Health and Human Services has the lead for health communications.

The Department of Agriculture is leading the issues on animal health communications. And in fact, I just saw in the wires today that the Secretary of Agriculture is giving some major speeches today in St. Louis, Missouri on avian influenza from the agricultural perspective. So he's out there also trying to inform people about that aspect of it.

And of course the Department of Homeland Security which leads incident management and communications. Now, one of the things that's come up in the media about this is people saying, well, who's really in charge of pandemic influenza? We want to know who's in charge? And what we've been trying to explain to them is that with regards to the medical response, the Department of Health and Human Services, the Centers for Disease Control, which is part of HHS, that is the lead for the medical side of it.

But the fact of the matter is that a pandemic outbreak in the United States is going to affect all aspects of our society, all aspects of

our economy, and therefore it's going to require significant coordination among all the departments and that's the role the Department of Homeland Security plays in coordinating activities like that where more than one element of society are involved.

So that's how the roles and responsibilities are broken up. Now, in order to coordinate activities, I know you can't read this slide, but let me just explain to you what's up there and I also have made copies of my slides that you can have at the end of my presentation. But the box in the middle, the square in the middle, represents a real first for us, and that is that we are actually going to form a National Joint Information Center. It will probably be here in Washington, and there will be lead public affairs officers in there from Health, HHS, from Agriculture, and from Homeland Security, and with a supporting cast of probably hundreds, and those folks are going to be developing public education and awareness activities.

They will be monitoring the media. They will be employing the message maps that we've developed, so forth and so on. The things that they will be doing are listed on the right hand side of the screen.

On the left-hand side of the screen are the people who will be participating along with these leads in there, and that includes both not only the three agencies I've described, but all of these other agencies, Treasury, Education, Transportation, Energy.

We will have international partners in there. The state and locals will be tied in via Internet and conference calls. The private sector will be involved. Non-governmental organizations will be involved such as obviously the American Red Cross and obviously this information center will also be briefing the news media.

So this is the planning model that we're using and we will employ in the event that we do have a pandemic outbreak.

Secretary Leavitt has taken the lead on

this, as I mentioned. He's been moving forward quite vigorously on this. He held a national summit here in Washington with representatives from all 50 states back on December 5.

They discussed the pandemic plan and what the states might expect and he listened to their concerns, and he announced at that time, that he has committed to holding summits like that in all 50 states. The first one which was kind of a pilot run summit was held in Minnesota back in December. Tomorrow, the Secretary and his team will be in Arizona.

They've already scheduled four more for January in places such as Vermont, West Virginia, Rhode Island and Georgia, and there's already five more being scheduled for February, and I think that is going to continue to snowball and more and more states will be added to that list of summits as we move forward.

So there's a lot of activity going on. One of the other products that my office is working on which I think is going to have its initial

rollout in Arizona tomorrow, that's a Citizens Guide to Pandemic Preparedness, which is a basic informational brochure that goes over some of the basic messages that are in those message maps for the public and includes a basic checklist for families and individuals on what they need to be thinking about with regards to pandemic preparedness.

So that is my presentation in a nutshell. If you have any questions at this point, I'd be happy to entertain them. My contact information is also listed on here, and again I have printouts of the slide show so that you can take them back. And if you have any questions when you get home, please feel free to e-mail me. I might mention that--it's probably been mentioned earlier today--but the pandemicflu.gov Web site has an awful lot of information on it including a lot of the risk communications information that I've been talking about today and ultimately this database of message maps will also be up on that Web site.

So with that, I'll open the floor. Thank

you.

CHAIRMAN BRACEY: Thank you. Questions for Mr. Wolfson. Yes, Jerry.

DR. HOLMBERG: Yes, Marc, will the brochure that you've just talked about, the Family Preparedness, will that be on the Web site also?

MR. WOLFSON: Yes, it will, and I'm not sure how, if they're going to be printing literally hundreds of thousands of copies of that. I think it's primarily going to be made available electronically. It's also the files will be made available to the states and local so that if a local health department decides they want to print out copies and hand them out, they can do that.

CHAIRMAN BRACEY: I've got a question. You mentioned it in your presentation, but it strikes me in this era where you can get information from just about anywhere, a major issue is validating the source of the information, and I would imagine then that a big part of the plan would be to in some way make this message the tool, a validated message, but could you speak a little

bit more on that?

MR. WOLFSON: Yes. And again, as I mentioned, the issue of subject matter experts and who's speaking and the fact that people can use the Internet to search out information and sometimes get incorrect information is a real challenge to all of us.

The message that we always try to impart is that we want to be first, we want to be right, and we want to be credible, and being first is often the big challenge. And in order to be first, sometimes it means getting your boss, and that oftentimes is Secretary Leavitt or Dr. Gerberding, out there in front of the cameras before they're totally comfortable with the situation.

And in order to do that, you know, they need to be able to do that and say what we don't know and know--and it's been shown in the research that we've done and the reaction that we've gotten from the public that they would rather hear Dr. Gerberding say we don't know this yet, but here's what we're doing to find out than for us to not to

say anything and let them find their information from another source.

CHAIRMAN BRACEY: Dr. Epstein.

DR. EPSTEIN: You may have already answered the question I have in mind, which is your advice on communications regarding risk and uncertainty. It's well and good to tell people to follow public health recommendations for prevention and so forth.

But the bottom line often is we don't know the risk and, for example, one of the big issues is going to be whether people are going to hunker down in their homes or they're going to go to work. And, you know, how exactly do we get our arms around the uncertainty and risk issues?

MR. WOLFSON: It's a real challenge obviously, and we're going to have to rely heavily on our experts to give it our best shot in terms of when do you pull the plug, when do you say it's time to go into a "snow day" mode and have people try and telework and minimize social contact?

I'm not sure when that happens, but I

really don't have an answer for you on that.

CHAIRMAN BRACEY: Dr. Pierce has a question.

DR. PIERCE: Within the various phases that lead up to the pandemic, what are the trigger points. What are example trigger points that would tell you to initiate this whole communication cascade?

MR. WOLFSON: Well, what I focused on in my presentation was the move from phase four to phase five which was where we have localized--we have pockets of cases where it's obviously being human-to-human transmission, but it's just beginning to spread, and as I mentioned, the challenge there is we're at a point where it has not reached the United States yet, but it's clearly become--human-to-human transmission has become an issue and the possibilities of it jumping the borders or reaching our shores are much greater.

Trigger points, I think that we need to go into full pandemic communications mode as the media. We have to try and help the media

understand the situation, and as I said, as soon as they see human-to-human transmission is easily occurring, they're going to start talking pandemic, and they're going to start speculating on how long is it going to take to reach the United States, and they're going to get people to come on the air who are willing to speculate, who have letters behind their names that make people think they know what they're talking about. So there's the challenge right there.

CHAIRMAN BRACEY: Follow up?

DR. PIERCE: So then a related question. For instance, the case in Turkey, are you prepared to address whatever the media may be developing in the way of stories to give it more--

MR. WOLFSON: Yeah. We very closely monitor that, and that's one of the other challenges that we have in today's world and that's media monitoring and what we call rapid response, and that is making sure that we know as things are reported, and how the press has characterized it, what our appropriate responses will be.

Now, in the case of--well, the cases in Turkey. It's my colleagues down at CDC who are going to take the first calls on that, and I, you know, I trust in them. We work very closely together with them, and what will happen is as those calls start to come in and they start asking for CDC reaction on, okay, what are you doing about these cases in Turkey, what do you know about the cases in Turkey, they immediately are reporting that information up to Washington, which then alerts all of us where they're at with the situation and what the message is.

One of the challenges is that what good reporters love to do is call around to a number of government sources and try and catch people unawares and say, you know, did you know about these cases and what are you saying, and that's why it's so important for all of us to stay on the same sheet of music and, as I mentioned earlier, one of the big challenges for all of us now is that we're dealing with messages that are being relayed not just within the various agencies of the United

States government, but the entire world and all of the countries that would be facing an outbreak.

So that's why we're all very excited with the fact that we're finally actually meeting in Geneva and working on strategies on how to share information and have the other countries of the world understand where we're at with our message and have them have a means to let us know what message they're imparting.

So it's a new world for us. Yes, sir.

CHAIRMAN BRACEY: Dr. Bloche.

DR. BLOCHE: As I'm sure you know being first and being right can often be at odds with each other and the tragedy in West Virginia wrenchingly underscores that. Human beings--there's lot of cognitive psychology research to support this--human beings have a way of when there's ambiguity and when there's tension of filling in the blanks. It's something that we do at all different levels.

It's our visual fields and with more cognitive processing as well. Especially if folks

are going to be on the same page while they're being first, how do you and how does the department think about the tension between those two?

MR. WOLFSON: Right.

DR. BLOCHE: I can remember just as one example, I remember the previous Secretary of HHS in the first hours after the anthrax scare, the theory that somebody was sipping water from a spore infested stream.

MR. WOLFSON: Right, right. Yes. I remember that well. Well, I think one of the important strategies and what we try to do is work with--it doesn't matter how good a communicator I am or my colleagues that work in this line of business are because we're not the ones that end up on Meet the Press or on Wolf Blitzer. It's Secretary Thompson; it's Secretary Leavitt; it's Dr. Gerberding; it's Rudy Giuliani.

So the challenge for all of us is to try and arm them and prepare them for making these appearances and communicating. And one of the things, you know, in terms of your question about

being first and being right and such is making people understand that the person they're listening to, yes, they're an authority figure, and they're leading an effort and they have a lot of power at their fingertips, but they're also human beings, and they also have limitations with regards to how much information they have and how much they can do about a situation.

One of the key phrases that Dr. Gerberding employs so well is when you're in a situation like this is to say I wish we had more information at this time, but we're trying to find out this, this, this, and this.

By using the phrase "I wish," you're connecting with people and that's a human being up there that's talking, you know. It's not just an image on the screen.

DR. BLOCHE: Just a quick follow up.

MR. WOLFSON: Yeah.

DR. BLOCHE: Doesn't this underscore perhaps the benefit of having the science person out there, having Julie Gerberding out there--

MR. WOLFSON: Right.

DR. BLOCHE: --and maybe not having the political figure who doesn't have the scientific credentials?

MR. WOLFSON: Right. And that's one of the successes that Giuliani had was that every news conference that he did, he had his experts standing at his side and he never answered one of the technical questions himself. He stepped back from the podium and he let the right person answer the question. And that's also key.

By the way, one of the other, and I'll make a pitch for this because I think it's a very important product, the CDC, the team down there has developed a very short course. It's called "Risk Communications by Leaders for Leaders."

And it's basic understanding how to communicate in a crisis like this risk communications messages and it's put together in a way, it uses examples like Rudy Giuliani, like Governor Keating in the Oklahoma City bombing, like Dr. Agwunobi in the initial anthrax cases in

Florida which happened two weeks after he took over down there as the Director of the Department of Health in Florida.

We have about five or six different individuals who were in key leadership situations and went through crises, and we use interviews with them as teaching points within this course. It's on a DVD, and it's aimed at somebody who is a mayor or a county executive or a governor who needs quick inoculation of how to communicate in a crisis, and it's available from the CDC.

It's on their Web site and if any of you are interested in getting a copy of it, please contact me and I'll make sure you get a copy.

CHAIRMAN BRACEY: Dr. Sayers.

DR. SAYERS: Thanks. Those of us in blood banking have frequent interaction with the media and while we'd like to think that the media's role in society is educational, obviously it isn't.

I'm sure they see their role as more entertaining, alarmist, ratings race and what have you. But potentially the risk of an influenza

pandemic is so high that I wonder if you would even consider identifying media leaders and saying to them, look, the national threat here is so serious that we really would like you to consider taking on an educational role rather than one of the more conventional media roles?

MR. WOLFSON: I think that's a very, very important idea. That sort of approach was used when Secretary Ridge initially took over with the Department of Homeland Security's formation. He had a series of meetings with key executives with the networks and with major newspaper editors and basically did what you had suggested. They sat down in a closed room, and he said, look, if we're attacked again, if there's a biological attack or whatever the attack might be, here's my concerns about how we inform the public and he asked--he enlisted their support in that effort.

And I think that I will take back with me to Secretary Leavitt the suggestion that you've made, that a similar session would probably be appropriate on the topic of pandemic outbreak with

major news media, talking to them about how best they could serve their country and their fellow Americans.

Thank you.

CHAIRMAN BRACEY: Thank you, Mr. Wolfson. Any additional questions? If not, we'll move on to the next speaker.

MR. WOLFSON: Thank you, and the presentations are available for you along with the message maps.

CHAIRMAN BRACEY: Okay. Our next speaker is Dr. Indira Hewlett. Dr. Hewlett is the Chief of the Laboratory of Molecular Virology at the Laboratory of Molecular Virology, Division of Emerging and Transfusion Transmitted Disease, in the Office of Blood Research and Review.

Dr. Hewlett has extensive experience in this area including working with a number of transfusion transmitted viruses and development of vaccines and diagnostics.

She will be speaking to us on "Identifying Gaps of Knowledge in Transfusion and

Transplantation Medicine."

Thank you.

DR. HEWLETT: Thank you, Mr. Chairman, and good afternoon. I'd first like to thank Jerry for inviting me to speak at this meeting. This morning and today we've actually heard a number of presentations on various aspects of avian flu including global coordination efforts, vaccine and antiviral strategies. We've also heard about communicating risk.

All of this is based on actually knowledge that we have or for the most part on what we actually know about avian flu at this point. In my presentation, I'm going to focus on what we don't know about avian influenza, particularly on the scientific aspects of it, as it relates to transfusion and transplantation medicine.

Just to give you a brief background, Dr. Likos talked about this influenza virus in great detail this morning, so I'll just recap by pointing out that influenza viruses are noted for their antigenic variability and adaptability, and as a

result, we see periodic epidemics of the virus. Therefore, despite annual vaccinations, the U.S. faces approximately 36,000 deaths and more than 200,000 hospitalizations each year.

Pandemics that are caused by influenza A strains have occurred intermittently in 1918, 1957 and 1968, and they caused millions of deaths worldwide at the time.

The current pandemic threat is from an unprecedented outbreak of avian flu in Asia with recent spread to Europe. There is also heightened concern because of the possibility of mutations and reassortments that could occur during spread of the virus across Europe and Asia, and a generation of new strains with potentially higher efficiency for human-to-human transmission, and this of course is a major knowledge gap.

The primary causative agent of avian flu is the H5N1 strain and that's what I'll talk about today. These stains of highly pathogenic avian flu actually established infection in poultry in several parts of Asia during the past decade. And

a highly pathogenic form emerged in 1997.

These avian flu strains, as we know, are not generally infectious for humans but several cases of human infections have been reported since 1997, and as of December 30, the WHO noted that there were 142 cases of infection and 74 deaths due to the H5N1 strain, and in today's paper, of course, there were reports of bird flu and I believe the thought is that this is H5N1 that's been reported in Turkey.

So the numbers are growing, but I'm going to, on this slide I've listed concerns for transfusion and transplantation in the event there's a major outbreak of avian flu infection in the U.S., and as you can see there are a number of concerns, and these are just some of them.

They include but are not limited to the points noted on the slide. First, there could be an impact on donor availability due to illness. This came up in previous discussions. There could be deferral of donors due to potential viremia.

Donors could also be additionally deferred

because of treatment with medications. There's a potential for falsely reactive screening tests either from influenza or from vaccination. Again, there could be potentially an increase in demand for blood and for organs and tissues.

And finally, illness in blood, organ and tissue center personnel could affect collection capabilities which would have an impact on supply.

So it's really difficult to accurately estimate the magnitude and impact of avian influenza on the effects that I just mentioned in my previous slide in the absence of critical scientific knowledge. So there are some gaps here, and data regarding avian influenza infection and transmission in humans.

In the next couple of slides, I just listed off some of the knowledge gaps that exist in the pathogenesis and virology of avian flu.

First, we don't know what the extent and duration of viremia is in H5N1 infection. We don't know what the length of the asymptomatic incubation period is. We don't really know if there's viremia

during the asymptomatic phase. We need to understand what the infectivity of blood that is collected during the asymptomatic phase would be.

Other questions include is there viremia during the convalescence period and is the virus infectious? We know that the virus is spread efficiently by contacts and by nasal secretions, but what are the most effective means of virus spread to contacts for avian flu infections?

What is the range of organs and tissues that may be affected and what is the infectivity of virus that may be present in susceptible organs and tissues?

And finally, we know that the virus mutates and is capable of reassortment, so how will virus mutation, reassortment and development of drug resistance, and drug resistant H5N1 has been reported, and there have been deaths that resulted from drug-resistant H5N1, so we know it's a reality, how do these changes affect the evolution of a potential pandemic and transmissibility through transfusion and transplantation?

Would vaccination and antibody responses in recent infections cause interference with tests that are used to screen the blood supply?

And should vaccination and/or medications that are used to treat flu infection affect donor deferral?

So these are some of the broad knowledge gaps that we have. I'm sure there are many others, but these are the most apparent ones that would have impact on blood safety.

I'd like to now briefly review what we actually know about human influenza A and compare that with what we are learning about avian influenza infection of humans.

First, we know that the asymptomatic period in human influenza A is generally about one to four days. We heard this from other speakers. The viremia in most influenza A infections lasts from one to three days post-inoculation. Virus has been detected in mouse models and in infected individuals, but it's most frequently isolated from nasopharyngeal swabs during the first three days of

illness, up to eight days, nine days after onset, and one to two days before onset of fever.

And this particular reference was cited by Dr. Likos this morning, so I won't go into it in detail, but basically in the Khakpour study they identified live virus in the blood, and also in contacts. It was one contact who became ill 12 hours after virus was isolated during the asymptomatic period.

This is one of the few reports that exists, but there's really little additional data on viremia and it appears that it has not really been investigated in any major fashion.

Therefore, the presence of virus in blood has not been well established and infectivity during the asymptomatic period is really not well understood.

Now, moving on to H5N1, we are beginning to understand that the pathogenesis of H5N1 may be different from that of usual human subtypes, H1 to H3, and there are a number of reports that talk about this, but I'm just going to focus on two

reports, one from 2001 that was published in the Journal of Medical Virology, where this group studied 18 case of H5N1 infection, and found that there was significant cytokine perturbation and activity in the early phase, in the acute phase of infection.

The cytokines were pro-inflammatory in nature, the interferon-gammas, TNF-alpha, IL-6, sIL-2, et cetera, and there was also complication of reactive hemophagocytic syndrome which is about, found in two out of six fatal cases. So this is one feature that has been described, both by this group and some other investigators.

And the second report was published by the Writing Committee of the WHO Consultation Group on human influenza. This was published in the New England Journal of Medicine in September 2005. This group noted that the incubation period for the virus may be longer. It's two to four days, but there's an upper limit of eight to 17 days which is much longer than what is traditionally seen with human influenza.

They also noted that viral RNA levels were higher in pharyngeal than in nasal respiratory tracts and higher levels were found in avian flu than with usual human flu infection.

They also noted that there were two patients who presented with encephalopathic illness and diarrhea without apparent respiratory symptoms.

And I should mention that the involvement of the gastrointestinal tract appears to be a feature of the H5N1 infection, and the speculation is that it perhaps replicates in the GI tract, although there is no data or evidence to support this at this point.

So in order to address some of the issues that I've just listed, an informal PHS group was formed and we sort of developed a study plan, talked about different ways to address these gaps of knowledge in transfusion medicine, and one of the study plans is something I will discuss very briefly today, and the idea here is to address the scientific knowledge gaps in highly pathogenic avian influenza, focusing on viremia, tropism and

transmission through blood transfusion.

The group felt that use of animal models could be a feasible approach to address some of these gaps in regard to H5N1. There have been reports, particularly from the Osterhaus Laboratory in the Netherlands that have demonstrated that cynomolgus macaques may be a good model for infection by avian flu, that they are susceptible and show pathology that is similar to that seen in humans.

So some of the proposals, and I'm just going to go through them very quickly, but these are just some ideas and thoughts that the group is putting together and the goals, of course, would be to demonstrate transmission or lack of transmission by transfusion and to see if blood is infectious when it's collected in the asymptomatic phase by doing secondary infection of macaques.

We may want to look at the organ engagement, what are the different types of organs and tissues that are affected, and in order to do this, actually I should go back to the last slide,

and of course to look at the utility of current inactivation methods for inactivation or removal of H5N1.

And in order to do this, we will also want to develop sensitive methods to detect and quantitate both the nucleic acid and to culture the virus in order to look at virus specific or virus-induced effects.

The anticipated outcomes of such an investigation would be to identify possible transmission by blood transfusion during the asymptomatic phase, to identify the minimum infectious dose for transmission by blood, to further identify cell, tissue and organ tropism, and to understand and establish utility of current viral inactivation methods for inactivation of highly pathogenic strains of avian influenza.

And of course, animal models do have their limitations, but if one is developed and validated in a certain way, it would allow us to study, to actually do studies on pathogenesis and to test new drugs and vaccines.

So I'll close with that and acknowledge the group that actually discussed some of the details of the plan that I discussed today which is actually one of many proposals that we are considering in order to address the knowledge gaps that I mentioned. I should also say that in informal discussions with Mike Busch and Philip Norris, who will be speaking tomorrow, I understand that they will actually be doing some studies in the donor population using PCR and PCR-based assays for influenza looking for viremia in blood donors and the combination of animal studies and donor studies would certainly give us a large amount of data on pathogenesis of avian flu.

And thank you for your attention. I'll take questions.

CHAIRMAN BRACEY: Thank you. Questions? Dr. Roseff.

DR. ROSEFF: Since this disease isn't currently in our country, but it is in Southeast Asia, are we working with WHO to develop assays and tests to use in anticipation for blood donor issues

as opposed to just the global issues of the pandemic?

DR. HEWLETT: We in our group obviously would like to work with the investigators in Southeast Asia through the CDC to see if there is some way to utilize what they've already done in their country looking at the particular issues that I've listed on the slides here.

I'm not fully aware of how much technology transfer, transfer of information there has been between the international investigators and U.S. product developers. You know this would obviously, if you were developing a nucleic acid test, for instance, you know, it would have to be--it would have to be good facilitated communication and exchange of materials between the industry here who would be developing these assays and so on, but the CDC, as I understand it, has, in fact, obtained some materials and primers and probes and so on from Southeast Asian investigators, and they will be helping us to do these types of studies in the event we move forward.

These are not funded; these are just proposals. These are just ideas that are on the table to address some of the questions that seem to be unanswered at this point.

CHAIRMAN BRACEY: Dr. Pierce had a question.

DR. PIERCE: The cynomolgus monkey studies look particularly relevant. What are the impediments to getting those studies underway because there's a whole--

DR. HEWLETT: Funding.

DR. PIERCE: --series of studies that would need to be done. It will be very time consuming and labor intensive project.

DR. HEWLETT: Yes. But, you know, right now we really having brought in people who are at primate centers that have the BL3 facilities and so on, and having access to BL3 enhanced facilities in our own, not in our facility but having access to them in the area will allow us to move forward. So that would not be a major impediment.

Right now, really the major impediment is

funding. There is no funding to do this work. It would be, you know, it's a blood issue. It's an issue that has to be handled by, you know, the blood community and/or investigators who work in the blood area.

We've actually tried to reach out to people who are looking at vaccines and who are looking at just pathogenesis, and again, you know, people have their own areas of focus and it's to add a couple more monkeys to a study is not cheap. So that's why we think there's a need to have a focused effort on blood-related issues.

DR. PIERCE: Is there an agency that's taking the lead on this? Is it the FDA or the NIH?

DR. HEWLETT: I think at this point it's within the FDA. We have engaged NIH. Harvey Alter from the NIH, George Nemo, the Centers for Disease Control, Matt Kuehnert, and some folks from their office have been engaged. But it's going to be an interagency collaboration if we move forward with this.

CHAIRMAN BRACEY: If I may, this could be

one of the recommendations that could be forthcoming from this group, and I think it would be important for us to consider making that recommendation.

Dr. Ramsey.

DR. RAMSEY: Yes. Just for the record, I know this would be obvious for everyone working on this, but just one of the other topics of many that your thoughts could address would be the issue of recalls and withdrawals of blood products after donors have been either infected or exposed. So just for the record--we'll probably have a chance to talk more about various issues later, but--

DR. HEWLETT: Yes, I agree. I think that's a good idea.

MR. WALSH: I mean wouldn't this be appropriate for some bio-defense support, the research?

DR. HEWLETT: Well, that's a good thought. We've thought about it, but bio-defense focuses more on, you know, on basic pathogenesis. We've looked at a number of solicitations that have come

forward. Believe me, we've written white papers, concept papers, and, of course, you know, we're still waiting for some of the--what we've heard is that there are solicitations that are going to come out in regard to avian flu, but the focus on the bio-defense side of things is really on vaccine and antivirals. Just standard pathogenesis is not as high a priority.

And, of course, infectiousness of blood because of the concept that influenza is, you know, the viremia is really short, and it may be so in the case of avian flu, but we just don't know. You know nobody has really looked at this. And that's why I think, you know, we certainly will give bio-defense funding opportunities a good try, but when you look at the--read the solicitations, it's really to look at antivirals and to look at SiRNA and things of that nature to, you know, to act as antivirals in the event of a pandemic, not so much infectivity of blood or blood components inactivation or ineffective storage. These are not things that, you know, are of much interest to the

bio-defense agencies.

CHAIRMAN BRACEY: Additional questions? If not, thank you, Dr. Hewlett.

DR. HEWLETT: Thank you.

CHAIRMAN BRACEY: On our agenda now, our next item is the Open Public Comment, and we do have a comment from Michelle Vogel. Is Michelle in the audience? Oh, are you speaking for Michelle?

MS. WYATT: No, I'm not.

CHAIRMAN BRACEY: Okay. Could you come to the mike and state your name?

MS. WYATT: I'm Gretchen Wyatt with the Plasma Protein Therapeutics Association. I'm not speaking on behalf of Michelle Vogel, but another comment if possible, to first commend you for recommending a progress report on the different activities that this committee has done, and also for CMS who has taken your lead and with the IVIG situation to make sure that there is a temporary preadministration code for 2006 for IVIG for the access for Medicare beneficiaries, and related to that and to your progress report, PPTA would like

to also say that we have submitted comments as PPTA and as part of the IVIG community related to this issue as well.

PPTA applauds these Centers for Medicare and Medicaid Services for the recognition of the importance of ensuring that Medicare beneficiaries have access to IVIG and a need for additional payment for preadministration services related to IVIG. Yet we do not believe that given the drastic payment rate reductions, CMS has exhausted all options within its authority to preserve access to IVIG in hospital outpatient and physician office setting.

We remain concerned that the payment rate reductions listed in the final rule will impede access to IVIG by Medicare beneficiaries. Since beneficiaries that need IVIG have migrated away from physicians' offices for treatment in 2005 because of reimbursement concerns, we see no other site of service capable of handling patients no longer able to obtain IVIG through a physician's office or a hospital outpatient department.

PPTA and the IVIG community urge CMS to take immediate action including the issuance of a program memorandum effective immediately to ensure that outpatient and physician office payment rates for IVIG treatments are sufficient to ensure continued access in both settings. We believe that the agency could do so in three ways:

One, by establishing a comprehensive permanent add-on payment to the rate for IVIG that captures the true acquisition, direct and indirect handling costs associated with this therapy.

Two, by establishing unique health care common procedure coding system, or HCPC codes, for each brand of IVIG so that the average sales price, or ASP, for each product is based on information submitted for that IVIG therapy, and thus reflective of each product's unique formulation.

And third, they could clarify that IVIG is a biologic response modifier for purposes of paying for administrating this product.

I would like to note that these solutions are endorsed by the broad IVIG community and are

identical to the recommendations made by this committee.

Thank you.

CHAIRMAN BRACEY: Thank you. Are there any comments or follow up? If not, we're slated for a 15 minute--oh, we have another comment. Sorry.

MR. CAVENAUGH: Thank you. I'm Dave Cavenaugh with the Committee of Ten Thousand. I wanted to let you know that Corey Dubin, who is our board chairman and has been able to come to these meetings pretty regularly for the last 12 to 15 months, cannot be here today because he's in rural Missouri at the home of Linda Lewis who is about to lose her 26-year-old Grant to the HIV that he contracted from his blood clotting factor. Born in 1980, he could not get out of its way although he's fought a good fight, been in NIH trials, been a real trooper.

That by way of saying response to emergencies is not new in this community, and we'd like you to take that into advisement. I realize,

that I've not heard much in the comprehensive planning that has been described today about consumer input. When I think back to the one-year effort to put a test in place for West Nile Virus that was successful and streamlined, used SBIR grants, went very rapidly, and was a bit miraculous, and accomplished a wonderful purpose, I think that it was great to have.

This we have a lot of preparation time. We know about flu, flus, if I may, and we hope that you will include those possibly in the gun sights most directly through blood. The macaques reminds me of discussions that I have when I get up to this microphone before this and other committees about cows and the CJD threat and the transmissibility, the dual transmissibility there, if you will.

This is not quite that, but we do need to work with other agencies on this who may or may not recognize the importance. I can understand fully had FDA cannot with existing budgets and certainly with the massive budget cuts that are being proposed on Capitol Hill last month and this afford

to expand into new areas to cope with new epidemics, but I do hope that we'll all be able to make them see the light on that.

Thank you.

CHAIRMAN BRACEY: Thank you for your comments. Any additional comments from the public? If not, then we will take a 15 minute break and reconvene at 15:35. Thank you.

[Recess.]

CHAIRMAN BRACEY: We are now at the phase where we are set for our--committee members, committee members--we are now at the phase where we're ready for our discussion.

One of the things that we talked about is--and I've after lunch talked to a few members of the committee to serve in a capacity of working on a draft statement, not for today but for tomorrow.

We're at a phase now where we're ready to begin discussing some of the items that we've heard today so that we can highlight particular areas of focus. Jerry has drafted, well, actually has several bullet points, and I think that one of the

things that we can do is we can perhaps start off with his bullet points and then I've got a few to add, and then the rest of you can jump right in, and we'll develop perhaps a hot topic list, remembering that there still is a lot of information that we have yet to hear from the donor side, the blood collecting agency side, and that will be coming tomorrow.

So, Jerry, you want to start?

DR. HOLMBERG: Well, thank you. I just jotted down some points here, and I didn't realize Marc was going to talk, Marc Wolfson, was going to talk about the three point plan, but these are small little bullets and I'll try to elaborate on each one.

But the messages that I heard throughout the day were primarily, the first thing was the importance of state, involvement with the state government. We heard how much is going to be allocated to the state. We also heard about the state plans, even the state communication, and I think that, as I think Dr. Katz mentioned, you know

the state is involved with a lot of things and really trying to make sure that the state plans are in place I think is very important, and sometimes they need to have a little bit more emphasis so that they know what direction may be doing.

Also heard loud and clear about the inclusion of other groups such as the plasmapheresis groups and also as Dr. Schwartz put up there, the emphasis on some of the progenitor cells, maybe the stem cells, cord cells. The Department of Transplantation at HRSA had mentioned about to me offline about the importance of maybe putting the vaccination of donors for bone marrow on this priority list.

I think that may need further discussion. I think also a message that I picked up was the importance of making sure that blood is considered as a critical infrastructure. Blood is part of the critical health care infrastructure. Also, the brochure on family preparedness, I think that something that I keep conscious about is, very cognizant about is the success that the government

of Japan had just in enforcing or really advocating a lot of hygiene, especially within their families, and so I think that brochure on family preparedness may be something good that we could even advocate to not only our donors but also to staff workers.

And I also heard that we need a coordinated message. There's a short course on risk communication. I think the three point plan that Marc Wolfson brought forth was very good. The risk communication, the importance of having the messages ahead of time, and having a unified coordinated message.

And I also like the idea that he mentioned that I can't remember exactly who to give the credit to--I think it was somebody on this side of the table--identifying media leaders and moving forward on educating them in the right way. And then following up on Indira Hewlett's discussion on the research, just what research needs to be done to close the gap and to identify those or find answers to those places where there are scientific gaps.

So those are just comments that I picked up throughout the day.

CHAIRMAN BRACEY: Maybe I can add just a couple of other items that seemed resonant. One of the things that was recurrent, and it crosses over into the realm of communication, but it is focusing on what will actually be the trigger point for communication, and perhaps layering out a strategy wherein as one of the last messages in the communication tool is, you know, best practices at avoiding germs. Well, that's something that one should practice all the time, so in essence I don't think that all of the communication needs to be directed at the pandemic.

There are certain things that as a matter of public health and public education that could happen all along. While at lunch and Jay Epstein may want to say more about this, but it appears that, you know, currently there are some potential clinical/surveillance analyses that could be ongoing as we speak.

You know there are opportunities now for

us to learn, you know, about viremia, about the, you know, the asymptomatic case controls within family settings, and so I think that is another area that would warrant some consideration.

We've touched on the issue of the trials, the spiking studies which I think would be very important. So those were the elements that I had, and I'd open up the floor now to see if there are any other comments from the group in general, and one comment that I think that I believe Karen made and she may want to follow up on this, is that when we develop the communication message to make sure that the blood centers are key players in crafting that message because sometimes if the message is left to others, it (a) may be diluted or it may be lost in terms of our focus.

DR. HOLMBERG: The only thing I would add is that I think we need to expand and not just think blood centers but also, you know, there's plasma products around here, around the table, plasma industry.

CHAIRMAN BRACEY: Yeah, that's a key point

because, you know, one of the things that occurred to me is as we look, you know, if we find that there is, in essence, no evidence of significant viremia, it's a non-issue, but on the other hand, if there is, then certainly it's important for the plasma product side.

And then lastly, one of the things that I was also thinking about is as we experience, hopefully we will never experience a pandemic, but if indeed we do, then our method, you know, there will be people hunkering down. In our model for collecting blood as a model that puts us in sort of a mass setting, and we're really going to have to rethink the model and we may need to consider relaxing certain, you know, donor criteria, not necessarily infectious criteria, but some things such as, you know, frequency of donation, et cetera, et cetera. But we may need to reconsider our current model for collections.

Dr. Epstein.

DR. EPSTEIN: Thank you, Marc. Yeah, I wanted just to take the opportunity to elaborate on

this point about studying asymptomatic contacts to look for viremia. I would just note that Dr. Hewlett mentioned a proposed study, or initiated study--I wasn't quite sure--by Mike Busch to look at donors to see if there is influenza viremia during the annual influenza outbreaks in the U.S. That will give us some helpful information because it may potentially debunk the myth that there is no viremia in asymptomatic persons.

On the other hand, it's not going to tell us a lot about pandemic flu and I think one really ought to try to go for where the money is. The cases are occurring right now in Southeast Asia, predominantly, and there are apparently teams investigating each case and getting tissue samples, nasal swabs, et cetera, from the contacts. Why can't they get blood samples?

And I think that that's a point that we really ought to press. I agree that other studies are important such as the spiking studies to see what we might learn about transmissibility by the intravenous route through transfusion. I tend to

think that the studies with cynomolgus monkeys may be informative, but they're going to be fraught with caveats because we'll be working with the avian virus rather than the human adapted virus because that doesn't exist yet, and we're going to be wondering how well the cynomolgus monkeys mimic the human situation. It will just be a speculation at best.

So I do think that we, not that we should discourage that effort--quite to the contrary. I think we should encourage it and specifically recommend funded research to explore the potential for transfusion transmissibility of pandemic flu, but that we ought to look at the human situation and extract the most that we can from the human situation.

Now to whom we target that message is a little bit less clear because we're advisory to the department, but presumably the department has some ability to help direct the effort toward cooperation with the WHO and currently affected countries, so I think that that's a key point.

I'd also like to comment on the issue of the blood system as critical infrastructure. I think it was made clear by several speakers that the focus of the HHS plan puts a lot of the effort in the hands of the states, and that predicts a lot of disparities that may occur, and I think that Dr. Katz made the very important point that it's an uphill battle to convince every state public health authority to treat the blood system, including the donor as well as the center staff, as part of the critical infrastructure and specifically identify it as a target for, you know, preventative measures.

And I think one of the most important things that we could do as a committee is to recommend that the Secretary make a clear statement on the blood system as critical infrastructure and spell out what that really means.

One dimension of that, though, is the issue of whether blood centers will be encouraged to offer vaccine onsite or through referral, and we haven't had any discussion about the historic legal

issues that surround that, and I recall that when we were discussing a similar issue with smallpox vaccination, that the issue of incurring blood center liability by advocating, let alone offering, vaccination is a very delicate matter to the blood community, and I just think that we ought to spend some time looking at the legal dimension.

So anyway, those are my comments on those two points.

CHAIRMAN BRACEY: Okay. And I think that tomorrow, we will be hearing from, you know, the blood collecting agencies and perhaps some of that will come out and we'll have more extensive discussion at that time.

Ms. Birkhofer, you've got a comment?

MS. BIRKHOFER: Thank you, Mr. Chairman. Un-huh. I concur with the list that you and Dr. Holmberg and Dr. Epstein have put forward and my observations would include a little more build-out on the importance of early education, and I guess I'm looking at model that the Office of National Drug Control Policy has used with regard to the

Public Service Announcements, PSAs, something short and pithy that reaches a broad audience. I think, you know, we could perhaps look at funding for that type of initiative.

In addition, reflecting back on Dr. Goodman's presentation, I think the importance of availability of vaccines and that the industry has the capacity in place to make the vaccines available, I mean that's the first step to assure the safety and to assure the public health.

And then in addition, just from my experiences in the plasma community, I think the importance of access once those vaccines are available, that there's appropriate and adequate reimbursement because clearly we've learned, if we learn anything from our experiences with the immunoglobulin debate, it's been, you know, adequate reimbursement.

So I would ask us to look at that as well, and then finally just reflecting upon the government's response to, you know, various national disasters.

One presenter talked about the need to have coordination among agencies, interagencies, and communications, and I think that coordination of the information flow and the dissemination is vital.

CHAIRMAN BRACEY: Thank you. Dr. Angelbeck.

DR. ANGELBECK: Something I think we're probably going to hear more about tomorrow, but an immediate potential impact if you have a third of a population in any given area infected would be on the availability of blood products, particularly if you look at patients who are supported chronically for red cells or platelet products.

I mean if you were operating a blood center and tomorrow you didn't have a third of your plateletpheresis donors, would you have a way to immediately adapt to make a whole blood derived product available or triage or manage that circumstance?

I think that's a very immediate pragmatic situation that the committee has to think about as

well as anyone in the blood community.

CHAIRMAN BRACEY: Yeah, that's an excellent point. One of the things that we talked, I think I talked about--no, I did talk about it at the last meeting is generally what happens is when we have blood shortages, the folks within transfusion services begin to interdict particular orders that may be somewhat questionable because there's a great variance in terms of practice.

And so clearly, somehow or another tying in, you know, activism, if you will, to make sure that in fact what is used is, in fact, needed because there are a community of people--I don't know how large that community happens to be at this point, probably not enough, but in hospitals that may be able to influence those activities.

Karen.

MS. LIPTON: If I could say one thing. We're going to hear a lot more about this tomorrow because the task force really has been working on these issues, but one of the things I think that's important for this committee to think about is

really whose responsibility each one of these things are, and when we talk about managing plateletpheresis donors, I would suggest that that really is the blood collection facilities' responsibility.

We may need something from the state or federal government, but I, you know, it's pretty easy for our committee to get into and then the government should do this and this and that, and really and truly what we need to figure out is have we identified all of the issues and does the blood community believe it has the appropriate level of response or support from the federal government and from the state governments and how we affect those requests.

CHAIRMAN BRACEY: Dr. Kuehnert.

DR. KUEHNERT: I think to that point, I mean I think that probably this has been emphasized before, but what we really I think have to do is figure out concerning communication, I mean there is one-way communication where information is going out, and then there is two-way communication where

there needs to be an exchange of information, but no matter what, there needs to be a point person for every organization that's relevant.

So what I think would be very helpful is to see, to go through and see what organizations need to be involved with each topic, particularly concerning preparedness, and then see who are the point people. So, for instance, tomorrow we're going to have the task force speak. We're also going to have Al DeMaria speak who represents CSTE and so knowing those particular organizations involved with, for instance, state and local health departments will be critical and then making sure that those interface.

Secondly, just on Dr. Epstein's point about looking at viremia in existing protocols, we went through this to some extent with SARS and this was, it was very challenging because the people who were doing the research were not primarily thinking about viremia as an endpoint to look at, and so we repeatedly reminded them that they needed to put it in the protocol before it gets to IRB and then

there are those barriers to putting that in.

And we were successful, but these were primarily CDC protocols. That I think we can address, but it sounds like really a lot of these are where CDC is not involved, and so what we have to figure out is what protocols exist, how we can interact with these investigators and try to urge them to just include blood samples even if they aren't going to do anything with them primarily, but just store them so that something can be done later on down the road.

And also if there are detailed epidemiologic components to it, to also ask about blood donation and transfusion receipt.

CHAIRMAN BRACEY: Dr. Pierce.

DR. PIERCE: I very much agree with the idea of collecting blood samples for future use for humans, human transmission. But I want to come back to the animal work and make sure that that's not lost. When I think back on the last half of the 1990s, a lot work occurred with CJD and variant CJD, and the infectious agent was much more

difficult to work with than this one.

The animal models were much more challenging that this one, and, in fact, probably had much less relevance to the human situation than a cyno model would have for a human situation, for human infection. So I really think that a lot of valuable information can be gained from doing this work that was outlined by Dr. Hewlett, and I think the cost of doing that is really relatively low for the amount of information that would be gained, especially when I go back and think about how useful it was in CJD and variant CJD to really define the risk.

CHAIRMAN BRACEY: Thank you. Dr. Epstein.

DR. EPSTEIN: Well, I think there's a communi--first of all, I agree. I think there's a communication issue that we need to deal with about research on viremia.

There's a general bias that, well, this is a respiratory disease and if you have a pandemic, you know, all the harm is coming from the respiratory spread, and, you know, why worry about

this, you know, fringe risk from potential viremia, but I think that above and beyond the need to clarify the intrinsic risk so we can deal with it scientifically, we need to get the message out that if we lack that information, we're going to overreact by deferring donors needlessly and by withdrawing components needlessly which could very seriously aggravate the shortage situation due to the illnesses themselves.

And I think that that message has not really been clear enough to the people who are presently directing the resources toward the research effort, and it may be that viremia is rare, but knowing that can help us avoid a lot of needless blood loss.

CHAIRMAN BRACEY: All right. Dr. Bloche.

DR. BLOCHE: I'm not remembering your name, but I would second your comment. I think that the issues of credibility and risk of panic are central here. And although from the scientific perspective, and I'm in no position to judge this, the animal model may well be pretty valid, it's

simply not going to have the credibility that really aggressive surveillance for viremia both of the avian flu and for that matter just everyday seasonal flu would have.

I want to make a couple of other comments on these questions of credibility and panic and risk communication, which I do prefer to think of as risk education.

First, I think it's really essential that the department be proactive with respect to the notion that we're talking here about balancing risks, and not about safety in the sense that perhaps many people think of safety as something of absolute. Being proactive before a pandemic occurs about the impossibility of absolute safety would really lay the groundwork.

And a second related point is that I think it's really important that it be, should a pandemic occur, the professional and scientific leadership within the department that takes the lead on communication and not the political leadership. And if I may be perhaps a bit two-pointed. On

questions of assessment of risk and fears of politicization of risk, the last several years in other areas of public policy have, well, underscored this.

I think there's a diminished credibility of the current national government on issues of risk out of concern that assessments of risk by professional staff have been politicized in the foreign policy arena, and given that backdrop, it is an urgent matter that it be the professionals and the scientists that be the voices on risk assessment.

CHAIRMAN BRACEY: Thank you. Dr. Pierce.

DR. PIERCE: I'd like to make two points. One is that I don't think we should get ourselves caught in animal versus human. They both answer completely different questions and they both have relevance. So let's not fall into that trap. Let's make sure that both get the attention that they deserve.

And secondly, there's another dimension to this as well. One can just spike plasma that's

been collected and do the work that was done back in '83 or so when HIV was first isolated, to find out what happens during the processing of these materials? Are they tracked with a particular fraction? Are they inactivated? Are they partitioned out?

And that kind of work, the CDC did in a period of two or three months. It didn't take a lot. So I'd like to see us consider that kind of a recommendation, too. And that's totally in vitro and would answer a lot of very valuable questions.

CHAIRMAN BRACEY: Thank you. Dr. Roseff.

DR. ROSEFF: Thank you. I just want to reiterate what Jay said. I think it's very important to have an opportunity now. We're here before the pandemic so it would be great to answer these questions, so when it is upon us, we have some answers.

If it turns out that we can prove in some way that this is not a transfusion transmissible disease, we've eliminated a whole area that we have to delve, that we have to respond to. And we can

give good information, reliable information and push that aside and then deal with what will probably be the problem, which is not having enough donors, not having enough staff.

And I think it's important that this committee make as strong a statement as we can as possible to not forget this because I think that's what we've heard, that these things seem to get pushed aside and pushed aside because it's not the primary issue on everyone's mind.

The other thing I want to bring up, and I know that we'll be talking about this tomorrow, but I was interested, too, to see if the UK has a plan in place about how to deal with blood shortages as a nation, and this--I think what will occur if there's a pandemic is that this will be a blood shortage, and that will be what we're dealing with, and how important it may be for us to have a plan in place that we can at least disseminate to have a response that's consistent throughout the country in how do we deal with this.

You know, we know there aren't donors, we

know there aren't collection people available; what should we do as a nation to address this? Not just let everyone sort of at the grass roots level not know what to do or to do different things but to take this as our initiative coming from one central location.

CHAIRMAN BRACEY: Again, I think we'll hear some of that tomorrow. There was some discussion of systems that are currently in existence that allow data sharing, and I think that's something we definitely need to explore so that we're all not operating in a void.

But again akin to some of the challenges that we faced with 9/11 and perhaps other doomsday situations, you know, there may be a total disruption of supply and movement and shipment. So again I think we have to maintain an open mind about working out of the box while trying to maintain as much as safety as possible and balancing the risk.

Other comments? Dr. Bianco, former member, with always valuable input.

DR. BIANCO: Thank you. Celso Bianco, America's Blood Centers. Certainly a lot of these donor issues that are being raised will be discussed tomorrow in much more detail. But I think that you all are touching on the very important point of what is local and what is national and what should be national?

The research can only be done if there are funds, and if it is done nationally. It can be done by CDC or by other government organizations, or it will have to be funded by the usual means of NIH, National Science Foundation.

Susan Roseff just raised the issue of policies. That is what do we do as a country? Each state--I think Louie Katz said it much better than I can say it--each state is going to have small local policies and in certain states, if you go to New York, New York City is going to establish a policy that is different than that from the rest of the New York state.

Those things cannot happen. It will be chaos on top of chaos. So I think that the

intellectual leadership of this committee by defining what our central responsibilities, what has to be isolated from the national politics of giving the power to the states. That is what we see with Secretary Leavitt's approach, which is correct in many areas in terms of how they'll manage their schools or their things, but it's not the appropriate policy to support this activity. That's just a feeling I wanted to express.

CHAIRMAN BRACEY: Thank you. Okay. Then, if there are no more comments--Dr. Sayers has one sage comment or maybe two.

DR. SAYERS: No, I have two, neither of which is sage.

[Laughter.]

DR. SAYERS: A couple of points. If, and arising out of lessons that we've learned from the past, if something does emerge as a screening opportunity for evidence of an asymptomatic carrier state or pre--obviously preclinical state of influenza, if it's a surrogate test, then we need to ensure that if something like that is adopted,

it's done in such a way that it doesn't encourage test seeking behavior.

That was the first non-sage remark. The second non-sage remark has to do with I think the stage might well be set to encourage opportunities for director donation to emerge all over again. I think the chronically transfusion-dependent individuals suspecting that they might not get a safe supply from the community blood program might urge directed donations from family members who they view as being healthy.

I think a revisiting of directed donation programs in huge volumes could very well incapacitate blood programs short of staff, short of donors anywhere. So we'd have to guard against both of those possible events.

CHAIRMAN BRACEY: Thank you. Dr. Holmberg.

DR. HOLMBERG: Yeah. I just want to add a comment that Dr. Roseff commented about the UK strategy, and I think that's very important, and I think that a lot of these issues that we are

talking about really touch what we laid out back in September with the strategic plan. You know the good transfusion practices, what are the surveillances that we have in place of the funding for research, all of these things, and I think that what we're doing in the next couple of days, today and tomorrow, is maybe really laying out some ground work for how do we incorporate and build that strategic plan for the 21st century for safety and availability?

And so, you know, I think that that's very important. I don't think the government can dictate and should not dictate what is clinical practice in transfusion medicine, but at least I think what happened is that it will force the transfusion community to develop standards of practice so that there's a little bit better knowledge of the trigger point, and I just raise this question or this comment because it did appear in some of the communications back and forth, just as Dr. Bracey has mentioned, about in tough times, you know, there is triaging of the ample supply,

and that whole issue of even in a bio-nuclear event, what happens with platelets?

You know there's a lot of scenarios that we can carry this on to, and so I think I just really applaud the committee on thinking through some of these things because I think there's going to be payoff in years to come on us thinking through some of the events.

CHAIRMAN BRACEY: Dr. Kuehnert.

DR. KUEHNERT: Yeah. I was just going to ask about what kind of structure of discussion you were anticipating tomorrow because what we have done in the past is, you know, come up with some whereas statements and sort of where we're at and what we think is the major problems, and then we recommend some things.

So are you looking for that sort of a format or more looking like you just mentioned to be in the infrastructure of what happened at the last meeting concerning as strategic plan and here's how this fits into the strategic plan, which would also have the advantage of this isn't only

about avian flu. I mean this is about preparing for disasters and unanticipated events where both safety and/or availability might be compromised.

CHAIRMAN BRACEY: Right. My initial thought was that we would come up with specific recommendations to this particular issue, but, but I think what I hear, and it makes tremendous sense, is that, hey, wait a minute, what we're talking about here in large part may be simply how to deal with a severe blood shortage, and/or how we should manage our national resources or, yeah, what is blood, you know?

And so that fits into the whole notion of the strategic plan, so my thought would be if we could come up with some recommendations related to this specific topic and then to tie them into previous effort for the strategic plan, but I'd be happy to hear what others think.

Dr. Sandler.

DR. SANDLER: Maybe one of our government representatives might inform me because I'm quite in the dark as to where we fit into the bigger

picture. I don't know if there is, by analogy to HIV, an interagency group that is already looking at flu. We're a blood group. Is there an interagency group that's looking at flu? Does the Secretary have a big committee somewhere that's looking out for the police and for other things and we should ask to put a blood person up on the bigger committee?

Can someone who's got the bigger picture of where the government is on this sort of fill me in and maybe the committee as to whether we're in virgin territory or we're just another committee and don't quite know that?

DR. HOLMBERG: Well, I'll take a stab at that. There is not another committee as far as special government employees and committee that represents the community, the end-user community. However, the Department of Health and Human Services has developed different working groups on different issues such as the risk communication, such as the national surveillance, the international surveillance, the--Matt, maybe you

can help me out with the different categories--but there's quite a few of these groups that, you know, the goal--I've met once with one group of the international surveillance.

And we have put together a document that now--well, the first document was primarily bullets, and we will refine this more on where do we go from the bullets to maybe a full document. But it's basically taking the HHS Strategic Plan for Pandemic Influenza and really getting down into the granularity of it.

And so there are different areas, but once again it's the interagencies and not pulling in from the community the importance of this, and I think that's where many times that we get blind-sided because, you know, we don't have the scope that the community has.

CHAIRMAN BRACEY: Dr. Pierce.

DR. PIERCE: Maybe along those lines, I'm in the dark as well about the resources. What's the proportion of resources going into the avian flu versus pandemic preparedness? Can much of it

be ascribed to general pandemic preparedness or is there a lot of very specific activity that's being funded both in dollars as well as in human power for avian flu specifically?

CHAIRMAN BRACEY: That I don't know. Do you know that, Dr. Holmberg?

DR. HOLMBERG: Matt or Jay, can you have an answer on that? I can just tell you that Health and Human Services just had the budget signed off on last week. So I think that it's just numbers now, and really as far as line item for those specific areas, I don't think it's been really identified.

CHAIRMAN BRACEY: Dr. Epstein.

DR. EPSTEIN: My understanding is that there's supplemental appropriated funding in 2006 to address pandemic influenza. I don't know whether that's earmarked or broken down specific to avian influenza versus pandemic preparedness. I just can't comment on that. But there is money in pandemic flu for this year.

CHAIRMAN BRACEY: And one of the thoughts

I had again is that perhaps if there was something that came out of this particular meeting from the committee, that we would help try to carve out those pieces that we consider most important. That's why I think it would be important to have a few specific recommendations and then to tie the rest on to the, again the general plan as to how deal with the blood shortage.

But if there are funds that are available and haven't been carved out yet, that we would go after those. Dr. Epstein.

DR. EPSTEIN: I'd like to come back to Matt's point about what do we hope to achieve tomorrow in recommendations, and I think one of the important things that I learned is that the goal is to have three key messages and three short phrases.

[Laughter.]

DR. EPSTEIN: And my sense of what they are is, number one, establish universal recognition of the blood system as critical infrastructure; number two, fully fund research to resolve the critical questions regarding influenza and pandemic

influenza as a transfusion transmissible disease or potential transfusion transmissible disease; and three, to develop a national plan to address potentially massive blood shortages.

Now, again, there will be a lot of supporting subpoints, but I think those are the big picture things that we heard today.

CHAIRMAN BRACEY: Ms. Birkhofer.

MS. BIRKHOFER: Thank you, Mr. Chairman, and then, you know, just scanning this document from the Homeland Security Council, the National Strategy for Pandemic Influenza, a lot of the details and the substance of how our recommendations would fit in to the national plan, I mean this is very comprehensive.

I just scanned the first ten pages and it's very detailed as to coordination at the local and state level and the role of public health officials right down to veterinarians. So I think what we have to do is plug our recommendations into this broader context.

CHAIRMAN BRACEY: One of the things that

again that I took the liberty to do after lunch was to ask--and I'll go over the specific charges that I asked folks to look at. One is under the points for consideration from Dr. Holmberg, under number one, again, remembering that we haven't heard all that we need to hear, under bullets one and two, approach to immunization of blood center staff and encouraging immunization of regular repeat donors, i.e., some of the donor considerations.

I've asked Merlyn to help us with a working draft so that we can just, you know, chip away at that tomorrow.

DR. SAYERS: Mr. Chairman?

CHAIRMAN BRACEY: Yes.

DR. SAYERS: I don't want to doom everybody to disappointment when they heard you said working draft and they see my 30 words.

CHAIRMAN BRACEY: Well, yes, a communication tool, 30 words, and then I asked Dr. Epstein to consider working under number two, which I think he's really boiled down pretty much already in terms of the last statement made.

And then the one thing that wasn't included, though, it hits the blood shortage element of it, I guess hits it, is this notion about how do we manage the communications between all the public health elements? And I think that may be a little different because managing a shortage doesn't really necessarily deal with putting the word out that there is a problem now, let's go, you know, let's activate.

And so I've asked Dr. Kuehnert to come up with again a sound bite for that. So does that sound fair in terms of just a preliminary plan for tomorrow? Okay.

Further discussion? Well, I'm sorry that we held you so long prior to your lunches, but maybe you can all have an early dinner. Thank you.

DR. HOLMBERG: I just want to remind everyone that eight o'clock tomorrow morning for our ethics training, and the doors will be closed and opened to the public at nine o'clock.

CHAIRMAN BRACEY: And then one other item, and that is we will hear from the Assistant

Secretary's vantage point tomorrow but delivered by Dr. Holmberg.

[Whereupon, at 4:25 p.m., the Advisory Committee recessed, to reconvene at 9:06 a.m., Friday, January 6, 2006.]