UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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Monday, March 23, 1998

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Bethesda, Maryland

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The Advisory Committee met in the Embassy Ballroom of the Bethesda Ramada Hotel, 8400 Wisconsin Avenue, Bethesda, Maryland, at 7:45 a.m., Dr. Patricia Ferrieri, Chairperson, presiding.

PRESENT:

PATRICIA FERRIERI, M.D., Chairperson

ADAORA ADIMORA, M.D.

CAROLINE HALL, M.D.

KATHRYN EDWARDS, M.D.

MARY LOU CLEMENTS-MANN, M.D.

MARY ESTES, Ph.D.

HARRY GREENBERG, M.D.

CONSULTANTS AND GUEST SPEAKERS PRESENT:

ROBERT BREIMAN, M.D.

MARION DANIS, M.D.

THEODORE EICKHOFF, M.D.

JOSHUA FIERER, M.D.

STEPHEN HOFFMAN, M.D.

EDWIN KILBOURNE, M.D.

ERIC MINTZ, M.D.

CYNTHIA SEARS, M.D.

DIXIE SNIDER, JR., M.D., M.P.H.

HAROLD VANDERPOOL, Ph.D., Th.M.

ROBERT WEBSTER, Ph.D.

KATHERINE KNOWLES

MICHAEL APICELLA, M.D. (by telephone)

COMMITTEE STAFF PRESENT:

NANCY CHERRY, Executive Secretary

ALSO PRESENT:

DR. R. DOUGLAS PRATT

DR. DENNIS LANG

DR. MYRON M. LEVINE

DR. CAROL TACKET

DR. BERNARD IVANOFF

DR. JIM NATARO

DR. NANCY COX

DR. DOMINICK IACUZIO

ALSO PRESENT (Continued):

DR. PETER PATRIARCA

DR. CARL FRASCH

DR. ROLAND LEVANDOWSKI

DR. CAROLYN HARDEGREE

DR. BILL EGAN

DR. DRUSILLA BURNS

DR. NEIL GOLDMAN

DR. MARCELLO STEIN

DR. KARN MIDTHUNE

DR. GINA RABINOVICH

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

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

(7:53 a.m.)

CHAIRPERSON FERRIERI: Good morning, everyone. I'd like to call the meeting to order.

I'm Dr. Patricia Ferrieri, chair of the Vaccines and Related Biological Products Advisory Committee, and we'll do introductions of everyone at the table in a moment, but I'd like to turn it over to Ms. Cherry so that we can deal with all of the other administrative issues.

MS. CHERRY: Well, first of all, I'd like to say welcome and to congratulate all of you who found the correct hotel this time. I was so afraid we would lose everyone because by habit you just might got a little farther down the street.

We have a long program, so we want to keep this on track as much as we can, and I have to take the first several minutes to read the conflict of interest statement.

This announcement is made a part of the record of this meeting of the Vaccines and Related Biological Products Advisory Committee on March 23rd, 1998.

Pursuant to the authority granted under the Committee charter, the Director of FDA, Center for

Biologics Evaluation and Research, has appointed the following individuals as temporary voting members for the discussions involving the scientific and ethical considerations of the human challenge model using virulent salmonella typhi bacteria: Drs. Joshua Fierer, Stephen Hoffman, Eric Mintz, Dixie Snider, and Harold Vanderpool.

The Director has also appointed the following as temporary voting members for the discussion on the influenza virus vaccine formulation for '98-'99: Drs. Robert Breiman, Theodore Eickhoff, Edwin Kilbourne, Dixie Snider, and Robert Webster, and some of those will be joining us this afternoon.

Ms. Kathy Knowles, Executive Director of the Health Information Network in Seattle, is serving in the capacity of consumer representative for the Committee today. That's in the absence of Ms. Rebecca Cole, who couldn't make it today. Ms. Knowles is a nonvoting consultant.

By the way, I would also mention that Dr. Huang and Dr. Poland also could not be with us today.

Based on the agenda made available, it has been determined that all financial interests in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the Committee's

discussions and have been reported by the participating members, temporary voting members, and consultants as of this date present no potential for the appearance of a conflict of interest at this meeting, with the following notations and disclosures.

I've got to do something to liven this up.

(Laughter.)

MS. CHERRY: For members, Dr. Ada Adimora, an appearance determination amendment was approved by the agency on April 4th of 1997 for an unrelated grant from NIAID from which she receives part of her salary.

For Dr. Mary Clements-Mann, a waiver was approved to permit her full participation in today's discussions and any votes taken today. In addition, Dr. Clements-Mann reported that she spoke on October 24th of '97 at an unrelated grand round supported by a regulated firm where she received an honorarium.

Dr. Kathryn Edwards. A written appearance determination was approved for an unrelated grant and three unrelated contracts from NIAID, as well as an unrelated contract from a regulated firm. Dr. Edwards also has disclosed that she spoke in May of '97 on an unrelated issue sponsored by a regulated firm where she received an honorarium. In addition, she spoke on another unrelated topic sponsored by a regulated firm.

She did not receive any personal remuneration.

Dr. Mary Estes. A written appearance determination was approved for unrelated contracts from NIAID. In addition, she has an unrelated research agreement with a regulated firm. She also disclosed that she was an invited speaker for a regulated firm on an unrelated topic. She received an honorarium.

Dr. Patricia Ferrieri has disclosed that she is a local principal investigator on an unrelated NIAID contract awarded to her university.

Dr. Harry Greenberg has disclosed that he holds an unrelated patent with NIH which was licensed to a regulated firm.

Dr. Caroline Hall. An appearance determination was approved for Dr. Hall for an unrelated NIAID contract -- oh, for unrelated contracts, plural, for which she received salary. In addition, she reported that in the past she consulted with a regulated firm on an unrelated issue. She received an honorarium.

For the consultants, Dr. Stephen Hoffman reported that his employer, the Naval Medical Research Institute, is negotiating an unrelated CRADA with a regulated firm. In addition, Dr. Hoffman reported a

past unrelated speaking engagement with this regulated firm. He receives no personal remuneration.

Dr. Edwin Kilbourne reported that he is the co-investigator of an unrelated contract awarded by a regulated firm.

Dr. Eric Mintz reported that he co-authored a chapter on an unrelated topic with Dr. Myron Levine.

Dr. Cynthia Sears reported that she collaborates with a researcher at the University of Maryland on an unrelated grant which was awarded by NIAID. She receives salary for this collaboration.

The following participants did not have any financial interest to report: Ms. Katherine Knowles, Drs. Robert Breiman, Theodore Eickhoff, Joshua Fierer, Dixie Snider, Harold Vanderpool, and Robert Webster.

In regard to FDA's invited guest, Dr. Marion Danis, the agency has determined that her service is essential. She has no reported financial interests that would present a conflict of interest.

In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude

themselves from any involvement, and their exclusion will be noted for the public record.

Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in today's Committee discussions.

Copies of all waiver statements and appearance determinations addressed in this announcement are available by written request under the Freedom of Information Act.

With respect to all other meeting participants, we ask in the interest of fairness that you address any current or previously financial involvement in any firm whose products you wish to comment on.

And I would also mention one other thing. Late this afternoon when we have the short reports on the laboratories, Dr. Michael Apicella will be joining us by teleconference, but that's late in the day.

CHAIRPERSON FERRIERI: Thank you, Ms. Cherry.

I'll start then by introducing the table. If we could go clockwise starting with Dr. Danis, please, and your affiliation.

DR. DANIS: I'm Marion Danis from the Department of Clinical Bioethics at the Clinical

Center of the National Institutes of Health.

MS. KNOWLES: And I'm Kathy Knowles. I'm from the Health Information Network in Seattle, Washington, and I'm acting as a consumer representative today.

DR. EICKHOFF: Ted Eickhoff, Department of Medicine, University of Colorado.

DR. HALL: Carolina Hall from the University of Rochester.

DR. ADIMORA: Ada Adimora from the University of North Carolina School of Medicine, Infectious Diseases.

DR. GREENBERG: Harry Greenberg from Stanford University and the Palo Alto VA Hospital.

DR. VANDERPOOL: I'm Harold Vanderpool of the University of Texas, the Medical Branch in Galveston.

DR. MINTZ: Eric Mintz from the Foodborne and Diarrheal Diseases Branch, CDC.

DR. HOFFMAN: Steve Hoffman, the Director of the Malaria Program, Naval Medical Research Institute in Bethesda.

DR. FIERER: Josh Fierer, the University of California, San Diego, and the VA Center.

DR. EDWARDS: Kathy Edwards, Department of

Pediatrics, Vanderbilt University.

DR. CLEMENTS-MANN: Mary Lou Clements-Mann, Johns Hopkins University School of Public Health.

DR. SNIDER: Dixie Snider, Associate Director for Science, CDC.

DR. ESTES: Mary Estes, Molecular Virology, Baylor College of Medicine.

DR. SEARS: Cynthia Sears, Johns Hopkins University School of Medicine.

CHAIRPERSON FERRIERI: I'm Patricia Ferrieri of Departments of Lab Medicine, Pathology, and Pediatrics at the University of Minnesota Medical School.

As we proceed with the morning and afternoon program, when you wish to speak, I'd like you to raise your hand, and I will acknowledge you here at the table, and that you will state your name because our recorder needs to know that, and some of you are not as well known to me, and I may not remember your name when I need to.

Good morning. Dr. Robert Breiman, would you like to introduce yourself and your affiliation?

DR. BREIMAN: I'm late, and I'm Dr. Rob Breiman.

(Laughter.)

DR. BREIMAN: From the National Vaccine Program Office.

CHAIRPERSON FERRIERI: Thank you.

Well, we'll move ahead then, and I'll turn the program over to Dr. Douglas Pratt from FDA, who will then make a presentation, and then we'll move to the sponsors.

Good morning, Dr. Pratt.

DR. PRATT: Good morning, members of the Committee, colleagues, and guests. My name is Douglas Pratt. I'm a medical officer in the Division of Vaccines and Related Products at FDA.

The purpose of this morning's meeting is to consider a proposal to conduct human challenge studies of typhoid fever. The Division of Microbiology and Infectious Diseases at NIAID, working with investigators at the University of Maryland's Center for Vaccine Development have proposed in pre-IND submissions and discussions to initiate a series of studies based on a human challenge model of typhoid fever.

The challenge model under consideration proposes to infect human volunteers with live, nonattenuated, pathogenic salmonella typhi.

The stated objectives of the study are:

One, to identify vaccine candidates worthy of evaluation in large scale trials in endemic areas;

Two, to demonstrate whether the candidate vaccines protect immunologically naive individuals as would be the case of travelers from nonendemic to endemic areas; and

Three, to investigate the pathogenesis in human immune response to wild type salmonella typhi and to attenuated vaccine strains.

Beginning in the 1950s, human challenge studies of typhoid fever were conducted by investigators at the University of Maryland School of Medicine. Hundreds of adult male inmates at the Maryland correctional facility at Jessup, Maryland, served as human subjects. Investigators elected to terminate these studies in 1974.

The proposed model differs in important respects from the earlier challenge model. Drs. Levine and Tacket will be presenting details of the proposed study shortly.

A draft protocol was submitted to FDA in October of 1997. FDA questions and comments regarding the protocol were conveyed to the sponsor, and a face-to-face meeting took place in November.

The sponsor has been responsive to FDA's safety concerns and considerable of protocol modifications suggested by FDA reviewers intended to enhance safety of the study.

A revised protocol, along with responses to FDA comments is included in the sponsor's briefing packet.

Clearly, thoughtful efforts have been made to minimize serious consequences to study participants and to reduce the chance that secondary cases may occur in the community.

However, the serious nature of systemic infection with this bacteria make even a rare possibility cause for concern.

A determination that a human challenge may proceed deserves the benefit of unbiased expertise in evaluating the risks to subjects and the usefulness of the data that may be generated.

Due also to the complex nature of human challenge studies in general and given the history of typhoid challenge studies among inmates, we in the Reviewing Division of FDA feel that the typhoid fever challenge model and associated ethical issues should be carefully considered and discussed openly among experts in the field.

During the sponsor's presentation, please be mindful of the questions posed to the Committee, and I'll read them now.

Number one, does information likely to be gained from this model justify the risks to subjects and the community?

Number two, if yes, please discuss any recommendations for modifying the study protocol and consent form. Specifically, please comment on the criteria proposed for initiating antibiotic treatment, which are temperature greater than 38.3 degrees Centigrade for 12 hours or bacteremia occurring on days seven through 14. Please comment on whether blood cultures should be obtained on days five and six. Please comment on the proposal for out-patient antibiotic treatment of subjects who continue to have positive stool cultures after an initial in-patient course.

And are there other changes to the protocol entry criteria, monitoring procedures, or study design which you would suggest, for example, staging of enrollment, stopping rules, monitoring of in-patient and out-patient contacts?

And, finally, does the consent form adequately address the potential risk to volunteers?

Following the sponsor's presentation, I will return and present some additional points to consider in your deliberations, and the questions will again be projected at that time.

So I'll turn it over now to Drs. Levine and Tacket.

DR. LANG: Good morning. I'm not Drs. Levine or Tacket. I'm Dennis Lang, the Enteric Diseases Program Officer at NIAID.

And we are, as was just mentioned, the sponsors for this study to look at a new human challenge model for salmonella typhi in humans, and I would just like to take a few moments prior to turning it over to Drs. Levine and Tacket to try and put this study into the context of our institute's support for both enteric diseases as a whole and specifically salmonella research.

The total budget of my program in enteric diseases, which covers everything from astro virus to ursinea enteracholitic (phonetic), alphabetically, is about $33 million a year. Currently, we are spending about just a little bit over $5 million of that on salmonella research. That $5 million is equivalent to the amount that we spend on the other two largest supported organisms in my portfolio, which are

vibriocholera and all of the E. coli combined.

There are 32 awards presently supported by our institute on salmonella, and to a large degree, that support is really for two organisms: salmonella typhi and salmonella typhimurium as a model, a mouse model, for human typhoid fever.

Largely unsupported are the other salmonella that you read about in the newspaper every day, those causing food-borne diarrheal diseases. So the vast majority, over 90, 95 percent of our total portfolio goes basically to understand typhoid fever.

As will be pointed out by Dr. Levine, this is a huge problem, and I'm sure all of you are aware of that, worldwide, and I think for years we have -- the institute has -- supported this with that realization that this is an important problem and deserving of a lot of activity.

I think, moreover, the fact that salmonella is an organism that's so well studied, so well understood at the genetic level that it has served in a lot of respects as a model for other enteric organisms, and its role as a potential vector for the development of other vaccines for other enterics and other diseases, in fact, I think is a statement of that effort.

Okay. What does our research focus on in salmonella organism? Four areas essentially.

Mostly the genetics of virulence, that is, understanding the various genes and their role in pathogenesis, their isolation, their cloning, their overexpression, their deletion, in fact, to create potential vaccine strains.

Vaccine development per se is a reasonably large effort, and there are now currently three live attenuated vaccine vectors that have been developed as a result of NIH support. Dr. Levine will be mentioning all three of those, and I don't need to say anymore about it at this point.

In addition to these strains being developed as vaccines against salmonella typhi, as I've just mentioned, there's also a lot of effort in using salmonella and these attenuated strains to express foreign antigens as well, to protect not only against salmonella, but against other enteric diseases, and there's a lot of activity in our portfolio in that regard.

And I think last but certainly not least is the more recent effort just in the last few months with two awards having been made to completely sequence the genomes of both salmonella typhi and

salmonella typhimurium, and I think needless to say, within the next couple of years, this information is going to revolutionize the way we look at pathogenesis of this organism, as well as produce new ideas and new thoughts about how to attenuate these strains as vaccine candidates.

The other important aspect of the work that we support is not necessarily just in the grant support, although that's certainly an important part, but we also commit large amounts of money in contract support essentially to test pathogenesis and vaccine development, not only for salmonella, but with a lot of other in my portfolio at least enteric organisms.

And those activities occur at what we have funded as the vaccine testing and evaluation unit, and a large contract called the enteric pathogens research unit. So these contracts are supporting both basic research, as well as applied research and the testing in volunteers and humans, pathogenesis and vaccine efficacy.

Those studies would be largely facilitated by the availability of a human challenge model similar to what we've had available in cholera and some other organisms for the identification of really good candidates, I think, for large scale trials.

To be able to have in a small number of volunteers some indication that we're producing a vaccine that's efficacious and safe is a very important first step, I think, towards making choices, expensive choices, about how to proceed with vaccine testing on a larger scale.

So I think with that introduction I will stop, and I look forward to the discussion this morning. I think it's going to be very interesting and informative for all of us, and I'll turn it over to Mike Levine.

Thanks.

CHAIRPERSON FERRIERI: Thank you, Dr. Lang.

Dr. Levine.

DR. LEVINE: Thank you.

Good morning. I'd like to thank the Committee for the opportunity to present this proposal.

If I might have the first slide, this is a summary of the approach we'll take in presenting the proposal. I'll provide a rationale and background. Dr. Carol Tacket will summarize and describe the clinical protocol. Dr. Bernard Ivanoff will, from the World Health Organization, will describe the

importance of this model from the World Health Organization perspective.

Our approach is that typhoid fever is a reemerging infection on the world scene, and this proposal is part of a multi-agency attempt to provide a better immunoprophylaxis. This multi-agency approach includes the National Institute of Allergy and Infectious Diseases, the Center for Vaccine Development, and the World Health Organization.

One of the estimates of the worldwide burden of typhoid fever is that there are approximately 30 million cases that occur each year with between 500 and 600,000 deaths, almost entirely in the developing world.

What makes typhoid a reemerging problem is the appearance in many parts of the developing world of salmonella typhi strains that carry resistance plasmids encoding resistance to all the antibiotics that have been useful during the past decade.

The targets for use of vaccine include travelers from the United States and other industrialized countries who visit those developing areas of the world where this problem is highly endemic and increasing; microbiology technicians. The Centers for Disease Control showed some years ago that

clinical microbiology technicians have about a 30-fold increased risk of developing typhoid; and lastly, and from the burden point of view, children in endemic areas, that group that together suffers the greatest number of cases worldwide.

Typhoid fever was originally an emerging infection in the early 19th Century, and once again in the 1990s is a reemerging problem, reemerging because although salmonella typhi generally does not like to carry plasmids, which is an interesting feature, it does accept plasmids of incompatibility Group H1 and strains that are found in the Indian subcontinent, in the Middle East, in Northeast Africa, and in Southeast Asia, are now carrying INK (phonetic) H1 plasmids that encode resistances to chloramphenicol, trimethaprim sulfur methoxizol, and amoxycillin, the antibiotics that were the primary drugs of choice in the 1980s.

Until 1997, from 1990 to 1997, ciprofloxacin in these parts of the world was a very useful antibiotic. However, because of the availability and uncontrolled and widespread use of ciprofloxacin, very low potency, in Southeast Asia and parts of the subcontinent, there have now appeared ciprofloxacin resistant strains, with the resistance being encoded by chromosomal genes. These are being

selected for by this widespread, promiscuous use of antibiotics, and we're reaching the point where in poor communities of Southeast Asia and the subcontinent, this is a very, very difficult disease to treat because the only antibiotics, such as sephtriaxone are beyond the means for routine use for those communities.

What is the risk of typhoid for U.S. travelers? This was reviewed in the late 1980s by the enteric diseases group at CDC. This represents the incidence per million travelers with countries at highest risk for the period of the 1980s.

A risk of 174 or 119 per million travelers, that is, 17 or 11.9 per 100,000 travelers, if that were an annual incidence, that would be an incidence of some import, not super high, but certainly of concern.

Bear in mind though that most of these travelers go to these places for one or two or maybe four weeks. So one needs to multiply these incidence rates by 50 or 26 or perhaps 12, and one then reaches what would be an equivalent of an annual incidence rate of from 200 to over 1,000, and these are impressively high incidence rates equal to what one sees in hyperendemic areas.

I'm going to briefly mention our understanding of the pathogenesis of typhoid fever, and I'm going to say that this is an approximation because of the fact there are great questions that we have.

Understanding the pathogenesis comes from four main sources. It comes from the mouse model that utilizes salmonella typhimurium and salmonella enteritidis. It comes from human autopsy studies with large series in the pre-antibiotic era. It comes from a chimpanzee model of typhoid that was developed in the 1960s at Walter Reed, and it comes from human volunteer challenge studies in the 1960s and early 1970s.

What we know then is that salmonella typhi is always ingested in food and water vehicles. It must pass the important gastric acid barrier of the stomach, a potent defense mechanism.

When the organisms reach the small intestine, they translocate. They do this by two ways. They're taken up by N cells, the micropholic cells that cover gut associated lymphoid tissue, such as the peyer's patches in the ilium, or if the inoculum is a bit larger, salmonella have the propensity to be taken up in a pinocytotic vesicle

that involves cross-talk, if you will, between the bacteria and the intracite, and in this vesicle, the vesicle then passes to the basolateral surface where they're released.

From the N cells they are taken up by the lymphoid tissue below, particularly by the macrophages. If they reach the laminapropia, they call in a potent macrophage chemotactic response, and they are then ingested by macrophages.

Virulent salmonella typhi have virulence properties that allow them to survive within phagocytic vesicles within the macrophages. The organisms drain to the mesenteric lymph nodes and either as free bacteria, which is probably the rarity, or as macrophage associated bacteria, they enter the lymph circulation and then via the thoracic duct they enter the blood circulation. A primary bacteremia is believed to occur and the organisms end up in the spleen, liver, bone marrow, the organs of the reticular and endothelial system.

This is very clear in the mouse model. That is, there are two clear bacteremias, a very low level primary bacteremia that seeds the reticular endothelial system.

One of the most pressing questions in

human pathogenesis is whether, indeed, this occurs in humans. Be that as it may, after eight to 14 days of sitting quietly in an individual during incubation period, the clinical illness begins with fever, abdominal discomfort, and headache, and there is an associated secondary bacteremia.

The clinical picture of acute typhoid classically begins with fever that increases in a step-wise or step ladder fashion. It's associated malaise, with headache, with abdominal discomfort.

Adults often have constipation. Some may have diarrhea. Children more often have diarrhea, and when diarrhea occurs a bit later in the course, it often has a so-called green, pea soup characteristic appearance.

One not uncommonly sees a bronchitic cough with typhoid. Uncommonly one sees chills or rose spots.

In the pre-antibiotic era, if one reads Sir William Osler's chapter on typhoid in his book, and I left it as a reference his chapter from his 1898 edition of his Textbook of Medicine, you can see virtually every organ system involved.

Pre-antibiotic era typhoid was a disease that could extend for four, five, six, seven weeks,

and at different periods, different weeks, one saw different complications. I want to stress that these things one overwhelmingly sees in delayed or suboptimal or in the pre-antibiotic era type of situation.

Let me speak to several complications that should be of import to us. In the pre-antibiotic era approximately ten percent of individuals suffered relapses. They had acute typhoid. They got better, and then they came down again with fever. Almost always the relapse was much milder.

In the antibiotic era, with the advent of chloramphenicol, which in 1948 changed entirely the natural course of typhoid, the occurrence of relapse actually increased to about ten or 15 or 20 or 25 percent.

A few percent of individuals with wild type illness may develop chronic gall bladder infection. The propensity to become a chronic gall bladder carrier is a consequence of preexistent gall bladder disease. This is why the occurrence of this complication follows the same epidemiology as cholelithiasis or gall bladder disease. It is much more frequent in women than in men and increases with age.

Chronic gall bladder disease is extremely uncommon in young children who have acute typhoid fever for that reason.

Almost any organ system involvement has been described in pre-antibiotic era typhoid. However, I'd like to point out that the complications that one might see is very much a consequence of the population.

Let's begin with the concept of case fatality. In pre-antibiotic era, a typical water borne outbreak, as in Olean, New York, would have been associated with a ten or 12 or 15 percent case fatality.

This is a summary of the published outbreaks in the United States in what I call the modern era, post 1970. There are two other outbreaks. I made this slide on Friday, and it should have been passed out to you.

There are two additional outbreaks that I couldn't lay hands on, but those outbreaks occurred in the State of Washington and in association with a large Hispanic family picnic on the East Coast also were not associated with case fatality.

The complications that one sees very much depends upon the population. To give some examples,

in Latin America, typhoid fever tended to be a much milder clinical infection than is seen in Asia and some parts of Africa. The clinical syndrome of typhoid that one sees in these outbreaks in the United States is very, very different than one sees in endemic disease in the poorest countries of the world for obvious reasons.

And I would suggest that it's this population that should be one measure of the way typhoid infection is handled in the U.S. population, and this should be recognized as being an unselected population if one limits -- if infection were entirely limited to healthy young adults, as has happened, for example, in some British army groups in Northeast Africa. The illness tends to be very, very mild and limited and virtually without complications.

When you look at percentages of complications, please consider what is the denominator.

Typhoid fever has an iceberg effect, if you will epidemiologically. The tip, the tip of the iceberg ends up in hospitals whether it's in an endemic area or in an industrialized country. For each individual who ends up in the hospital, there are many other cases of much, much milder infection.

And so I think we can briefly summarize the situation as follows. In the pre-antibiotic era typhoid was often severe. There was no way to modify the clinical course. Complications were common, and case fatality was ten to 20 percent whether we were speaking of the United States in 1940 or a developing country.

In the post antibiotic era we see endemic disease, and we see travelers' typhoid. Endemic disease as we saw it in Latin America, for example, during the four large scale field trials of Ty21A that our group carried out in Santiago, Chile, an endemic area. There were hundreds of cases of typhoid in the placebo control groups, and there was no fatality and there were few complications in that particular environment.

In Asia, in parts of Asia, particularly in the poorer countries where health care services are more limited, the case fatality can be somewhat higher.

And then there is the experience of experimental challenge where there was a generally mild illness because of prompt intervention, where complications were extremely rare, and of course, there was zero case fatality.

Chronic typhoid carriers. To reiterate, in the acute infection, salmonella typhi always ends up in the gall bladder. This is why duodenal string capsules that sample bile are such an effective diagnostic tool.

But the propensity to become a chronic carrier relates to whether the gall bladder has preexistent mucosal disease and, in particular, whether there are gall stones. For this reason, to reiterate, the prevalence of carriers after infection parallels the epidemiology of gall bladder disease, females greater than males, increases with age.

There are good typhoid vaccines today in relative terms. In the United States and many other countries, there are three vaccines licensed. The old, killed, whole cell parenteral vaccine, which for civilians is a heat enacted phenol preserved preparation.

There is oral Ty21A, and there is parenteral purified Vi polysaccharide.

Now, these are good vaccines, the old killed whole cell vaccine being, I would suggest, the exception because of its unacceptable reactogenicity, but Ty21A and parenteral Vi, these are good vaccines that represent an advance over the old killed whole

cell. These are well tolerated.

But these vaccines also have significant drawbacks that limit their use and their compliance and their acceptability. For example, Ty21A requires four doses in the U.S. and Canada, three doses in the rest of the world. The need for multiple doses really diminishes compliance and uptake.

The efficacy of all of these vaccines is only moderate. We'd like to do better. The parenteral Vi vaccine, we have data on efficacy, 50 percent efficacy at three years and no data beyond that.

So for each of these vaccines, we really would like to do better.

On the global scene, we have to do better, and the reason is that even though typhoid is a reemerging problem, it's becoming a major and increasingly important public health problem in many countries in Southeast Asia and in the subcontinent. None of those countries, not a single one, has elected to use in a programmatic fashion either Ty21A or Vi.

Why? The reason is that the infrastructure to give out vaccines in a systematic way is the expanded program on immunization, which is limited in those countries to the first year of life,

and these are not vaccines that work in the first year of life.

With Ty21A, we know nothing about its even immunogenicity in infancy, and with Vi it's not very immunogenic in infancy.

We can use these vaccines in school based programs, but countries say that they don't have the resources for that type of use. So the health ministries have asked World Health Organization and groups that develop typhoid vaccines. They have said, "Give us a well tolerated, but more potent vaccine that we can use in the EPI and that will be so protective, immunization in infancy will protect all the way through the high school years.

And that's the goal of groups that work on developing new and improved typhoid vaccines, and there are candidates now that are coming along and are at an important stage.

There's the Vi conjugate that come from two groups. One of those groups, an NIH group, has a Vi conjugate in a field trial in Vietnam.

Another group, a regulated company, has a vaccine that's in Phase 2 trials.

Engineered single dose, live oral vaccines, there are three candidates that have

completed Phase 1 studies. One at least is in Phase 2 studies.

Chi 4073 was developed by Roy Curtis and his group at Washington University. It's a CYA CRP CT triple mutant.

Ty800 was developed by Elizabeth Holman and Sam Miller and has mutations in pho P/pho Q.

CVD 908 HTRA was co-developed by our group at the Center for Vaccine Development and Mediva and Imperial College in London. These are attractive vaccine candidates that we would like to see move in an accelerated fashion towards becoming potential public health tools for the less developed areas of the world that need typhoid control, and also to protect travelers.

The fact is we see several hundred cases of typhoid each year amongst U.S. travelers, the overwhelming majority in individuals who have not take typhoid vaccine. Usually they have not taken it or in great part because of the limitations of the vaccines.

Through the typhoid challenge model we would expect to reestablish strains that would be useful, demonstrating that they can elicit an attack rate of clinically acceptable abbreviated disease. By means of a bicarbonate buffer, we would hope to have

a challenge dose that would give a high attack rate with a relatively low inoculum.

And with this, we would hope to measure vaccine efficacy of these new candidates, selecting strains that could go out for large scale field trial and establishing that these vaccines can work in the immunologically naive North America.

And ideally we would hope to identify correlates of protection that would allow us to look at formulations and immunization schedules.

As secondary aims, there would be the opportunity to identify host risk factors, to elucidate pathogenesis, perhaps answering those fundamental questions that remain, and to characterize in an intensive way the immune response.

I don't seem to be advancing. There.

In seeing up such a challenge model, there are ethical issues. There are microbiological issues. There are practical and logistical considerations.

With any challenge model, the whole concept goes against the grain of what we as physicians are trained to do to prevent disease, to treat disease, to diminish the discomfort of disease.

But a fact of life, as Dr. Lang mentioned, is that there are in the United States a number of

challenge studies that are carried out to help advance vaccine evaluation, and the key to this is to be sure that the risk is truly minimal, indeed, minuscule, and we would hope to show you that in our opinion and based on past experience, this is our expectation.

There is no problem, in our view, informing the volunteers. There's no problem establishing consent, and indeed, individuals by their own volition in the course of work and in the course of play put themselves at risk. They climb mountains. They go down rivers with gorges, with six foot waves. They jump out of airplanes.

That's not the point. The point is in this instance we are giving wild type organisms to a healthy young adult population, and we must be sure that we are comfortable that there is minimal risk, and we believe there is.

There are microbiologic issues. There is a strain that was used extensively some years ago. There's also a modern strain. We ask the Committee for help and guidance with respect to prioritizing these two strains.

And lastly, there are rather daunting logistical and practical considerations to carrying out such a challenge, essentially a month of physical

containment to be able to control the situation.

This is a list of what I call modern challenge models, models that have been undertaken since approximately 1970. There have been bacterial challenges. There has been a rickettsial challenge. There are viral challenges and parasitic challenges.

There are some invasive organism challenges, rickettsia. There are some challenges with organisms that were untreatable. Cryptosporidium is an example.

And so in considering this, we ask that a degree of balance be kept in mind in terms of what is ongoing, such as invasive malaria, in other vaccine development programs.

The challenge studies to measure vaccine efficacy will use defined strains and inoculum. They will establish whether these vaccines in this model protect U.S. subjects, information that we believe is important.

They will allow a measure of the period of onset of protection, something that's quite difficult to establish in the field.

They are relatively economical compared to field trials for which there are few limited field areas, and they can provide relatively rapid answers.

We must consider the severity of clinical illness in experimental infection versus what we see with natural infection, and the point I want to make is that if you look at untreated malaria or malaria treated in the least developed parts of the world, that's a completely different situation than the experimental challenge.

The same is true for cholera, El tor or classical. The same is true for shigellosis.

Experimental illness is much, much, much milder compared to natural infection, and the key for these three is prompt therapy that ameliorates that illness, limiting the severity.

These are some questions that our group grappled with and shared in discussions with NIH and with the WHO.

What is the severity of natural disease in the group that's as close as possible to the participants in such a trial? That is to say healthy young adult subjects in the United States.

Is the clinical disease treatable? Our answer is yes. Ciprofloxacin is one of the two drugs that has had an extraordinary impact on typhoid fever treatment over the past half century, chloramphenicol being the other.

What is the risk to the community, and is physical containment required? We believe yes, and in that way we minimize the chance of salmonella typhi organisms being released into the community.

Can we document the subject's baseline health? To us in great part this means demonstrating that an individual is not an individual with chronic gall bladder disease.

And can follow-up be assured? Our track record in many other studies over the years, I believe, establishes that we do good follow-up and can assure that.

And so there are several concerns, and this is how we propose to answer them. We must limit the severity and the duration of clinical illness, and we do this by early ciprofloxacin therapy with a ciprofloxacin sensitive strain. This is an extraordinarily effect antibiotic in our experience in the field.

This antibiotic also limits short term excretion. It precludes long term carriage for all intents and purposes, and particularly if we exclude individuals who do not have gall bladder pathology, the chance of having a chronic carriage, we believe, is minuscule, and furthermore, we would suggest that

not only is ciprofloxacin a unique antibiotic compared to chloramphenicol, compared to amoxycillin or compared to trimethaprin sulfamethoxizol. Not only does it virtually preclude chronic carriage, but in our experience in Chile, when you have individuals who are chronic carriers with gall bladder disease and other antibiotics have been attempted, we had a very good experience, a 90 percent success rate in treating chronic carriers with oral ciprofloxacin during a several week therapy.

Now, let's talk about this earlier model that took place from about 1959 to 1975. A total of 1,886 volunteers participated in those typhoid vaccine studies. Six hundred and seventy-two ingested this wild type strain that we call Quailes, at a does of ten to the five colony forming units.

Two hundred and thirty-five of these 672 developed clinical illness. At 20 days post challenge, 60 percent of the ill and eight percent of well subjects had positive stool cultures when they were treated with chloramphenicol.

In this population where screening for gall bladder disease was not done initially, there was one long term carrier, and this occurred after actually most of these challenges had taken place, and

that individual in the pre-ciprofloxacin era was cured with cholecystectomy and antibiotic therapy.

There were several other complications that were seen in association with these studies that I'll mention. There was an instance of diarrhea where it was considered sufficiently heavy diarrhea so that an individual received rehydration fluids.

One individual developed a pleural effusion. However, it was the opinion of the clinicians that this was not associated with the typhoid, but rather was associated with intravenous drug abuse, a practice that did occur even in incarcerated individuals.

Another individual had gastrointestinal bleeding. This is an individual who was not treated with antibiotics during his acute infection and had a relapse and had the GI bleeding. The model that you will hear about that we will propose, everybody gets antibiotics.

And lastly, there was an individual who developed diabetes, and we don't attribute this directly to typhoid per se. This could have happened with any other type of challenge study.

There was one individual who had had a history of psychiatric problems who had psychiatric

problems for a period of time, of days after challenge.

In that early model typhoid fever was defined as an oral temperature of 38.3 degrees or greater in association with isolation of salmonella typhi from blood or from stool.

Indications for treatment were a bit more stringent, much more stringent than what we are proposing. Initially it was 39.4 degrees Centigrade for 24 or even 36 hours in the early studies or 101 degrees Fahrenheit for 48 house. One had to have reached these criteria for therapy in that model.

This shows the dose response with increasing doses for three logs, five logs, seven, eight, and nine logs carried giving the organisms in 45 milliliters of milk. You see that at three logs there's a zero attack rate, and at nine logs there's a 95 percent attack rate, and at five logs, in those dose response studies, a 28 percent attack rate.

Now, what is the -- I'm having a little trouble here. Carol, if you could advance that. Thank you.

What is the consistency of the attack rate? In this slide I summarized the attack rate in the control group in various challenge studies that

evaluated vaccines, such as Ty21A, strep dependent vaccines, parenteral whole cell, et cetera.

One see here then the -- I must apologize for the way I used -- I'm color blind. So I have great difficult with this little dot. I have to see it as a light spot against the dark. So bear with me, please.

Anyway, you see the attack rate, and it's fairly consistent, mostly hovering around 40 to 55 percent, a couple of outliers.

I would also like to mention that the individuals who developed this model and had the greatest experience originally include Theodore Woodward, Richard B. Hornick, and Herbert DuPont. Those three individuals went on at various points in time to become presidents of the Infectious Disease Society of America. There are highly respected infectious disease clinicians and investigators.

Carol.

The two strains that we're proposing and that we're asking for guidance in selecting the challenge strain, Quailes is the one given to almost 2,000 volunteers. It was isolated in 1958 from a chronic carrier in Maryland. It's Phage Type D1. There is this vast challenge experience, and we think

it's important to use this strain.

In addition, we're proposing that perhaps we can look at a more modern strain, if you will, ISP 1820, isolated in 1983 from a Chilean child with typhoid fever during Ty21A field trial. It is Phage Type 46. It was never used for challenge, but we suspect that it is, indeed, a pathogenic strain because one vaccine strain made from this parent was not fully attenuated, and that's a hint that the wild type parent would, indeed, be.

And lastly, I want to reiterate that we have potent antibiotics to treat sensitive strains. Ciprofloxacin is an extremely effective antibiotic. It is almost in a class by itself compared to earlier generations of antibiotics, including chloramphenicol, amoxycillin and trimethaprin sulfamethoxizol.

I'd like to stop at this point and pass the baton to Dr. Tacket.

CHAIRPERSON FERRIERI: Thank you, Dr. Levine. The Committee appreciates very much your adherence to the time allotted, and I'd encourage all the other speakers to also adhere to the schedule.

DR. TACKET: My job this morning is to describe for you briefly the clinical protocol which we have been developing for typhoid challenges.

As Mike has summarized already, the broad purposes of such a study would be to identify vaccine candidates which are worthy of evaluation in expensive, time consuming, large scale field trials in endemic areas; to measure vaccine efficacy in persons from nonendemic areas, namely, U.S. citizens; and to intensively investigate both the pathogenesis and the human immune response to wild type S. typhi.

More specifically, the goals would be to achieve an attack rate of typhoid fever of about 75 percent without causing unduly severe typhoid; to induce illness with a relatively low inoculum of three or four logs of organisms; to evaluate a modern S. typhi isolate, ISP 1820, as a possible alternative to the previously used Quailes strain; to identify a strain which causes illness with a relatively short inoculation period, for practical reasons; and to use sodium bicarbonate instead of skim milk to buffer the stomach acid.

The study design is very simple. There would be 24 healthy adults recruited and randomly allocated to receive one of the two strains, Quailes or ISP 1820, which Mike described for you just now.

Quailes strain would be given at ten to the third or ten to the fourth colony forming units

with bicarbonate, and recall that in the previous model this strain was given with skim milk.

And then ISP 1820 would be given at a dose of ten to the three CFU also with bicarbonate.

The outcomes would be attack rate for typhoid fever, incubation period, and a description of the characteristics of the clinical illnesses.

Inclusion criteria are shown here. Our volunteers would have normal medical histories and physical exams and normal urinalysis, complete blood counts, serum chemistries, liver function tests, and normal electrocardiogram.

The exclusion criteria have been generated to both insure safety and minimize risk of transmission. So I'll take you through this long list.

The volunteers would not have any clinically significant history of immunodeficiency, heart disease, lung disease, endocrine disorder, liver disease or gall bladder disease, renal or bladder disease, gastrointestinal disease, disorder of the reticular endothelial system, neurologic illness, psychiatric disorder, or drug or alcohol abuse.

We would perform ultrasound examinations of the right upper quadrant to rule out gall bladder

pathology, and they must not have had typhoid vaccinations or typhoid fever. They must not be allergic to the antibiotics that we might potentially use beyond ciprofloxacin, including amoxycillin or trimethaprim sulfamethoxizol; no antibiotic use in the seven days before challenge; no pregnancy or nursing mothers; negative HIV serology, Hepatitis C serology, and Hepatitis B surface antigen; no syphilis serology; no family history of stroke or atherosclerotic disease in a family member under the age of 50 years. This is an attempt at eliminating volunteers who might have increased risk of endovascular infection during the bacteremia.

Similarly, no history of a significant heart murmur or systolic murmur greater than Grade 3 or a diastolic murmur of any grade, also an attempt to eliminate an individual who might have valvular heart disease and might be at increased risk of the remote possibility of an endovascular infection.

In addition, they must not be commercial food handlers, day care workers, or health care workers to decrease the risk of transmission outside the containment ward.

We will screen them for HLA-B27. We will eliminate those who have young children at home or who

have household contacts who are immunocompromised.

Their stools will be screened for enteric bacterial and parasitic pathogens.

They will undergo an extended consent process which will include passing a written examination, and they'll also have a psychological examination with a staff clinical psychologist.

Now, illness will be defined as shown here, and contrast this with what Mike has just shown us for the old model. In the new model, typhoid will be defined as fever greater than 38.3, persisting for 12 hours without any anti-pyretic medication.

Severe typhoid fever will be defined as any illness which includes any one of the following: oral temperature greater than 40, systolic blood pressure less than 85 or lethargy or disorientation.

The volunteers will be admitted to our in-patient ward and undergo 48 hours of orientation and acclimentation before challenge. Assuming that they meet the criteria for entry to the study, they will be challenged and remain on our ward for a minimum of 28 days followed by two additional days to document that their stool cultures are, indeed, negative before discharge. So we're talking about a 32 day in-patient stay, which will be very arduous, I think, for healthy

volunteers.

During that stay, they'll be monitored in the following ways. They'll have their temperatures take every six hours. They'll be interviewed daily by one of the physician investigators, and if indicated, they'll have a physical exam.

Every stool that they pass will be cultured for salmonella typhi. Blood cultures will be obtained at the times indicated. Early on they'll have frequent cultures, 12, 24, 36, 48, 72, 96 hours, and that we think is the time when we would expect to see the primary asymptomatic bacteremia that Mike described.

Then beginning on day seven they would receive daily cultures until antibiotics have been started for one of the indications.

We're also interested in recovering the organism from the small intestine if possible. So we'll ask the volunteers to swallow gelatin string capsules on days seven, ten, and 13, and this capsule contains a string about the caliber of dental floss, which after remaining in the small intestine for four hours can be retrieved, and fluid from that string can be milked and cultured for salmonella typhi.

The management of fever is shown on this

slide. At the onset of fever blood cultures, an additional set of blood cultures will be obtained. The volunteers will undergo a brief, four-hour fast in order to prepare them to swallow the gelatin string capsule so that we can attempt to recover the organism from the upper small intestine.

After the persistence of fever of 38.3 for 12 hours, they'll begin ciprofloxacin, 500 milligrams b.i.d., for a 14-day course.

Also after their fever has persisted for the 12 hours, they'll have a CBC and the chemistry shown on the slide. These will be repeated day 28 in those volunteers whose illnesses met the definition of fever.

The indications for ciprofloxacin are shown here. As mentioned, any volunteer who meets the definition of typhoid fever, that is, a 38.3 degrees Centigrade for 12 hours; all the volunteers beginning 14 days after challenge, regardless of whether or not they have symptoms; and any volunteer whose blood culture after day seven is positive, regardless of whether or not he has symptoms, as soon as we get that result.

We propose not treating volunteers with positive blood cultures drawn early on, that is days

zero to four, who do not have fever because we are suggesting that bacteremia during that period represents the primary bacteremia, and if we treat it then, we will abort the clinical illness that is our goal to produce. So blood cultures early on we suggest not be treated.

Before discharge, the volunteers must be well, specifically afebrile, for two days after completing their antibiotics, and their stool cultures must be negative for S. typhi.

If the stool culture is not negative after 14 days of antibiotics, then a second course of ciprofloxacin would be given. We propose that this be as an out-patient, and certainly we welcome feedback on this point.

The concern is that after 32 days in the hospital that it would be difficult to ask volunteers to stay for an additional two weeks, and that the risk of transmission outside the hospital in the remote possibility that their stools are positive after one course is sufficiently low to justify discharge.

After they've left our isolation ward, they'll be instructed to call or visit our out-patient facility if they have any febrile illness that occurs after discharge up until day 90, and if such an

illness does occur, the volunteer will return for interview and examination and blood cultures.

The volunteers will have stool cultures in follow-up on days 60, 90, and 180 after challenge to insure that they are, in fact, cured of excretion.

In addition, we will ask volunteers about illness in their household contacts at their follow-up visits at 60 and 90 days to attempt to capture any illness that might result from transmission after discharge from the hospital.

Finally, there are a number of immunologic studies which will be done that are listed on this slide. First, S. typhi antibody measurements at the times indicated.

We'll also be doing exhaustive studies of cell mediated immunity at the times listed and a search for specific antibody secreting cells and looking for fecal antibody at the times shown.

Dr. Ivanoff.

DR. IVANOFF: Yes. Thank you.

I'm Bernard Ivanoff. I am working in WHO within the Global Program for Vaccine Immunization, and within this program I am responsible of the steering committee on diarrheal disease vaccine, and I would like to show you in three or four

transparencies why our program is interested in having such a human challenge development.

First, the question is: is typhoid fever important? It seems to be a trivial question. In this room everybody knows what typhoid fever is, but when you meet people, you are able to find people who thought that or think that typhoid fever is an old disease. It's finished. It's not an important problem on a global point of view.

The second thing I would like to show you, it was a priority of our program in the Global Program for Vaccine in relation to typhoid fever.

And finally, why does the GPV support salmonella typhi challenge model in volunteers?

Next one.

Typhoid fever is not a trivial disease. It's very important. You see in this pie that typhoid fever is the second killer with shigella after rotavirus. In the estimated number of deaths per year, it's between 2.5 and three million deaths per year. It's not peanuts. Quite, 600,000 deaths per year. It's a very important disease.

We have antibiotics. That's fine, but the next transparencies will just show you -- I will not go into detail -- but just show you in red where

you're able to find isolates, between 50 and 80 percent of isolates, multi-drug resistent salmonella typhi strain distribution in the world. You see that it's very, very important.

And the last example we had recently last year is this Tajikistan outbreak of typhoid fever where most of the strain, between 80 or 90 percent of them, were resistent against chloramphenicol, cortramoxizol, and ampicillin. It's a very, very important disease.

It means that we need to have good and effective vaccine against this disease and to have all the tools in hand to provide all the necessary answer to the requests.

It's important to see what are the priorities of our steering committee. They recommend to have clinical evaluation of existing new candidate vaccines. That centers on the question, why are you interested in new vaccine because you have a good vaccine, Vi polysaccharide and Ty21A.

Yes, for polysaccharide and particularly with a conjugate. Okay, yes, but with a small why for Ty21A. Why? Because you obliged to give three dose two days apart. It's a major drawback of this vaccine, and if you would like to use it in refugee

camp situation, for instance, it's very difficult to come back twice, three times to provide the vaccine.

And we have another idea. Maybe it's a dream, but it's an idea of the committee to have enteric vaccine. It means that we are willing to develop one vaccine for most of the pathogenic agents, and we are recommending the development of a human challenge model that can be safely used for evaluating vaccine candidate, and this new vaccine candidate, particularly, I'm thinking about the one drug dose.

Development of parenteral or oral vaccine that can be effective after one dose and that can be incorporated in the existing EPI schedule of vaccine delivery.

Another question is why you would like to have two kinds of vaccines, a parenteral one and an oral one. It's important for our point of view to have these two ways, the alternative way. It depends on the context we would like to introduce the vaccine, the acceptability, the feasibility of this introduction of the vaccine.

If you look just measle vaccine, you have just one vaccine. There is some question now. It's very difficult to reply.

For the enteric vaccine, we have two

vaccines for typhoid fever. We will certainly have two vaccines, different vaccines for rotavirus. The current vaccine in development are given by oral route, but I can tell you that there is also a high interest for a parenteral one.

As a last priority, the definition of immunological correlate or immunological marker for protection, and that's very important to be conducted in challenge model in a closed ward (phonetic) and challenge model under own man (phonetic).

And just to add what I'm saying, you know that for typhoid fever these two different vaccines are stimulating two way of immunity, the mucosal immune system and the systemic system, and a lot of people think many, many years ago that why don't combine the two way to see if there is an announcement (phonetic) of your vaccine protection. This can be done in a closed ward in volunteers, not in the field.

Next one.

So why we are supporting this challenge model in volunteer? You know that it's more and more difficult to find a site for enteric vaccine for diarrheal disease. It's difficult to find a site for cholerized (phonetic), difficult to find a site for shigella. There is some site. We are looking for

some country, but it's more and more difficult.

From an ethical point of view, you know that the ethical committee in WHO will never accept to give a vaccine in a developing country without being evaluated, tested in industrialized country. That's an important point of view.

Again, the efficacy can be different in people from industrial country and people from developing country. We have saw that for choleratics (phonetic) on a concentration of ten to the eighth and ten to the ninth. The efficacy of the seroconversion was equivalent if you're increasing one log of your vaccine in developing country.

We also saw something with rotavirus vaccine, ten to the four, ten to the five.

Finally, and to conclude my presentation, it's important to have the ability to conduct study of pathogenesis and to better know what is the pathogenesis of typhoid fever and the immune response leading to this definition of immunological markers of protection. That's very important.

I thank you for your attention.

CHAIRPERSON FERRIERI: Thank you, Dr. Ivanoff.

Does the Committee have questions for any

of the sponsor presentations?

Well, we have several here. Dr. Hoffman, you had your hand up first.

DR. HOFFMAN: Actually I have a lot of questions.

CHAIRPERSON FERRIERI: Well, keep them as concise as possible, please.

DR. HOFFMAN: I actually would like to just make one comment regarding what Mike Levine stated about the severity of disease.

Even in countries where there is very severe disease, like in Indonesia, the tip of the iceberg phenomenon that he referred to, meaning that what you see in the hospital is only a very, very small percentage of what is in the field, is absolutely true, and I would present the fact that in a hospital, say, in Jakarta where ten to 20 percent of patients presented with severe typhoid fever in a field study of Ty21A vaccine with 21,000 participants and hundreds of cases, my recollection is there were no fatalities and rare, if any, cases of severe typhoid fever with rapid diagnosis and treatment.

My questions have to do with, one, the microbiological diagnosis, and I'm interested in why you have omitted days five and six from taking blood

cultures, and is that because you don't want to know because you wouldn't know what to do with the result on that day?

And second, why you're not including PCR. The old studies showed that at least, I guess, 70 -- only about 75 percent of the patients that have typhoid fever were blood cultures positive in, which goes with your criteria for treating without positivity. Having seen a PCR would perhaps complete that picture.

CHAIRPERSON FERRIERI: Dr. Tacket. Please use the microphone.

Your questions are quite relevant Dr. Hoffman, and they also address some of the FDA's questions. We can discuss them now as well as later.

Dr. Tacket.

DR. TACKET: It's a somewhat arbitrary decision, frankly, and it's not because we didn't know what to do with the results since we've decided that any positive blood culture would be treated. We would treat a blood culture at day five and six.

The volunteers are undergoing a number of invasive procedures, including blood drawing every single day, and the thought was that the high risk for positive blood cultures is early on, and after day

seven, and we thought we'd give them -- there is an opportunity for them to recover their veins on days five and six, but it's not a strong reason that we chose not to culture blood on those days.

We're also, frankly, at the upper limit of the guidelines for blood drawing, and so that if the consensus is that we need to survey their blood on days five and six, that's easily added to the protocol.

CHAIRPERSON FERRIERI: Dr. Edwards.

DR. TACKET: Actually, excuse me. Mike wanted to address the PCR issue.

CHAIRPERSON FERRIERI: Yes, please.

DR. LEVINE: Yeah, I believe in the back Dr. Jim Nataro from our group -- I think I see him back there.

We intend to do PCR, but we don't believe that at the moment the primers and the methodology is such that it's considered a standardized test. We hope after -- in the course of developing this model that we may be able to bring it to the point where we consider it standardized.

Jim, would you like to expand beyond that on the question?

DR. NATARO: Just simply to say that there

obviously are protocols in the literature. We plan to evaluate them, in fact, evaluate a couple of different protocols for --

CHAIRPERSON FERRIERI: Would you come to the floor, please?

DR. NATARO: -- preparation of --

CHAIRPERSON FERRIERI: Could you give your name and the microphone? This is all being taped, you know. Everything we say here is taped.

DR. NATARO: I'm sorry.

CHAIRPERSON FERRIERI: Even the hidden microphones, beware of.

DR. NATARO: Yeah, Jim Nataro, University of Maryland.

We are going to evaluate the published methods for template preparation and for PCR initially using flagella primers, and I think that, in fact, this is one of the important questions that we can answer, is how PCR correlates with blood culture results.

And in the initial studies we will use essentially the published protocols, and then if they turn out to perform less well than blood cultures, then we have the opportunity of changing those in future protocols.

CHAIRPERSON FERRIERI: Along these lines, do you have DNA probes to probe feces for the organism rather than routine cultures?

DR. NATARO: We certainly do. That's not a plan at this point, is to put that into the protocol, but it is something we can do in the future.

CHAIRPERSON FERRIERI: We'll move to other members of the Committee. Dr. Edwards.

DR. EDWARDS: The assessment of immune correlates and correlates of protection is not an easy task, and I would like perhaps to have you comment on what data was obtained by the studies early on in terms of certainly the antibody to H appeared to have some protective correlation. Could you discuss whether antibody in stool was assessed in the earlier studies?

And also could you hum a few bars of what you're going to do about CMI, please?

DR. LEVINE: This is Mike Levine responding to the first question.

When those studies were done in the 1960s, 1970s, in terms of local antibody, IGA, a secretory IGA had just been discovered. It was in its infancy, and there were not very serious attempts or very good attempts to look at local antibody.

The H antibody correlation was originally discovered by Bob Gilman and turned out in subsequent studies to be a consistent finding. Those serum H antibodies were consequent to individuals having been immunized with parenteral killed whole cell vaccine when they were in the military.

Dr. Marcello Stein will respond to the CMI questions.

DR. STEIN: Marcello Stein from the Center for Vaccine Development.

What we are planning to do with some of the neurological studies is related to a number of new discoveries over the past I would say three or four years that deal with the simulated immune responses that were not identified before in typhoid. Those involve the interferon production, response to specific antigens, and one that we are particularly interested in is the presence of cytotoxic to the lymphocytes that are Class 1 restricted and CDA mediated.

And it is possible being a pathogen that the presence of this CTL might be a correlate of protection. We just don't know, but this is the idea in which to study it.

One thing that I may add is that these

CTLs have (unintelligible) responses, have been observed not only in the strength that we have been discussing this morning, but also in unpublished data in a vaccine with Ty21A, meaning that at least in those volunteers that were tested, this particular response was present.

Now, in addition of this specific immune responses -- and by "specific" I mean specific as a response to in vitro stimulation with antigen -- we are going to try to identify which cell populations are involved by studying in detail the phenotype in the circulating lymphocytes and other lymphocyte populations, as well as if possible at all trying to identify specific immune responses by defined cell populations.

I don't know if that covers the whole scope of your question.

CHAIRPERSON FERRIERI: Dr. Greenberg is next, and then Dr. Adimora.

DR. GREENBERG: I wasn't clear -- Harry Greenberg -- I wasn't clear other than a new strain what the rationale was for adding another salmonella strain, considering you've had so much experience with the first one.

Also, why is it important to use a smaller

inoculum? What is going to be the advantage?

And then finally, what's the history of blood cultures in the early phase in the old studies? Were blood cultures positive when they were done on days one, two, three, and four in the original studies?

DR. LEVINE: Okay. I'll answer the first question. You answer the second question. I'll answer the third question, if I can remember them.

First question was why a new strain. Very reasonable question.

There was a time in the early 1970s, mid-1970s even, when salmonella typhi was published or reputed to be a clone, and it was thought that all over the world salmonella typhi was essentially the same.

Subsequently, with the development of more sophisticated molecular fingerprinting methods, it was found that, in particular, using a pulse field gel electrophoresis that one could detect differences amongst salmonella typhi clones.

The world's guru on doing this is Dr. Tiki Pang in Malaysia, and some of the things he has done has been to show, for example, that in a hyperendemic area in Papua, New Guinea, there is a particular

pattern that was associated with more severe disease in that local area.

So new questions have been raised amongst typhoidologists about whether there may be, indeed, subtle differences that have some public health implications amongst strains, and so we proposed the possibility of looking at a more modern salmonella typhi strain.

Dr. Tiki Pang was kind enough to do PFGE on both the Quailes and the ISP 1820 isolates. He has informed us that they are relatively similar, and that the two strains have similar or are very similar in pattern to strains he's found from Malaysia and Pakistan, for example.

So in summary, Harry, there's probably not a pressing reason, but there have been individuals who asked about the possibility of looking at a more modern strain of salmonella typhi.

Carol, do you want to answer the second question which was?

DR. GREENBERG: Why is it important to go from ten to the fifth to ten to the third presumably?

DR. TACKET: It's an attempt to make the model more physiologic or more like natural infection in that we think that probably three logs of organisms

or four logs contaminating a food item in a developing world might be more realistic than seven or nine logs that have been used in the past.

We have some experience with a shigella challenge model which had in previous years been -- the shigella inoculum had been administered with skim milk, and we found that when it was administered with sodium bicarbonate, the same number of organisms produced a higher attack rate, say, from 40 to 50 percent with skim milk to 70 to 80 percent with sodium bicarbonate, which seemed more like the natural infection.

CHAIRPERSON FERRIERI: We'll move on. Dr. Adimora.

DR. LEVINE: The last question I guess I should respond to.

CHAIRPERSON FERRIERI: Yes. Let's keep the answers as concise as possible then.

DR. LEVINE: Okay. There was very good experience, high yield, with collection of blood cultures within the first few days of onset of clinical illness. So we would expect a high yield, and bacteriologic methodologies today are better than they were.

DR. GREENBERG: Meaning the first four

days after inoculation?

DR. LEVINE: I'm sorry, and what was the question again? What we expect the yield?

Oh, very difficult to because this would be such a low, low level of vaccine. Even the secondary bacteremia is one to ten organisms per milliliter, and it's buffy coat associated. I think it's a long shot, Harry, but short of more invasive procedures, it's probably the only way we could get an answer.

CHAIRPERSON FERRIERI: Thank you.

Dr. Adimora.

DR. ADIMORA: I guess this question is probably for Dr. Tacket.

This relates to preexisting heart disease and the risk of endocarditis, also preexisting atherosclerotic disease.

I notice in your protocol you exclude people who have clinically significant heart disease, and am I correct in assuming that that includes mitral valve prolapse and bicuspid aortic valve, things that are pretty common in the population, but aren't necessarily that pathological?

It sounds as if they would be excluded if they were associated with the appropriate murmur, but

those things don't necessarily have that distinctive murmur.

DR. TACKET: If the volunteer has no symptoms related to heart disease, and if we don't hear the murmurs that I described in the exclusion criterion, there's a possibility that volunteers with those lesions that you just mentioned could be included. We're not planning to do screening echocardiograms, for example, to, you know, look at the anatomy of the valves.

The risk of an endovascular infection with salmonella typhi, unlike non-typhoidal salmonella, is very, very remote, especially in individuals who are treated after 12 hours of fever or as soon as possible after the bacteremia is documented.

So I think the risk is sufficiently low, and the possibility of there being enough turbulence around a mitral valve prolapse or a congenitally bicuspid valve is not likely to make doing echocardiograms, for example, something that would be reasonable.

CHAIRPERSON FERRIERI: Dr. Tacket, could you stay at the microphone and, Dr. Levine, could you join her because we'll save time in not having you both bounce up and down.

Dr. Hall next please.

DR. HALL: I have two questions. One is considering the definition of illness, which I like in the terms of its simplicity, but I wonder if it is a little bit too simply in terms of what about the timing. Are there any other ways to define this illness that could be -- it looks like from a number of other things.

What if it occurred on the first day? Are other types of cultures being taken? I mean, are there other signs or symptoms?

DR. TACKET: That's a great idea because we have trouble with concurrent infections in our vaccine studies, during flu season especially.

Part of the reason that we isolate the volunteers for 48 hours, in addition to continuing the consent process and the orientation is that they are, in fact, isolated from community viral pathogens which might infect concurrently with our challenge.

We haven't put into the protocol, for example, influenza cultures or antigen assays, and that's something we could consider. However, at the time that the fever occurs, we've been asked to treat with ciprofloxacin, and we probably, unless the consensus is to do otherwise, we wouldn't wait for an

influenza culture or even an influenza antigen determination.

So that's kind of a -- we might in retrospect be able to look back and say, oh, we treated an influenza when we were, in fact, seeing early typhoid. So that might be worthwhile.

DR. HALL: Well, there could certainly -- I mean if a person had had a lot of respiratory tract symptoms or signs, it would seem that you may be using ciprofloxacin for colds or something that would be the most common cause of a very short illness with fever.

The other question I had though is why in the third strain or the new strain -- let's see -- ISP 1820 there are eight volunteers, if this is enough, and why the choice of ten to the three was chosen. Is there a basis for this?

I mean my worry would be that with just only eight volunteers you might miss everything, that it may not be adequate, and yet it's one-third of this study at this point.

DR. TACKET: The original protocol, an early iteration had an additional eight volunteers who got the higher dose with ISP 1820, and that would be a little more symmetric and look a little more reasonable.

It really is, again, an arbitrary decision to limit the number of volunteers, the number of people at risk.

Our experience with CVD 906, which is a derivative of ISP 1820, was that, in fact, it was virulent. So we suspected that it may be more virulent than Quailes, and so we chose the lower strains with the eight volunteers, but it's certainly not totally logical that that should be done.

If I might take a moment to add something that I deleted from my presentation earlier, and it refers to your first question about what criteria might occur that lead to treatment other than fever, certainly there are a complex of symptoms with typhoid fever that might occur with a temperature below the 38.3 that we are expecting to see.

And we will add to the protocol that any of the following three -- any three of the following six symptoms occur that leads to the patient, the volunteer going to bed, in other words, loss of normal activity, we would treat them with ciprofloxacin, and that list of symptoms includes headache, malaise, anorexia, abdominal pain, nausea/vomiting, myalgias/arthralgias, or severe typhoid fever as defined in the protocol, which is a blood pressure

less than 85 or disorientation of lethargy.

CHAIRPERSON FERRIERI: Thank you.

We'll move on. There are several others with questions. Dr. Fierer is next. I'm cognizant of all the others of you who have had your hands up.

Please.

DR. FIERER: Josh Fierer.

I have several questions. It seems to me that what you want to do is produce infection in these people. That's the whole point, so that you could study vaccines. Have you considered using imiprazole rather than bicarbonate in this modern world?

The second is if you really are interested in detecting the early bacteremia, why don't you draw more blood? I mean five cc's is really a paltry blood culture, and that is, you know, in the first three or four days when you're doing blood cultures.

And then I'd like to know why you chose ampicillin rather than trimethaprim sulfa as your second line drug, although it could go either way.

And I would suggest also that you screen your volunteers for G6PD deficiency.

DR. TACKET: The imiprazole idea is really interesting. The reason that we used bicarbonate is because of the tremendous weight of previous

experience showing how effective the inoculum of the various enteric pathogens can be reduced by giving sodium bicarbonate.

It's well tolerated. Imiprazole is yet another drug, and in the experimental setting, we would be doing an experiment within the experiment, and I think we'd prefer to use sodium bicarbonate, which we're very comfortable with and know achieves the buffering that we want to achieve, but it's an interesting idea.

Certainly more blood for the blood cultures would increase the sensitivity of that microbiological study, and that's something that can be easily done, but that would mean we would sacrifice other volumes of blood for other studies because of the large amount of blood that's already being drawn. So we'd have to shift around some of our priorities.

We can certainly screen for G6PD -- oh, ampicillin versus trimethaprim sulfa. Amoxycillin, not ampicillin, but amoxycillin I'm sure is what you meant, is probably very similar in efficacy to trimethaprim sulfa, and Mike and I discussed it and looked at the literature, and we don't see a clear preference of one over the other, and if you're aware of such data, we'd be interested in seeing it, but

they seem very similar.

CHAIRPERSON FERRIERI: Thank you.

Dr. Eickhoff next.

DR. EICKHOFF: Two questions for Dr. Levine. One, regarding the strain selection, the challenge strain issue again, just to continue with one more question along that line, the, quote, more modern, close quote, strain ICP 1820 is already 15 years old. Is there any evidence that you're aware of that there has been any evolution of new clones since 1983?

DR. LEVINE: The new clones are clones that carry the HI ink plasmid alone or the most recent strains, which are the buzz of the international typhoid media in December in Indonesia, which were these strains that in addition carry this chromosomal gene mediated resistance to ciprofloxacin.

Aside from that plasmid and that chromosomal resistance, as far as we can tell the background host strains really do not differ. There's not been a change.

The increased severity, increased case fatality that has been reported in the past decade is entirely related to inappropriate and suboptimal therapy with antibiotics that work as far as we can

tell.

DR. EICKHOFF: And one further question. The cipro resistant strains that now you've identified in Southeast Asia, can we assume that this is, indeed, a class resistance, and that resistance is also present or will also be present to the newer floraquinolones, such as tropoflox and sparflox and so forth?

DR. LEVINE: Regrettably that's an affirmative.

DR. EICKHOFF: And one question for Dr. Tacket.

Regarding possible discharge of people who are still culture positive by stool culture or rectal swab, is one negative culture after several days of positives considered to be negative in your protocol? It's not the traditional negatives times three or something like that?

DR. TACKET: It actually would be two negative cultures. Well, it would be all of the stools that are passed in two days, which will be at least two rectal swabs if no stool is passed.

DR. EICKHOFF: So negative times two would be considered negative?

DR. TACKET: Right, but we would

anticipate that after 14 days of cipro that the cultures would have been negative for some time before that, stopped the cipro and continued culture for two more days.

DR. EICKHOFF: Is there any quantitative information available on excretion of S. typhi in people convalescing from the disease or chronic carriers?

DR. TACKET: Carriers there certainly is. It's up to ten to the ninth CFU per gram of stool. It can go from zero to two weeks later, ten to the ninth colony forming units per gram. So it can be very high.

DR. LEVINE: It's particularly high in chronic carriers if you get bile, but many of those individuals, depending upon their stool pattern, can actually have negative stool cultures, and it's known that in constipated chronic carriers, the normal flora are so suppressive that the salmonella typhi are suppressed below the point of detection with typical stool culture methodology, but you make them positive by purging, which is a classical method. So it's very variable.

DR. EICKHOFF: Thank you.

CHAIRPERSON FERRIERI: Dr. Estes.

I'm going to -- you had your hand up?

DR. ESTES: My questions have been asked.

CHAIRPERSON FERRIERI: Thank you.

Dr. Danis.

DR. DANIS: I wanted to ask about the sample size, and it has been asked about before, but there is one particular reason I raise it, and that is in the consent form, the stated purpose of the study is to determine which of two strains of salmonella typhi produce illness and to determine the number between the two.

It sounds like you're doing comparisons, and I'm wondering whether your sample size will allow you to get to the answer.

DR. TACKET: You're right. It's a small sample size for determining statistical significance to any one of a number of parameters, in addition to significant differences in attack rate between those two strains. The only differences that will be able to be detected will be very large differences. So that that's true.

In terms of informing the volunteers of the purpose, certainly that wording could be changed to say something less than that we're going to compare attack rates. It could be compare the illness that

occurs after or some other wording that might be less confusing.

DR. DANIS: Then I wanted to ask the issue of the need to give antibiotics if all cultures, blood and stool, are throughout the study negative.

DR. LEVINE: Throughout the study the answer is to maximize safety for the volunteers. There was that one individual amongst the almost 1,900 subjects in the old model who did not reach the criteria for treatable disease, and his acute episode was not treated, and at the time of a relapse developed gastrointestinal bleeding.

Gastrointestinal bleeding, in the view of most typhoidologists, is something that is rarely seen, rarely, rarely in the first week of illness, and therefore, if it was seen that individual, our assumption is that individual had low level infection in his peyer's patches, and therefore, we believe that everyone should be treated. We feel rather strongly about this.

DR. DANIS: I had some questions about the consent form. Should we leave that for later?

CHAIRPERSON FERRIERI: Yes, please.

Dr. Mintz briefly, and then Dr. Breiman and Snider, and then we'll do FDA presentation. We'll

have lots of time for discussion later.

I thought you had your hand up, Dr. Mintz.

DR. MINTZ: Yes.

DR. VANDERPOOL: I did, too.

DR. MINTZ: Dr. Mintz, CDC.

Two questions. In the literature lately there's been some discussion about cipro resistant typhoid fever and how perhaps the NCCLS breakpoints should be reconsidered, but in vitro and in vivo correlates of sensitivity may differ. In particular, some discussion of nalidixic acid resistance as a marker for clinical resistance or decreased sensitivity to cipro.

And I wondered if you would be able to provide data on nalidixic acid sensitivity of the two strains, the two challenge strains you propose. I would be surprised if they were resistant, but I would be reassured to know that they're not.

DR. LEVINE: Yeah. Jim, do you want to speak to that?

There are certainly cipro sensitive. Did we test nalidixic acid? Yes, and it's sensitive.

DR. MINTZ: Okay.

DR. LEVINE: For a decade ciprofloxacin sensitivity and response to therapy was not a problem.

This appearance in Southeast Asia is very recent.

DR. MINTZ: Yes. And to be sure I understand the protocol correctly, the stool cultures that will be done after 14 days of antibiotic therapy, will there be any delay between the last dose of ciprofloxacin and the first stool culture? How many hours do you expect to wait?

DR. TACKET: Not many. I know what your point is.

DR. MINTZ: Yes.

DR. TACKET: That there'd be an effect after the last dose of cipro. The last dose of cipro would be on day 14 after challenge, and then day 15 and day 16 stools will be collected for culture to document that they're still negative immediately after ending cipro.

DR. MINTZ: As you're probably aware, most state health departments, for example, before allowing a food handler to return to his profession would recommend that the negative cultures be documented at least 24 or 48 hours after the cessation of antibiotic therapy.

DR. TACKET: Right. I think that's an excellent point. We're going to be at day 32, and it's an arduous study, but certainly we could add

another 48 hours if that was felt to be important, and certainly that makes some logical sense.

CHAIRPERSON FERRIERI: Dr. Breiman.

DR. BREIMAN: I have a follow-up question about the issue of cipro resistance, and I think it's potentially terribly important if there's induction of resistance. Do you know what is know about prolonged therapy with a floraquinolone in actual reduction of resistance?

DR. LEVINE: In vivo with appropriate therapy in the experience in Latin America, in particular, there was a large experience gathered with both cipro and norfloxacin. There was experience in a number of other countries. This was not a problem.

The problem seems to have risen with the import into several countries in Southeast Asia of very poor quality cipro that is available in a promiscuous manner. Also nalidixic acid is available in those countries as anti-shigella therapy, and in that unusual environment, that's where the selection of these cipro resistant strains has appeared.

But for years it was not a problem with appropriate therapy, with good drug in the first years that cipro came out.

CHAIRPERSON FERRIERI: Dr. Snider.

DR. SNIDER: I had a question about the inclusion criteria or exclusion criteria. I just wondered since it appears that certain things, certain psychiatric illnesses like bipolar disorder, are grossly underdiagnosed and a person wouldn't necessarily have a history of hospitalization, if there would be some kind of screen for those disorders.

It seems to me this is a perfect study for a person with bipolar disorder who is in the manic phase, which I don't think you particularly want on your ward.

The other has to do with the monetary incentive, and I just wondered what your discussions might have been with your IRB since it's going to be a little over $2,000 just for the month which people would be hospitalized. It seems to me people from lower socioeconomic circumstances or jobless might find it particularly attractive. I just wondered if that had been discussed.

DR. TACKET: With regard to uncovering latent psychiatric illness, that's certainly a risk in studies like this, especially given the confinement, the locked door, the lack of contact with family and friends, and we're very concerned about that.

This would be, as I've said over and over, a 32-day study minimum, and we're thinking about extending it now with additional days waiting for stools to turn negative, and so forth.

We have a staff psychologist who will interview all of the volunteers, as he does for all of our in-patient studies, and we readily discharge volunteers on the basis of his recommendations.

Our nursing staff is also very good at identifying such potentially difficult patients, and they're discharged early on during that 48-hour period of acclimatization.

But you're right. That's a great concern. I think if we had a psychiatric problem, that we would immediately treat that volunteer, and after 14 days discharge him.

With regard to the monetary compensation, this is an issue that we grapple with frequently, and I would be very receptive to feedback about it. The volunteers are paid $75 a day in the hospital and $20 a day for a follow-up visit.

The aim is to compensate them as though this were a job and not to financially induce them or coerce them because it's such an exorbitant amount of money, and it's a thin line to walk.

One of the reasons that I think that we're probably not overpaying in terms of enticing them or coercing them because of the huge amount of money that they're being compensated is because during times such as the present, when the unemployment rate is very low, it is very difficult to recruit volunteers. So that our volunteers are people who have choices.

These are not people that have no other choice in their life. In fact, people that don't have choices I don't enroll. If you are so destitute and so illiterate, so unable to work at McDonald's, an entry level managerial job in a store, if you don't have choices in your life -- and this is not in the protocol, but this is our own philosophy -- then you are not encouraged to go through the consent process in one of our studies.

So the fact that we have so much difficulty during good economic times makes me think that we are competing with other jobs in our community, and in fact, if people have an opportunity for a long term job, they'll take that rather than a month on our ward at $75 a day.

But I think that's an excellent point, and we would very much welcome feedback about it.

DR. LEVINE: Dixie, may I add to that as

well?

We also look upon participation as a volunteer in vaccine evaluations as a civic duty in the same way that jury duty is a civic duty, and for jury duty there is reimbursement.

If you look at the level of reimbursement, this is not dissimilar from participating in jury duty in a federal jury in this area.

CHAIRPERSON FERRIERI: Thank you.

One last question will be from Dr. Vanderpool, and then we will do Dr. Pratt's presentation.

Please.

DR. VANDERPOOL: You mentioned, Dr. Tacket, that the subjects, quote, will undergo an extended consent process. I would like for you to give us information on what that process is and also to give us more specific information on your recruitment populations.

While I have a problem with the intelligibility of the consent form for ordinary people, and we can discuss that much later, and some information on the form, the real ethics of the issue comes down to what process is used. So I think we do need a grid on that, and I do think we need to discuss

considerably further the issue of the degree to which $2,500 for a month would or would not be coercive for certain -- a form of coercive or undue persuasion for some people. That's going to be a tough issue to resolve.

The final issue is just a matter to alert us to a concern I have, and that is whether these people are or are not volunteers will depend on the process in this consent form, and it loads that just a little bit to call them volunteers before we know the degree to which they are or are not volunteering.

That doesn't suggest that there's some coercion involved or any undue pressure on your part, but I think the reason why the phrase "the subjects of research" or something like that, "adult research subjects," is a little bit more of a neutral term until a volunteer proves itself to be an accurate description.

CHAIRPERSON FERRIERI: Can you address these relatively briefly, Dr. Tacket, or not?

DR. TACKET: I'll try. Perhaps the most important was the description of the consent process.

The volunteers are recruited primarily through advertisements in our local newspapers and by word of mouth among themselves. They call our

recruiting office and are asked one or two very brief questions: for example, have you been in the military, which would exclude them if they've had a typhoid vaccine, and are invited to a seminar which is given by one of our recruiting staff.

The seminar for this study will be an hour and a half to two hours in a classroom setting. Some volunteers will get up and leave during the seminar because it's overwhelming. It's too much.

The volunteers that choose to stay to hear all of the information are then given a copy of the consent form and sent home and told to contact us. We don't contact them. In fact, we don't even take down their names at that point. We just say, "If you think this is something that is of interest to you, go home and read the consent and discuss it with your family, and if you're interested call us back for yet another visit."

When they come back to the out-patient facility, if they continue to express interest, fine. If they have questions, we discuss those with them. If they would like to go ahead with the process, they have their screening blood work done, including things like HIV and other serologies which would absolutely eliminate them.

They undergo a one-on-one interview with the recruiter, during which time the recruiter asks specifically what is S. typhi, what are the symptoms that you're going to get, what is the likelihood that you could spread this to your family, what is the likelihood of your becoming -- what's a carrier, what does that mean, and there's a one-on-one process in which these issues are discussed, and the volunteer is sent home again.

If the volunteer chooses to continue in the process, then he or she calls back, and they make an appointment for a physical exam when they come back in and meet the physician investigators, undergo a physical exam, and have any screening blood that needs to be repeated, and further discussions and questions are asked in an informal way.

And then they're sent home again, and if they are still interested, they on their own initiative come on the day of admission to the hospital, and for 48 hours there is a period of further discussions and opportunity for questions before the challenge occurs.

During that 48 hours they have screening bloods completed, electrocardiograms, interviews with Dr. John Reed, our clinical psychologist. The

clinical nurses on the ward get to know the volunteers.

There's yet another orientation seminar by the physician investigator, which is, again, an hour or more process in which all of the risks and procedures are discussed pretty much in the consent form. The consent form is read aloud by the group and to the group in the presences of the physician investigator. Questions and answers are exchanged. The consent form is signed, and that becomes the consent form of record.

There's also a nursing orientation when procedures are described in detail. The gelatin string capsule is brought out and showed to everybody, for example. The volunteer gets to taste the food and sleep on the bed, and if it's acceptable to him and he has no further questions, then he's enrolled in the study for the challenge.

DR. LEVINE: Can I add two brief things?

CHAIRPERSON FERRIERI: Yes, please, Dr. Levin.

DR. LEVINE: Which I think are important. There are two aspects to informed consent. One is the consent; the other is informed.

With respect to informed, despite all of

these descriptions and reading a consent form and answering of questions, the volunteers must pass an examination, a written examination that covers the procedures, the rationale, the risks, the benefits. If they don't pass, no matter how motivated they are, they don't participate in the study because we don't have an evidence that, in fact, they understood.

In terms of the consent aspect, this is not different in any way from the studies that involve malaria challenge or cholera challenge or shigella challenge. It's the same process. It's not in any way an inducive (phonetic) or coercive environment.

Although $2,000 for 30 days' participation may seem like a large sum, think of it as compensation per day just like jury duty. There's a lot that they're giving by being enclosed on this ward during that time, and they deserve to receive some minimal compensation as they do for participating in a jury duty.

If it's a short jury, then it's a small compensation. If it's long, it adds up to more.

DR. VANDERPOOL: I guess in the State of Maryland you get considerably more for jury duty than the State of Texas.

(Laughter.)

DR. VANDERPOOL: But I understand. Your answers are very thoughtful, and thank you very much, and I'm impressed by the consent process. I think we'll need to revisit these issues as the day goes on.

CHAIRPERSON FERRIERI: As the morning goes on, Dr. Vanderpool.

(Laughter.)

CHAIRPERSON FERRIERI: We will only be discussing this issue this morning.

Since we're all very hot intellectually now, I want to continue the theme with Dr. Pratt's presentation. We will not have the break at the anticipated time. I don't want to interrupt the thought processes. Everyone is very sensitive to several of the issues that Dr. Pratt will be bringing up.

Dr. Pratt.

DR. PRATT: Dr. Tacket has described the protocol. I would like to briefly summarize and point out some protocol related issues before addressing issues relating generally to the challenge model. However, it seems that many of the issues have already been touched upon. So I'll go through this quickly.

The proposed study is a randomized dose ranging infectious challenge model to be conducted in

patient in an isolation facility. Subjects are to be healthy, male or female, 18 to 40 years old.

There are a number of exclusion criteria that Dr. Tacket has gone through. So I'll skip over those now.

The inocula have also been discussed, and the Quailes strain was used in the earlier challenge models and was isolated from the bile of a chronic carrier, while the ISP 1820 strain was isolated from the blood of an infected child.

The initial study is of 24 patients -- excuse me -- 24 subjects, and subjects will be challenged, monitored, and treated during, I guess, a 32-day in-patient observation period with three years of follow-up planned.

Patient monitoring will include body temperature measurements every six hours, blood cultures on the schedule already discussed, as well as stool cultures daily during in-patient and then after two, three, and six months.

And subjects will be treated with ciprofloxacin, 500 milligrams given orally twice a day for 14 days if temperature is greater than 38.3 degrees persisting for 12 hours or blood cultures positive on days seven through 14, and then all

subjects will be treated on day 14 if not already receiving antibiotics.

The primary endpoints are attack rate and typhoid fever or -- excuse me -- attack of typhoid fever or severe typhoid fever where typhoid fever is defined by temperature greater than 38.3 degrees Centigrade and severe typhoid fever is defined by any one of fever greater than 40 degrees Centigrade, systolic blood pressure less than 80 millimeters mercury or signs of lethargy or disorientation.

The specific aspects of the protocol to consider are that no blood cultures are to be obtained on days five and six, as Dr. Hoffman pointed out, and treatment decisions in the first week are based solely on fever, while in the second week either fever or bacteremia will be the basis of treatment.

The consequence of this plan is that bacteremia in the afebrile subject will not be detected on days five and six, and any subject who is not febrile before day seven will not be treated regardless of bacteremia or other symptomatology.

However, on hearing Dr. Tacket, I guess symptoms will be considered in a revised protocol.

Another aspect of the protocol to consider is that subjects who continue to excrete typhi in

their stools at the end of 32 days will be released into the community on out-patient antibiotics.

A final point regarding the protocol is that it appears that all 24 subjects may be enrolled and inoculated simultaneously. If adverse events occur more commonly or are greater severity than anticipated, it may not be possible to stop the study or modify the inoculum in order to prevent the entire cohort from exposure to an excessive risk.

In assessing risks of the proposed model, it may be useful to examine some of the safety findings from the previous challenge model. A number of non-IND human challenge studies involving 1,886 inmate volunteers were conducted over a 15-year period ending in 1974. Infectious doses ranged from ten to the third to ten to the ninth colony forming units of the Quailes strain.

A dose of ten to the fifth CFU was deemed most appropriate for trials of eight different candidate vaccines. The incubation period following inoculation to fever ranged from three to 52 days at ten to the fifth dose, and 25 percent were ill within the first week.

A summary report provided with sponsor's background package states that 235 of the 672 subjects

receiving ten to the fifth developed fever greater than 37.8, and that 200 met the treatment criteria of fever greater than 39.4.

Various treatment regimens were used, most containing chloramphenicol or ampicillin.

The summary report also states bacteremia was demonstrated in 75 percent of those with fever and relapse defined here is two consecutive febrile days following defervescence occurred in 35 percent of 124 volunteers receiving antibiotics.

Relapse occurred up to 63 days after the last febrile day.

It was reported in some early studies that nearly five percent of subjects had asymptomatic bacteremia occurring on day four or later, and five afebrile subjects were bacteremic for up to five days with symptoms of headache, cramps, or abdominal pain.

Liver transaminase levels were reported as elevated in about 50 percent of subjects by day seven of illness, and platelet counts were less than 100,000 in about 30 percent by day four of illness.

Vaccine recipients and controls were considered together in the reporting of disease as there was no discernable difference in their clinical course.

No deaths occurred. One subject developed a pleural effusion requiring thoracentesis. One subject developed gastrointestinal bleeding and a six percent fall in hematocrit. One subject had diarrhea requiring intravenous fluids both during the acute phase and during relapse, and latent diabetes became manifest in another, and one subject had a psychotic reaction on the fifth day of disease.

One subject became a long term carrier and was excreting salmonella typhi in stools for over two years. He subsequently underwent a curative cholecystectomy.

Safety data reporting from these studies is limited. Protocols and original data were not reviewed by FDA. Numerous individual laboratory assessments, including bilirubin were not provided in the summary report, and findings of jaundice and hepatosplenomegaly which were noted in a publication from some of the studies were not mentioned in the summary report.

The proposed study has inherent risks in the sense that subjects will become febrile and bacteremic. One may reasonably assume that subjects can give informed consent to the expectation of a simple febrile illness. It is more difficult to

assess the risks of serious complications in the proposed challenge model.

This table lists some of the important complications of untreated or inadequately treated typhoid fever with estimated time of onset and approximately incidence, if available. These figures are compiled mainly from various textbook references, including Dr. Hoffman's nice chapter in Hunter's Tropical Medicine.

The table illustrates that virtually every organ system can be affected by salmonella typhi, and the fact that not 100 percent of patients with typhoid fever actually has fever reflects differing definitions of typhoid disease.

Some degree of intestinal hemorrhage is fairly common, and both hemorrhage and intestinal perforation can occur in the first week of disease, though typically they occur later.

Cardiac complications are fairly rare, though EKG changes are more common.

Meningitis occurs almost exclusively in neonates and small children.

Osteomyelitis and septic arthritis are late complications, and the incidence figures were not found. They are probably uncommon.

Reactive arthritis can occur relatively early in disease.

Neuropsychiatric disorders are well described and fairly common in some reports.

Urinary excretion during infection is common, occurring in up to 25 percent at some point during the disease.

And some degree of hepatitis is common, as seen in the previous challenge studies, and it can occur early in disease.

Clinical jaundice occurs in about two percent.

Antibiotics have had little effect on rates of relapse in the chronic carrier state prior to the use of quinolone antibiotics, which I'll be discussing in a moment. Historically chronic carriage occurred in about one to five percent of cases.

Today death due to typhoid fever in the U.S. is very uncommon. However, in areas where death is more common, bowel perforation is a frequent contributing cause of death.

It seems likely that early antibiotic treatment following onset of fever would prevent most serious complications. However, it may be important to note that some complications, such as bowel

perforation, gastrointestinal hemorrhage, hepatitis, thrombocytopenia, a psychotic reactions can occur during the first week of disease.

It's also not clear what impact antibiotics will have on reactive arthritis, which can occur fairly early in the disease process, and it should, again, be pointed out in this context that the protocol does not provide for treatment of bacteremia without fever in the first seven days after challenge.

Some predisposing conditions for the various complications of typhoid fever are shown. General risk factors include achlorhydria, bowel disease, and immunosuppression. Increased risk of chronic care has been associated with prior antibiotic use, particularly of chloramphenicol, and this may not be the case with ciprofloxacin.

Gall stones and risk factors for gall stones, including age greater than 40 and female gender, are also risk factors for chronic carriage, and chronic bacteriuria has been associated with nephrolithiasis and prostatic hypertrophine.

Salmonella have an affinity for endothelial tissue. Atherosclerosis and aortic aneurysms are risk factors for endarteritis, while the history of rheumatic heart disease and previous

endocarditis are risk factors for typhoid endocarditis.

Osteomyelitis and arthritis and spleen abscess share common risk factors of sickle cell and other hemoglobinopathies, systemic lupus and immunosuppression. As mentioned meningitis is almost exclusively a neonatal and childhood complication.

Risk factors of complications will likely be reduced by implementation of entry criteria intended to exclude volunteers with known risk factors. The sponsors believe the complications of typhoid fever will not occur in the subjects who meet entry criteria because they will be treated with ciprofloxacin after onset of fever.

Ciprofloxacin was first approved in the U.S. in 1987. The specific indication for the treatment of typhoid fever, enteric fever called by salmonella typhi, was approved in 1993. The package insert or drug label for ciprofloxacin also contains a note that the efficacy of ciprofloxacin in the eradication of the chronic carrier state has not been demonstrated.

However, accumulating data suggests that ciprofloxacin is probably the superior antibiotic of choice for the treatment of disease and the carrier

state in most adults with sensitive strains.

FDA approval for the treatment of typhoid fever indication was based on two well controlled studies of 37 and 104 adult patients. In the smaller study patients received ciprofloxacin, 750 milligrams twice daily for 14 days. Early bacteremic relapse occurred in two of 12, or 17 percent, of evaluable patients. Failure to eradicate typhi from stools occurred in one of 18, or 5.6 percent, of evaluable patients. There was no long term follow-up in this study.

In the larger study conducted at two sites, patients received 500 milligrams twice daily for ten days. Bacteriologic eradication was documented in 78 of 79, or roughly 99 percent, of the evaluable patients receiving ciprofloxacin. Mean duration of follow-up in this study was 63 days.

However, three nonevaluable patients withdrew from the ciprofloxacin arm for reasons of rash, intestinal perforation, and abdominal tenderness becoming worse on ciprofloxacin. Therefore, the clinical cure rate did not match the bacteriologic cure rate due to dropouts and adverse events.

Common adverse events listed in the package insert for ciprofloxacin and considered to be

drug related include nausea, diarrhea, vomiting, abdominal pain, and headache. Ciprofloxacin was discontinued due to adverse events in 3.5 percent of patients in clinical studies leading to the drug approval.

The package insert also contains warnings regarding central nervous stimulation, convulsions, toxic psychoses, fatal interactions with theophylline. It also raises caffeine levels considerably, and pseudomembranous colitis and anaphylaxis.

Among post market reports of adverse events reported through the Med Watch system, rash and pleuritis were most common. Creatinine elevations, convulsions, and kidney failure were among the most common reported adverse events. There have been 143 episodes of anaphylaxis also reported. The incidence rates for these post marketing reports cannot be determined.

Data cited by the sponsor as demonstration that ciprofloxacin is highly effective in the treatment of the carrier state shows that 11 of 12, or 92 percent, were treated successfully with 750 milligrams twice daily for 28 days.

The one treatment failure occurred in a 24 year old asymptomatic woman who was said to be

compliant with the medication. The isolated strain was sensitive to ciprofloxacin, and blood antibiotic levels were within the therapeutic range. Although not identified as having biliary disease prior to treatment, the woman underwent cholecystectomy two years after completing therapy and was found to have gall stones at that time.

This case raises concerns that potential carriers may not be identified and excluded from study participation, and that successful treatment of the carrier state with ciprofloxacin is not universal. I think that that woman did not have an ultrasound exam prior to treatment though.

Another woman was found to be excreting typhi during follow-up. This strain was of a different phage type, and it was concluded that this represented a reinfection.

Adverse events among the remaining subjects included one who stopped treatment due to an urticarial reaction, one who stopped therapy for falling hemoglobin thought to be drug related. Other adverse reactions included decreases in hemoglobin in two additional patients, gastrointestinal bleeding with falling hemoglobin, and one patient who developed candidal vaginitis while on therapy.

In assessing risks of secondary cases in the community, it is worth repeating that eradication of typhi by ciprofloxacin may not be 100 percent. According to protocol, subjects with positive stool cultures after an in-patient course of ciprofloxacin would be discharged from the isolation facility on out-patient antibiotic therapy.

In the event that a subject continues to excrete salmonella typhi after discharge, the sponsors assess the risk to the community as small due to the low infectivity of salmonella typhi without buffer and the level of hygiene and sanitation in the U.S.

In this context it should be noted that infants may be infected at lower inocula due to their higher gastric pH, and that infants are at increased risk of meningitis if infected, and as small children, the elderly, individuals with HIV infection, and other immunocompromised people are at increased risk of serious disease.

And as a further note, ciprofloxacin is not indicated for use in children.

Regarding the consent form, this has been touched on already. The consent form clearly states that no benefit to the subject will incur as a result of study participation. Subjects may derive some

satisfaction from contributing to medical research and the development of a new typhoid vaccine, and the subjects will receive monetary compensation.

The risk section of the consent form mentions the chronic carrier state, intestinal perforation and intestinal bleeding as possible complications. Other complications are referred to generally as follows. Although other complications involving almost every organ of the body have been described, these occur rarely in natural disease and almost exclusively in persons who have been ill for a long time without antibiotic treatment. Death as a possible complication, it was not mentioned.

A stated primary objective of the challenge model is to identify promising vaccine candidates for further evaluation in large scale field trials. Traditional strategies to identify promising candidate vaccines rely upon safety and immunogenicity studies in animals and humans. Vaccine candidates which induce high titered antibody to a pathogen specific antigen might be considered worthy of further development.

If it is known that antibodies to a particular antigen are associated with protection from disease, immunogenicity studies can be highly

predictive of protective efficacy.

Three vaccines are currently licensed in the U.S. for the prevention of typhoid fever. Typhim Vi, manufactured by Pasteur Milieux, is an intramuscularly administered vaccine which was licensed in 1994. It's composed of the Vi capsular polysaccharide from the Ty2 strain. It's indicated for children two years of age and older.

Efficacy in field trials has ranged from 55 to about 74 percent. Current recommendations for boosters are on a two-year schedule.

Vivotif Berna, manufactured by Swiss Serum and Vaccine Institute, is a live oral attenuated vaccine, strain Ty21A. It was licensed in 1989. Enteric coated capsules are ingested on four days over a one-week span. It's indicated in adults and children age six and older, and protective efficacy in field trials has ranged from 42 to 67 percent, with boosters recommended every five years at this time.

Typhoid vaccine manufactured by Wyeth-Ayerst is administered subcutaneously. It's a heat and phenol inactivated vaccine of the Ty2 strain. Two doses four weeks apart make up the primary series. It's indicated for the immunization of typhoid fever. The manufacturer does not recommend dosing below six

months of age.

Based on data from field studies, it is estimated to have -- excuse me. Based on field studies of similar preparations, it's estimated to have an efficacy of 50 to 70 percent or greater, with boosters recommended every three years.

Local and systemic reactions are common with this vaccine.

Protective efficacy for each licensed vaccine was demonstrated by testing in highly endemic areas.

Another candidate typhoid vaccine is currently in Phase 3 efficacy studies in an endemic area.

The licensed whole cell typhoid vaccine and the Vi capsular polysaccharide vaccine and the candidate vaccine now in Phase 3 trials have been developed without testing in a human challenge model.

Ty21A was administered to inmate volunteers in challenge studies pre-licensure, and these studies may have facilitated development of the oral vaccine.

The parameters of the immune response which correlate with protection provided by Ty21A are not know. It may also be difficult to identify

correlates of protection for other candidate vaccines, a challenge model which might facilitate development of some of these vaccine candidates.

Another stated primary objective of the challenge study is to demonstrate whether candidate vaccines can protect immunologically naive subjects, such as travelers.

In the United States, about three to 400 cases of typhoid fever occur each year, and about 70 percent of these are acquired while traveling internationally. ACIP recommends typhoid vaccination prior to travel to endemic areas, with preference stated for the Ty21A and the Vi capsular polysaccharide vaccines due to their less reactogenicity than the whole cell preparation.

In a recent survey of U.S. microbiology laboratories conducted by CDC, at CDC by Dr. Mintz and colleagues to assess the prevalence of antibiotic resistance and other risk factors of infection, it was found that about 80 percent of 200 isolates came from travelers, and that three percent of these isolates came from travelers who had received the oral typhoid vaccine. None had reported receiving the Vi capsular polysaccharide or whole cell vaccine.

These data are perhaps more informative

about the lack of utilization of licensed vaccines than about their protective efficacy among travelers since the number receiving vaccine who did not become ill is not known.

Nevertheless, it appears that one could conclude from these data, though it was not a conclusion of the authors, that if a more effective vaccine were to replace those in current use by travelers who elect to be vaccinated, an additional six to 12 cases of typhoid fever per year in the U.S. might be prevented.

Whether the benefit of a better vaccine for travelers alone offsets risks faced by study participants in the challenge studies deserves careful consideration.

Dr. Levine had mentioned a number of human challenge studies which have been conducted under the IND. Some of these are for pathogens restricted to mucosal surfaces or result in self-limiting disease. Models that we've had experience with in vaccine are the cholera, shigella, and ETEC models. A number of the models that he presented were therapeutic models.

Typhoid infections differ importantly from some of these other challenge models by their invasiveness and potential for multiple organ

involvement. A notable human challenge model of serious infection with systemic involvement is the malarial challenge model. Aside from the obvious difference that one is a gram negative bacteria and the other is a protozoa, the contexts differ in that three vaccines of demonstrated efficacy are licensed for typhoid fever while no vaccine has been licensed or shown to be effective for malaria.

But regardless of the rational for other human challenge models, the proposed salmonella typhi challenge model deserves critical assessment based on its own merits.

Then a final point regarding the scope of studies using the model. The initial study proposes to inoculate 24 subjects. Should the model proceed, a substantially larger number of subjects would likely be challenged depending on the number of vaccine candidates to be tested, the number of time points following vaccination that subjects will be challenged so that duration of protection might be assessed, and the number and kinds of investigations into the pathogenesis of salmonella typhi infections the investigators may wish to undertake.

So some summary points to consider in your deliberations are:

Number one, the probability of serious typhoid disease amongst study participants in the study is probably low.

Gastrointestinal hemorrhage and bowel perforation are among some of the complications of typhoid fever which can occur fairly early in the disease process.

Number three, relapse in short term or chronic carriage after ciprofloxacin treatment occur less frequently than with other antibiotics, but eradication of salmonella typhi is not universal.

Ciprofloxacin therapy is associated with its own risks which can be serious.

And risks for secondary cases within the community should also be considered. The community may be placed at risk without their knowledge or consent.

Subjects will derive no medical benefit from participation. Vaccine candidates for typhoid fever have been identified and developed in the past without invoking human challenge studies.

Licensure of three typhoid vaccines approved for use in the U.S. has been based on results of well controlled field efficacy studies.

And lastly, vaccination for typhoid fever

is currently recommended by ACIP for travelers to endemic areas, and most cases of typhoid fever among U.S. travelers to endemic areas at least in 1996 occurred in people who did not receive a licensed vaccine.

At this time I would like to again present the questions posed to the Committee.

Number one, does information likely to be gained from this model justify the risks to subjects and the community?

Number two, if yes, please discuss any recommendations for modifying the study protocol and consent form. Specifically, please comment on the criteria proposed for initiating antibiotic treatment, that is, temperature greater than 38.3 degrees Centigrade for 12 hours or bacteremia on days seven through 14.

(b) Please comment on whether blood cultures should be obtained on days five and six.

(c) Please comment on the proposal for out-patient antibiotic treatment of subjects who continued to have positive stool cultures after an initial in-patient course.

(d) Are there other changes to the protocol entry criteria, monitoring procedures, or

study design which you would suggest, for example, staging of enrollment, stopping rules, monitoring of in-patient and out-patient contacts.

And lastly, does the consent adequately address the potential risks to volunteers?

And lastly, I would like to acknowledge the other members of the review team: Lydia Falk, Dennis Kopecko, and Carolyn Deal.

Thank you for your attention. We look forward to your discussions.

CHAIRPERSON FERRIERI: Thank you very much, Dr. Pratt.

I think we'll take a break now while you're thinking about these questions. Ten minutes, please.

(Whereupon, the foregoing matter went off the record at 10:29 a.m. and went back on the record at 10:45 a.m.)

CHAIRPERSON FERRIERI: Ms. Cherry has an announcement first.

MS. CHERRY: Before all of you sit down, let me say that I realize that this room does pose some challenges. So please feel free to move around so that you can see or hear.

The other things is that we have an open

public hearing scheduled for this morning. We went right into the program, but at this time if there is anyone in the audience who wishes to make a public statement, let's do it now.

Is there anyone that would like to make a statement for the record?

(No response.)

MS. CHERRY: If not, then I'll return control to Dr. Ferrieri.

CHAIRPERSON FERRIERI: Thank you, Nancy.

I want to thank our sound engineer for helping us at the podium. Stimulated by Dr. Levine booming voice, we decided we had a little problem there, and we now have sort of a muffler to deflect the wind that we're blowing into the microphone there.

(Laughter.)

CHAIRPERSON FERRIERI: Apologies if it annoyed anyone earlier in the morning.

Well, we've heard a great deal of challenging information presented by the sponsors, as well as challenging questions from FDA. I think we should note before we get into any detail that we have to deal with question one from Dr. Pratt. If the answer is no, that the information is not likely to justify the risk, then you have a very prolonged

lunch.

However, if we vote yes, then we will proceed with the other questions, and so I'd like to open up discussion at the table. Some of you may not feel that you've had adequate opportunity earlier this morning to voice your opinions or to ask any pertinent questions, but I'd repose the question we would address this part of the meeting to: does the information likely to be gained from the challenge model justify the risks to subjects and the community?

So if there are questions raised that's pertinent to this rather than other details that are later.

Dr. Edwards, Dr. Hall. Dr. Clements-Mann, did you have your hand up also?

Dr. Edwards first.

DR. EDWARDS: I wonder if it would be possible to do this study in several steps to give 24 people typhoid and if they all get sick may be somewhat problematic, and also looking at the data from previous studies, suggesting that ten to the third was not infectious, certainly the addition of bicarbonate might make it infectious.

I feel that perhaps I might be a little more comfortable if we would start with two or four

subjects rather than 24. Is that logistically possible or is that something that could be done?

CHAIRPERSON FERRIERI: Dr. Levine, would you like to address that? And then maybe Dr. Pratt may have an opinion on this.

DR. LEVINE: That is a possibility, of course. The reason that Dr. Tacket and I had come up with this particular design was in an attempt to maximize the information gained with a very long, complicated trial that will tie up the research isolation ward and the nurses for a very long time.

We are comfortable with the expected clinical response to these dosages to be administered with bicarb., the expectation. The reason we're comfortable is it can't be different in attack rate from what was seen with seven or nine logs without a buffer, where there was a 95 percent attack rate.

One clear message that came from Dick Hornick's New England Journal review was that once clinical illness occurred, it was the same range and severity irrespective of the dose, and the very nice review by Judith Glenn a few years ago in Epidemiology Infection looking at attack rates and severity from water borne outbreaks that showed the same thing, that where water borne and food borne outbreaks -- food

borne outbreaks had shorter incubation, presumably larger inoculum. The clinical severity was the same irrespective of outbreak.

So it would be possible to do that, but we don't think that that's really necessary; that we could, with the expenditure of time and resources actually gain much more information within a single trial.

CHAIRPERSON FERRIERI: Dr. Hall.

DR. HALL: I just would like to sort of for that first question be very much in favor of this study in terms of not looking at it as just the idea of perhaps preventing a few infections in the United States, but what we may learn from this in terms of the pathogenesis of the disease, that certainly this disease is beyond our borders here, and that although it is a small study and I have concerns about how much information one can get initially, I think there are very important pieces of information that do not require statistical significance.

For instance, are they infected? When are they infected? At what doses?

And so that a limited study initially I think is important, and whether based on that to go on, but overall I think the broad potential of this

study is greater than perhaps we have noted so far.

CHAIRPERSON FERRIERI: Thank you.

Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes. I think the other aspect of this, I mean, it's clearly my impression that the initial challenge study that was done that demonstrated the protective effect of the Ty21A was really turning out to be pivotal in moving that vaccine forward because there had been another vaccine that had been shown to be ineffective, and the whole concept of the live attenuated vaccine was almost abandoned at that point.

So that it actually did provide a proof of principle, albeit without correlates of immunity, that made it possible to move into the field ultimately with the vaccine.

Now, the other thing that I don't think was mentioned as much today is that every time one changed the vaccine formulation or number of doses or age group or geographic area, one had to repeat the field trials, and so that if ultimately there is an ability to demonstrate in a very small number of people proof of principle that eventually could be correlated with the trials in the field, it could really make a big difference in terms of selecting

from these potential candidates.

And then one other point I'd like to make is that it would be very helpful for the use of salmonella vectors to express other antigens to be able to get that information of what the value of the vector is in these kinds of studies.

And then finally, I would just like to say that the University of Maryland group has a tremendous amount of experience, long term experience among the investigators in conducting these trials in the highest -- with the highest ethical and clinical standards, and that if anyone can do it, they can.

CHAIRPERSON FERRIERI: Thanks, Mary Lou.

Other points relative to information gained versus potential risk? Dr. Hoffman.

DR. HOFFMAN: Two points. One is it was mentioned that there's 500,000 deaths a year in the world due to typhoid fever, an estimate. Those deaths occur mainly in late adolescents and early adults, young adults. So the impact on society of those deaths in the developing world is enormous. They're the people that the society has invested the most in and has gotten the least from.

So that it's quite different in terms of that, and so I think that justifies a new type of

vaccine that could be used for them.

The second, I'd like to point out that sort of complementary to what Mary Lou said, with the Vi vaccine developed by John Robbins, that vaccine was developed in the late 1970s. There was no challenge model. The first study was done -- field study was not done until the mid-'80s in Nepal and then in South Africa, and it's quite likely that had there been a challenge model, that vaccine would have been tested much more rapidly here, moved to the field, perhaps studied more extensively in the field than it has been, and even perhaps compared to the Ty21A or even combined with it, and we would have seen a much more rapid movement into the licensure phase if we had had a challenge model.

CHAIRPERSON FERRIERI: Thank you.

Dr. Snider.

DR. SNIDER: I would like to just clarify a couple of points, which I think the previous comments have gotten to, but I think that we should understand it explicitly.

There have been some comments about the fact that it's difficult to find populations to do a trial in, and that seems to have been given as a rationale for doing this particular model or at least

I'll say it left me with that impression.

And I don't think that is really relevant. It seems to me that if there are not populations which we can do trials, then doing this challenge model clearly shouldn't be done because I don't think we're going to license vaccine based on this challenge model.

I mean, you know, the ability to generalize from these populations that we're going to study here to other populations is one issue. The sample sizes are other issues, et cetera.

So it clearly is a model, and it's a way of screening, as I understand it, candidate vaccines for use in field trials.

The other point that was made that I would take issue with is that you can't do studies in developing countries unless you do them in the United States. I think that is certainly not a principle which the CDC Ethics Subcommittee, which includes the authors of the most popular current bioethics text, would agree with.

I mean I'm not saying we shouldn't participate by any means, and participate by means of participating by having U.S. subjects participate in this challenge model, but just as a general principle,

again, I don't think it's necessarily relevant. There are plenty of issues and problems that occur only in developing countries for which studies in the United States would be irrelevant or unnecessary to do.

So that having been said, I think with regard to a more direct response to the question, I think I would generally lean toward saying that, yes, the information likely to be gained from the challenge model would justify it, with some of the modifications that have been suggested, and we'll get into that.

So it's a tentative yes, pending responses to some of the questions we had of the investigators about how they screen and some of the modifications in the protocol that are being considered.

CHAIRPERSON FERRIERI: Thank you.

Yes, Dr. Breiman.

DR. BREIMAN: Sort of along that line, I think when considering the risks to the subjects and the community, it seems like a couple of ideas came up that might be relevant to try to minimize those risks. I guess the thing that I've been most worried about, even though we've been reassured, is the idea that early in the study people will have at least a likelihood of primary bacteremia which may seed certain organs, and although there is a screening

ultrasound done for the gall bladder, I wonder whether there also should be other screens done, particular echocardiogram, to look at the possibility of occult valvular problem that might be seeded.

The other thing that occurred to me that I guess maybe may not be all that relevant, but given at least in the natural history of typhoid fever that a substantial proportion of patients with fever have intestinal perforation or hemorrhage is screening, at least guaiac screening of stools, early on, a reasonable precaution to take to actually detect that should it be, you know, beginning to occur.

CHAIRPERSON FERRIERI: Thanks, Dr. Breiman. We'll bring up those points later depending on the outcome of the vote on this.

Dr. Vanderpool, did you have your hand up?

DR. VANDERPOOL: Yes. I appreciate what Dr. Clements-Mann said about the advantages of having a challenge model. I would like for someone or ones to address the question, okay, if this were not approved, where would we be; if it is approved, where will we be going in terms of new experimentation, so that we'll have a better feel for the benefits versus the harms of approving or not approving.

CHAIRPERSON FERRIERI: Thanks, Dr.

Vanderpool.

I'd like to call on Dr. Pratt first to have an opportunity to address that question. Please use the microphone.

DR. PRATT: As was mentioned, there is a Phase 3 trial of a candidate vaccine ongoing now in an endemic area.

DR. VANDERPOOL: But could you go beyond that? I mean with this model how quickly would that vaccine be tested and possibly moved to field? How many other vaccine teams are willing, are ready to move other typhoid vaccinations to the research agenda, and so on?

Are we really opening a significant door by approving this or are we opening the door just a little wider than it was?

CHAIRPERSON FERRIERI: Is it a moot point or not, Dr. Pratt, is really the question, whether this proceeds or not? Is it relevant to what is ongoing? Will the absence of it inhibit?

DR. PRATT: Well, I can't comment about any vaccines that Dr. Levine's group may be hoping to use in the challenge model, but as I was saying, there is at least one other candidate vaccine in Phase 3 efficacy trials in an endemic area at this time.

CHAIRPERSON FERRIERI: Thank you.

Is there anyone else at FDA who wishes to comment on this point?

Dr. Mittoon.

DR. MITTOON: Dr. Mittoon, FDA.

I think it's somewhat difficult to comment further other than to reiterate what Dr. Pratt stated, namely, that there is a study currently ongoing in a Phase 3 efficacy study. I think we would have to look perhaps to Dr. Levine and Dr. Ivanoff because there were concerns stated that perhaps it would facilitate getting other vaccines into Phase 3 studies if one had this kind of model.

And so I would really ask for them perhaps to address this.

CHAIRPERSON FERRIERI: Thanks, Karen.

Before we do, Dr. Clements-Mann, did you want to follow up or add to this point in the discussion now?

DR. CLEMENTS-MANN: I think Dr. Levine should answer that, but it would seem to me that every case would be taken on its own merit; that, you know, if there was a proposal there would have to be justification for testing a vaccine against challenge; and that that would require another FDA review and

also extensive IRB review.

CHAIRPERSON FERRIERI: Dr. Hoffman, and then we'll have Dr. Levine respond.

DR. HOFFMAN: To me the answer to your question is actually very simple. A field trial cost a million, two million, three million dollars. If I have a vaccine or if Dr. Levine has a vaccine which he shows has 80 percent efficacy in a challenge, then going to get the funding, whether it's from NIH, WHO, or involving an industrial partner for the development of this is quite a different story than going to somebody and saying, "Look. I've got something that looks pretty good. It's immunogenic. It makes" -- Dr. Stein showed it makes CTL, "but we really don't know if it works, and we'd like you to invest a few million dollars in this and take it out to the field and develop."

There's plenty of typhoid fever out there, but putting together the team to develop a field site to actually study it when you don't have any efficacy data is very difficult.

So from my point of view it makes perfect sense. If you didn't have this, you could still do it, but you will never test as many things as efficiently as you would if you did have it.

CHAIRPERSON FERRIERI: Thank you.

Dr. Levine, would you like to answer, please?

DR. LEVINE: There are a number of vaccine candidates that we hope will offer the same safety profile, but much greater immunogenicity and protective efficacy than the currently licensed vaccines.

It is true that there is one Vi conjugate vaccine that's in a Phase 3 trial. That's a somewhat unusual circumstance that led to that trial in that particular country. There was a quid pro quo that would not be available to other vaccines to gain access to that particular country's field area. That's one point.

The second point is that to the best of my knowledge, that conjugate vaccine is not associated with a manufacturer. There is a manufacturer that also makes a Vi conjugate vaccine. That manufacturer is, indeed, interested in having access to a volunteer model.

Then there are the live vaccine candidates. We have a candidate that is in Phase 2 trials. It is appearing very well tolerated. The study is blind. We hope that if there are good immune

response and acceptable clinical profile, that that could be evaluated in a volunteer model which would then, indeed, in that circumstance expedite the possible field trial evaluation of that vaccine.

Then there are two other candidates that also come from academia. One of those candidates, or perhaps both, are associated with small biotech company associations, but not with large vaccine manufacturers.

Exactly as Steve Hoffman mentioned, if there were efficacy data, this would provide compelling acceleration to the possibility that those vaccine candidates would also be able to hook up with a vaccine manufacturer and to move expeditiously to field trial.

A week before last in Atlanta, there was an emerging infections meeting, an international meeting. One of the themes of that meeting was that we are a global village; that with emerging and reemerging infections, we have to work together. I think this is an example where there's much to be gained from working together.

Dr. Ivanoff would like to respond also.

DR. IVANOFF: Yes, I would like to come back to this very important point mentioned by Dr.

Snider. I would say that today it's impossible to get the WHO ethical clearance without a foreign antigen which has not been tested or evaluated in an industrialized country. I mean either in the U.S. or in Sweden or in England and U.K.

I can provide you with several examples. We are now trying to find a site for shigella vaccine. We are founding (phonetic) some sites, but the first question is that this vaccine is safe in human beings. Yes, okay. Is this vaccine protective? In other words, are you wasting your time or not?

If you have not this reply, you can stop your study. It's finished concerning the WHO ethical committee. Okay?

We have another example for the meninge (phonetic) conjugate vaccine for to put this vaccine in Niger, we have been obliged to show that it was safe and immunogenic, of course. We cannot say effective because we have not the possibility to prove that.

In industrialized country, it has been done in U.S., as you know, and in U.K. also. In other words, it's impossible to go through the WHO ethical committee without having this kind of data. That's an important point I would like to outline.

CHAIRPERSON FERRIERI: Thank you, Dr. Ivanoff.

Dr. Mittoon?

DR. MITTOON: I'd like to make a distinction between having a vaccine candidate initially be tested in an industrialized country versus actually asking that this vaccine be validated or somehow tested in a challenge model. I think there is a distinction.

CHAIRPERSON FERRIERI: Thank you for reminding us.

Other points from the Committee prior to our taking a vote on this question? Does everyone feel they have enough information to vote on this?

It appears so. Dr. Danis.

DR. DANIS: I just want to raise the point that the question as stated involves balancing the benefits and the risks. It seems like there is really a pressing need for vaccine, and this challenge model may be very useful in assisting that.

In terms of the risks, I think the team proposing doing the research has been extremely responsible. They are somewhat limited in dealing with a piece of the risk that I think we need to address, and that is that as it's stated, any medical

problems that fall out from participating will not be reimbursed in the consent form unless these people bring a claim forward, and I think that we need to, if we're going to use this kind of model for developing useful models for general societal well-being, we need to find a way to acknowledge to these folks and provide back-up so that they will get care that is not simply the product of negligence.

They're going to get excellent observation, but we need to find mechanisms for dealing with that. I think this is a problem that needs to be weighed in the balance.

CHAIRPERSON FERRIERI: This is very standard in consent forms, as you appreciate.

Dr. Vanderpool.

DR. VANDERPOOL: I think we all understand in keeping with this suggestion and one earlier that when we vote yes or no on this, if we vote yes, what we're saying is in light of the fixability of the points that were made earlier and the consent form.

So we're not just approving the entire thing with this vote. The question is upon being fixable, is this something we think should go forward.

CHAIRPERSON FERRIERI: Thank you for restating the issue.

We will deal with fine tuning the process and making suggestions as we proceed today. If there is anything else salient, I'll hear it. Otherwise we'll vote.

Dr. Snider and then Dr. Mintz.

DR. SNIDER: That was one question I wanted to add. I wanted to ask you about whether when we vote if it, you know, was contingent.

The other just in response to Dr. Ivanoff, which I think has helped a great deal. The practical issue then is clear about what the committee at WHO would do.

I would just point out that at least in my own view that that's not social justice because distributing benefits across rich and poor, black and white, et cetera, is the issue.

But so what we're talking about is a political decision, which is a reality that we have to accept.

CHAIRPERSON FERRIERI: Thank you.

Dr. Mintz, and then Dr. --

DR. VANDERPOOL: I want to underscore what Dr. Snider just said. The OPRR rules for the protection of research subjects require equivalent ethical protections in the field as in the U.S. In

light of that, the U.S. population did not have to serve as subjects prior to any testing in the field.

Now, if that is a political reality at the WHO that's good to know, but the protections are still in place for people off American soil, and it seems to me that I'd be willing to quarrel with that decision with WHO, but if that's their standard, then so be it, but that need not be the standard that the U.S. would accept.

CHAIRPERSON FERRIERI: Dr. Mintz.

DR. MINTZ: To return perhaps to more mundane matters, I think there has been considerable evidence presented today as to the risks and the potential benefits of this type of a study.

I'd like to add one small extra piece. The serologic markers for typhoid fever are not ideal by a long range, and often we're presented with cases that are suspected of having typhoid fever and can we determine through a serologic test, an antibody test whether or not they did, and I think an additional benefit from this type of study that would be more difficult to derive from a study in the field would be better markers for evidence of typhoid infection, which could be of use in the United States.

CHAIRPERSON FERRIERI: Thank you.

With the provisions we indicated earlier and with reassurance, Dr. Snider and others, we will vote, keeping in mind that the vote, if yes, will be contingent on the suggestions which will be made to FDA and transferred to the sponsor.

So there are several people at the table who have not been cleared for voting for reasons that I had nothing to do with.

(Laughter.)

CHAIRPERSON FERRIERI: And these include Dr. Sears, Breiman, Danis, Ms. Knowles, and Dr. Eickhoff. You'll have your chances later in the day. Some of you will.

So we'll start then with Dr. Hall. I can restate the question. Does the information likely to be gained from the challenge model justify the risks to subjects and the community? The vote is yes or no.

Dr. Hall?

DR. HALL: I would vote yes.

CHAIRPERSON FERRIERI: Dr. Adimora.

DR. ADIMORA: I would also vote yes.

CHAIRPERSON FERRIERI: Dr. Greenberg.

DR. GREENBERG: Yes.

CHAIRPERSON FERRIERI: Dr. Mintz?

DR. MINTZ: Yes.

CHAIRPERSON FERRIERI: Dr. Vanderpool?

DR. VANDERPOOL: Yes.

CHAIRPERSON FERRIERI: Dr. Hoffman?

DR. HOFFMAN: Yes.

CHAIRPERSON FERRIERI: Dr. Fierer?

DR. FIERER: Yes.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: Yes.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

DR. CLEMENTS-MANN: Yes.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Yes.

CHAIRPERSON FERRIERI: Dr. Estes?

DR. ESTES: Yes.

CHAIRPERSON FERRIERI: And for the record, I vote yes as well.

Thank you all.

And now we'll move on to helping FDA and the sponsors with the questions indicated, as well as any others that you all would like to suggest in refining the protocols and in strengthening all safety guidelines for subjects.

So it's medical and scientific input that is being sought from us. Question A then is: please comment on the criteria proposed for initiating

antibiotic treatment.

The criteria is, as you've heard, temperature greater than or equal to 38.3 degrees for 12 hours or bacteremia on days seven-14.

Any spontaneous remarks? Yes, Dr. Hall.

DR. HALL: Well, as I alluded to before, I'm somewhat concerned that this is a little bit too general and may involve a number of the more common infections that are viral.

I'd comment, first of all, that 48 hours of isolation is not long enough for many of the virtual incubation periods, so that that would not guarantee what we might call a, quote, infection that would appear within those first few days and not be related to the typhoid.

The other question though that I have with this is that if you do treat -- say that somebody gets a fever by these criteria -- within the first day or two after inoculation, what happens if you treat with ciprofloxacin immediately? What does that do to the course?

Does that person then have to be eliminated from the data because that would be one-eighth of the data?

If it's given simultaneously or close to

it, what would be the course that you would expect would be changed?

CHAIRPERSON FERRIERI: Dr. Levine or Dr. Tacket?

DR. LEVINE: Carolyn, that's an interesting question. We don't have a definite answer for ciprofloxacin, but the answer with chloramphenicol, which had a very different pattern of treatment, would be if -- and Dick Hornick did this. He administered chloramphenicol beginning 24 hours after challenge and gave chloramphenicol for a week or even several weeks.

When chloramphenicol was stopped at the end of the week, that began a new countdown, if you will, for incubation. It's as if with chloramphenicol there simply had been a delay by one week.

I believe that your point about exogenous agents interfering with interpretation is a very important one, and it has bothered us very much. I would suggest the following proposal to resolve that.

The incubation period with salmonella typhi in the field or in the old volunteer studies was such that the larger the inoculum, the shorter the incubation, but even at nine logs, I believe that the absolute shortest was about three days.

So if we said arbitrarily that it's not typhoid even if there is a febrile response within the first 72 hours, that's not considered towards definition of typhoid, if we add those 72 hours to the 48 hours of observation, that's five days. That should rule out most acute respiratory agents that have been a problem over the years during wintertime with volunteer studies. I think that that would be very helpful.

DR. HALL: Would you include then the rapid test for many of those viral agents at that point?

DR. LEVINE: We certainly can. We do them at Maryland. I think that's another excellent suggestion.

CHAIRPERSON FERRIERI: Is the Committee comfortable with this? I see lots of heads nodding yes, Dr. Levine.

Dr. Eickhoff.

DR. EICKHOFF: I've forgotten what blood culture technique is being used, but what is the duration of time from draw to first notification of positivity?

DR. LEVINE: Well, in the old days it was several days. In the old methodology, one actually

had to keep the cultures, the bottles for a minimum of seven days because salmonella typhi with old methodology could in a small proportion notoriously late come up in positivity.

The new BACTEC methods though give a rather rapid readout of positivity. So we really are in a new technology with respect to the bacteriology versus what was done in the early '70s.

PARTICIPANT: I thought you were using the lysis centrifugation.

CHAIRPERSON FERRIERI: Yes, in the protocol you indicate the isolator tube. Are you planning to do both, the BACTEC models as well as the trademark isolator?

DR. LEVINE: No.

PARTICIPANT: --lysis.

DR. LEVINE: Okay. That was in response to an FDA request. Take that back. Sorry.

DR. EICKHOFF: Are we talking 12 hours or less?

DR. LEVINE: Jim?

DR. NATARO: No, we're still talking 48 or more hours.

DR. LEVINE: Yeah.

CHAIRPERSON FERRIERI: Since you bring up

the issue of the blood culture bottles versus the isolator, at an earlier meeting relating to salmonella vectors in dealing with the issue of quantitative blood cultures, I believe I may have made the suggestion to use the isolator product because that would be very efficient and permit quantitation.

But I'm concerned about the volumes you propose, and given the low level bacteremia that one ordinarily sees in noncompromised adults who have typhoid, as well as the leukopenia that so many patients may have, the lysis centrifugation is going to be based on lysis of facocytes, and you are going to have, say, one to ten colony forming units per mL. I'm concerned about putting suboptimum five mLs into each of three isolator tubes.

The product was licensed, the isolator tube, with the requirements that one put eight to ten mLs, I believe, in each tube. The maximum is about ten, and the minimum we would accept in our laboratory is about seven.

And I'm sensitive to your issue on the volume of blood for all of the other tests, but I'm not confident in your ability to pick up low level degrees of bacteremia, given the volumes in each of the isolator tubes, and wonder if that could be

brought up to at least eight mLs.

But these sediments then, for those of you who don't know, the cells are lysed, and then the sediment is plated onto ordinary microbiologic media and then incubated and inspected every day, and so what we gain is the quantitation per mL blood. What we lose is the rapid detection that would be present in the current fully automated system, names of which cited by Dr. Levine, BACTEC system, BAC-T Alert, et cetera.

And so I think this issue has to be confronted.

DR. LEVINE: Okay. Your point is well taken. Nested within our last large scale trial in Santiago, Chile, near ten years ago, we did a comparison of multiple blood cultures versus one single, large blood culture to look at volume versus time of collection, and what was very clear is that with salmonella typhi volume of blood is the key. So your point is very well taken.

We could manipulate the volumes of other tests such that the volume could be increased. This clinical protocol has gone through multiple iterations, one of which was to switch from the rapid test to the quantitative.

I think that with larger volumes and the use of the methodology that would allow quantitation, we would gain a maximum volume. So we would be very receptive to making that change.

CHAIRPERSON FERRIERI: Okay. We'll pursue other points here then. Everyone wants something.

We'll start with Dr. Sears and then Dr. Estes and Dr. Hoffman.

DR. SEARS: A question about the clinical evaluation, which is at the other end of Dr. Hall's question, and that is the way the wording of the protocol is currently, it suggests that a temp. of 38.3 will be observed. Six hours later another temperature may be taken, and six hours later another temperature after that.

I think you're expecting mild clinical illnesses overall, but the reality may fall in between. For example, someone could get a temperature of 38.3, then have a rigor and spike to 39 in the next hour.

In the current word -- that's intuitive what needs to be done, but the current wording doesn't allow for the vagaries of clinical medicine and the sort of obvious implication that that person should be placed on antibiotics earlier than 12 hours.

I think it's probably less important to the protocol. What is important is what the message is to the people on the ward in terms of responding. There is a call beeper, but none of the physicians listed for the call beeper are likely to be readily available at 2:00 a.m.

So what are the back-up plans? You know, what is the ready response team in case a crisis is observed?

Now, again, my understanding is in the earlier studies no one ever became hypotensive, so that their extreme definition of typhoid fever is very unlikely to be observed, but an in between level of clinical illness may be seen, and what are the instructions to the team on the ward to manage that?

CHAIRPERSON FERRIERI: Very good point.

Carol, Dr. Tacket.

DR. TACKET: Yeah, it's an excellent point about if you take the temperature one hour, the next hour it could be much higher.

Certainly we could write a contingency for, say, if the temperature is at a certain point that additional temperatures would be made on a Q two-hours basis, which is what we have in other protocols.

My concern about arbitrarily measuring one

volunteer's temperature at the seventh hours, one hour after the sixth hour measurement, is that we really ought to measure everybody's temperature in order to be fair in terms of gathering that information. So we ought to perhaps add just a Q two-hour vital signs if the temperature is 38 degrees, for example, so that that would just be an automatic.

DR. SEARS: Yeah, I think that would be my suggestion, is that there be some mechanism that's very clear that that person doesn't go back to the room and then doesn't have a blood pressure or temperature taken until six hours later. I mean even in routine hospitals, those situations can occur and lead to real problems.

CHAIRPERSON FERRIERI: I think your point may be related to this. So I'll preempt Dr. Clements-Mann's.

DR. CLEMENTS-MANN: That's all right.

CHAIRPERSON FERRIERI: Dr. Hall.

DR. HALL: I was wondering if why not just take them Q-4 to begin with because if you're looking for a 12-hour duration of a mild fever, and since most of those fevers will not even occur until evening or late afternoon, you may entirely miss is one other aspect of it.

So I wondered if you started at Q-4 if some of these other alternatives would be less likely.

CHAIRPERSON FERRIERI: That seems a reasonable suggestion.

Dr. Clements-Mann.

DR. CLEMENTS-MANN: Well, I think having done that to volunteers, and you think about for 30 days, that pretty -- sleep deprivation is going to become a problem.

I mean, usually you can signal that when a volunteer feels like they're having a fever, that they could ask to have their temperature taken earlier, and then once they develop a certain level, then you could do it with more frequency, but please don't write in in every four hours.

DR. HALL: But aren't there certain times when it would be more likely that fever would develop and that you could then diminish that response thereafter?

DR. CLEMENTS-MANN: I think most volunteers know when they have a fever. Most people know when they have a fever and that some clinical judgment would be used here.

CHAIRPERSON FERRIERI: Wasn't your thinking that it would be in the first so many days,

not for the entire 30-day period?

DR. CLEMENTS-MANN: They're going to walk off the unit.

(Laughter.)

CHAIRPERSON FERRIERI: Dr. Sears?

DR. SEARS: But even since it's unclear what the onset will be, you're actually looking at two weeks of frequent vital signs, which is an awful lot. I would agree with Dr. Clements-Mann that if you educate the volunteers, alert the staff, and then you have a protocol for increasing clinical care, then you'll probably cover the possibilities.

CHAIRPERSON FERRIERI: Many grateful volunteers.

Dr. Clements-Mann, you had another point though that you wanted to bring up? Was your hand up earlier?

It was Dr. Hoffman perhaps -- Dr. Estes. Sorry. Please, Mary.

DR. ESTES: I think that getting slightly larger blood volumes is important even if you have to back off a little bit on the pathogenesis studies in the initial people. I think we're maybe going to talk a little later about how many people should be done with which strains, but I think initially to

really establish the baselines of what these challenges do to a few people is very important, and knowing the bacterial loads is important.

CHAIRPERSON FERRIERI: Thank you.

I feel very strongly about that point. I want FDA to appreciate the intensity of our belief in the importance here.

Dr. Hoffman.

DR. HOFFMAN: Yes. I just had one question, but let me just follow up on that point. One is I think that if you're going to initiate therapy without a positive culture, then you should take a huge volume of blood because you'd like to maximize the possibility that that individual was going to give positive. Then a tremendous amount would be learned from that.

So I would recommend quadrupling the size of the amount of blood.

The second is that --

CHAIRPERSON FERRIERI: Excuse me. Prior to starting therapy when prompted to start is your point?

DR. HOFFMAN: By fever, by fever.

CHAIRPERSON FERRIERI: By fever. Very good.

DR. HOFFMAN: The second point is that if there is an interest, and there probably ought to be, in rapidly identifying bacteremic patients, Fran Ruvin (phonetic) and I actually published a paper about ten years ago showing that if you culture the mononuclear cell layer in typhoid patients, most of them will be positive within 18 hours of blood draw and plating.

So you can more rapidly identify patients, the bacteremia, by a different technique, and I would suggest considering that anyway.

And my question is: where did you pick 38.3 degrees Centigrade from, and what's the logic for that? Why not 37.5?

CHAIRPERSON FERRIERI: Dr. Levine or Dr. Tacket.

DR. TACKET: It is, again, arbitrary. We actually did some informal studies among ourselves, measuring oral temperature after gum chewing, drinking office, taking a hot shower, a number of other activities, and found that these activities do raise the body temperature at least as measured under the time temporarily.

There are studies showing a range of normal temperatures in normal individuals that certainly don't cover 101 degrees, which is what 38.3

is, but we thought that that was a level that reflected pathology and not these other normal fluctuations or activities involving the mouth.

DR. HOFFMAN: But don't you know what the mean plus two or three standard deviations is in people?

DR. TACKET: I don't. That would be a good thing to use.

DR. HOFFMAN: You published a paper on that, Mike.

DR. TACKET: The Kobiaks paper, but I don't remember the mean and the standard deviations. Do you?

DR. LEVINE: Can I just add to that that I think we need to start with a model that's extremely conservative, Steve, and then as we gain information and gain comfort with the model, which I think will be instructive for all of us, then I think we can consider moving that level a bit to the right or extending by a few hours the period of time of febrile state prior to initiating therapy.

But we specifically wanted to begin with an extremely conservative point at which to initiate therapy. I think your suggestion of a large volume of blood, this is a typhoidologist suggestion. I think

it's great. We applaud it, and we'd love to do it.

CHAIRPERSON FERRIERI: Thank you.

If there are no further points and, Dr. Pratt, unless you feel you would like us to respond to something else, I'll be looking to you from time to time as we proceed here. Please interject if you feel we're not being sufficiently helpful.

Question B is comment -- and this might take the least of our time -- on whether blood cultures should be obtained on days five and six. We heard sentiment this morning supporting the need to do blood cultures on days five and six.

Could I have a show of hands at the table? How many thing we should recommend drawing blood on days five and six for cultures?

(Show of hands.)

CHAIRPERSON FERRIERI: Of those who are permitted to vote, it would appear it's pretty unanimous. If I'm overstating it and anyone dissents, please --

DR. FIERER: It's not unanimous.

CHAIRPERSON FERRIERI: Fine. You didn't think it was necessary?

DR. FIERER: No, I don't think.

CHAIRPERSON FERRIERI: Fine. Let's do

this again. How many people would like to draw blood on days five and six?

(Show of hands.)

CHAIRPERSON FERRIERI: That's about five of us roughly.

And those against drawing blood on those days?

(Show of hands.)

CHAIRPERSON FERRIERI: Three, four, five, six, of those who are permitted to vote.

MS. CHERRY: Do it again, please.

CHAIRPERSON FERRIERI: Again, no, the no vote.

(Show of hands.)

CHAIRPERSON FERRIERI: So no to yes by the difference of one vote here. Would the nay voters like to comment on their vote? At least one commenter, yes, please. Dr. Fierer.

DR. FIERER: I don't know what you'll do with the information. The problem is you don't know when the initial bacteremia ends and when the secondary bacteremia or, that is, true typhoid fever begins.

I think they probably didn't want to know in that interval because it's going to be extremely

difficult in an asymptomatic person with a positive blood culture on day five to know what to do at that point, and I think in a sense it's better not to know.

CHAIRPERSON FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes. Really if there, as I imagine there is, going to be an absolute volume of blood that's required, I'd much rather get the large volume right before you start treatment, to get the amount that you stated in each blood culture, and optimize detection of true typhoid fever rather than just do a fishing expedition and actually have to bleed those volunteers unnecessarily.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. CLEMENTS-MANN: And the risk to the volunteer. I mean, it's not --

CHAIRPERSON FERRIERI: No, your points are rather convincing.

Dr. Hall.

DR. HALL: I have essentially the same point. I think ideally if you had tons of blood, easy, and everything, you would draw blood all the time, but given the ratio of the benefit to feasibility here, I would choose the feasibility in this particular case of being able to put it where it's more important, more volume at other times.

CHAIRPERSON FERRIERI: Those of you who voted yes, anyone wish to speak? Yes, Dr. Edwards. Sorry.

DR. EDWARDS: I think this is a challenge model for us to understand all that we can understand about the model, and so I think for that reason it would be very nice to have an understanding of the dynamics and the magnitude of the bacteremia throughout the course of observation.

CHAIRPERSON FERRIERI: Dr. Hoffman and then Dr. Adimora.

DR. HOFFMAN: I would agree with Dr. Edwards, but would modify my vote by saying that in the context of the total volume and feasibility that it's not required. It's certainly probably not going to change management. It would be ideal to do it, but I would change my vote to a no in the context of the volume issue.

CHAIRPERSON FERRIERI: Thank you.

Dr. Adimora.

DR. ADIMORA: That's exactly what I was going to say.

CHAIRPERSON FERRIERI: Yeah, I was among the yes voters, and I think that arguments presented are more compelling not to do it. In a balanced world

it may not be feasible, given the requirements for everything else.

Well, let's move on to Question 6, the next three then, we'll tackle.

C is comment on the proposal for out-patient antibiotic treatment of subjects who continue to have positive stool cultures after an initial in-patient course.

Who would like to open the discussion on that? Dr. Clements-Mann.

DR. CLEMENTS-MANN: Well, I had two thoughts on this. One is, first of all, people would be treated on an out-patient basis who had normal typhoid fever. I mean we wouldn't hospitalize or isolate them necessarily in the real world.

But I would feel a little more comfortable -- I don't know if it's possible. I was looking at frequency of culturing stools, and I was wondering if one might come in a week after the in-patient, after the discharge and get at least, you know, one negative culture there, and that would get us past, well past, the antibiotic period.

So I was wondering if there might just be one out-patient visit for that, but I think with real targeted education of the volunteers about the

importance of this, these by this time are going to be very compliant volunteers and will want to get rid of that.

CHAIRPERSON FERRIERI: Dr. Adimora, and then we'll come back to you, Dr. Sears.

DR. ADIMORA: I have very little faith in people's ability to be compliant with much of anything on an out-patient basis. However, I think that it sounds as if the volunteers will be carefully selected.

Moreover, the fact that they're going to have to come in and get IV ampicillin on an in-patient basis for two weeks if they don't clear their stools is probably going to be an incentive to be highly compliant, I think, with the out-patient therapy.

CHAIRPERSON FERRIERI: Dr. Eickhoff -- I'm sorry. Dr. Sears and then Dr. Eickhoff.

DR. SEARS: I believe Maryland state law for positive stool cultures is that you have to have three negatives on every other day over the course of a week if you have salmonella typhi to reenter the workplace, and I'm wondering if the criteria for negative in this study at some point has to match Maryland state law since these individuals may want to go back and be a food handler or day care provider or

health care worker.

CHAIRPERSON FERRIERI: Well, they were not permitted to be in the study if they were.

DR. SEARS: But subsequently they may enter one of those areas, and having been given salmonella typhi, and we all know that individual stool cultures are unreliable in detecting S. typhi.

CHAIRPERSON FERRIERI: Dr. Tacket or Dr. Levine?

DR. TACKET: That's an excellent point. I think the law is for food handlers to go back to work.

CHAIRPERSON FERRIERI: It is.

DR. TACKET: But you're right. They might take a job with commercial food handling. They might get that McDonald's job after all. That's an excellent point. We could easily -- actually maybe we could do that second week after discharge and get the one that Mary Lou mentioned, and then additional ones that same week would be a good plan.

CHAIRPERSON FERRIERI: Dr. Eickhoff and then Dr. Hall.

DR. EICKHOFF: I think I'm not particularly concerned about a positive stool culture, positive volunteer going back into a family setting

and using good personal hygiene.

I am a little concerned if such an individual, stool positive at discharge, is in a gay male relationship and is the receptive partner in such a relationship. I don't know. Certainly salmonellosis has been described in the context of the so-called gay bowel syndrome. Whether S. typhi specifically was ever included I don't know, but this would be a setting where something like that could happen.

CHAIRPERSON FERRIERI: Any response from the sponsors on that?

DR. LEVINE: There was one Lancet letter, I believe it was, suggesting that salmonella typhi could be transmitted by sexual practices within the male homosexual community. I think that that's a fair point.

I will defer to Carol Tacket in terms of how we would deal with that in terms of the social aspects and avoiding any exclusion. I'll let you deal with it.

DR. TACKET: Thanks.

(Laughter.)

DR. TACKET: I think the way we would handle that would be in educating the volunteer rather

than excluding volunteers up front. It would be very difficult to exclude gay men who are engaging in low risk sexually transmitted disease type behavior. I think we would be likely to get dishonest answers if we excluded people on that basis, among other things.

But I think what we would probably do, having thought about it for the last 15 seconds, would be to --

(Laughter.)

DR. TACKET: -- perhaps add that to the consent form and explain that not only can typhi be spread person to person by food and water, but add that also by homosexual sexual practices.

CHAIRPERSON FERRIERI: Dr. Vanderpool and then Dr. Snider.

DR. SNIDER: Can I just point out --

CHAIRPERSON FERRIERI: Sure, go right ahead.

DR. SNIDER: -- that men are not the only ones that might have receptive male intercourse. So you might want to modify.

CHAIRPERSON FERRIERI: Thank you.

DR. VANDERPOOL: Right. I wanted to add that 30 days of abstinence is going to affect heterosexuals as well as gays.

(Laughter.)

DR. VANDERPOOL: And I think the consent form needs to address the issue that if infectivity continues, the following precautions will need to be taken by those who are in sexual relationships, and I don't know what all that would be, but I think we definitely need to address that question in the consent form.

CHAIRPERSON FERRIERI: Fine. I think we can trust them to devise the correct wording.

Dr. Hall and then, yes, Dr. Fierer.

DR. HALL: I think, just to put it in perspective, I think the risk of this occurring, first of all, is very low among the 24, and secondly, being on ciprofloxacin is going to reduce that from what we know to even further the possibility of spread, but should that occur, which I think is unlikely, the one other caution that you might add is that that volunteer not go into a situation in which is at very close contact with an at risk person, which would involve an infant, an immunosuppressed, or something of that sort.

And I don't know at what point you have to say that, but nobody who has any contact with it -- but most of these will not be coming from families in

which such a person exists. So that the compliance with at least telling them that they may not have close contact with those particular ones outside of their family probably would be an added precaution that would be of aid.

Dr. Fierer.

DR. FIERER: Yes. I think we all know how difficult it is to get patients to take medication when they're asymptomatic on a regular basis, and even though these are a highly motivated group of people obviously who have been through this, I would suggest that if you're going to have to retreat that you do it as a form of directly observed therapy. Probably once a day cipro would be done that way, could be done that way.

CHAIRPERSON FERRIERI: Other points? Yes, Dr. Edwards and then Dr. Hoffman.

DR. EDWARDS: To sort of underline the points that Caroline was making, I think that if, indeed, there is contact with individuals who then become febrile or have symptoms that are compatible, I think at this point you are asking them to report that when they come back at 90 days, but I think perhaps a little bit more encouragement, that if people that they are in contact with do have

illnesses, that they are seen and cultured. So I think that would be helpful in terms of making sure that if transmission occurs that you really have your hand or your finger on that situation.

CHAIRPERSON FERRIERI: We're steering into Question 4, which is fine, but before we leave Question 3, we have Dr. Hoffman. Dr. Estes, did you have your hand up as well? Hoffman, Estes, and then Clements-Mann. Then we'll move on to Question 4.

DR. HOFFMAN: To reiterate what Dr. Fierer said, it's unlikely that more than three, four, five individuals are going to be positive in this study when they leave the hospital, and having home visits to administer the cipro would seem to be warranted from the point of view of protecting the study, I mean, protecting the University of Maryland and really minimizing the risk because it is unlikely that an individual will take this for two weeks twice a day, I would think.

CHAIRPERSON FERRIERI: Thank you.

Dr. Estes.

DR. ESTES: My point is really for four.

CHAIRPERSON FERRIERI: Fine. We'll defer it for a second.

Dr. Clements-Mann.

DR. CLEMENTS-MANN: Well, it sounds to me that one could develop a standard operating procedure for people that are probably not going to be positive, but if they are positive, then that would go into almost a surveillance study to make sure that they're not positive, their family is not positive, and that they have taken their medications, and that may have to be in some way tailored for the individual and where they live and that sort of thing.

But it is probably unlikely that it's going to occur at all, but you could have that algorithm. If it does occur, this is what you would have to do.

CHAIRPERSON FERRIERI: Thank you.

Brief comment, Dr. Levine?

DR. LEVINE: Yes. Infants were mentioned on several occasions in terms of possible increased risk or increased severity. I would just like to say that the epidemiologic data shows that, in fact, infants are relatively spared, with the possible exception of the neonatal period. Infants, even when they acquire salmonella typhi infection, often manifest a very, very mild illness.

Epidemiologic studies done in water borne outbreaks where children less than 24 months of age

would be expected to consume their vehicle of transmission just like older individuals shows the same age specific incidence as one sees in endemic areas and in food borne outbreaks.

So I think that a special worry for infants may not necessarily be appropriate. It may actually be the opposite. They're relatively at lower risk.

CHAIRPERSON FERRIERI: For my own education, Dr. Levine, this is not the case, is it, in protein calorie malnutrition in young infants? They would not be in that category of lower risk.

DR. LEVINE: Well, most endemic typhoid occurs in areas where protein calorie malnutrition is widespread, and if you look at the age specific incidence, what you see is that there's relative sparing in the first three years of life, that the clinical syndrome of typhoid fever, what we recognize as a clinical syndrome is a school age disease, five to 19 years of age.

If you take the time to do systematic blood culturing of children less than two who come to a health care facility with fever, using that as the indication for taking a blood culture, then you find, indeed, some of these children, in fact, a few

percent, have bacteremic salmonella typhi infection, but what's surprising about this is how mild it is, and had there not been a systematic blood culture survey, these children would never have been recognized.

This is in areas where there is high prevalence of malnutrition.

CHAIRPERSON FERRIERI: Thanks.

Dr. Hall.

DR. HALL: My point is I understand that, but in terms of a young infant, what I really was thinking of is the first couple of months, one month or two months, and it's just for those reasons. It is often most difficult to tell, and this is not an epidemiologic situation. This would be a person going in with a known shedding, would have to be very close contact with a child who is under eight weeks of age.

So it should be in that case modified to the very young because those are the ones who may have asymptomatic overall, but still have the seeding.

DR. LEVINE: Sure.

CHAIRPERSON FERRIERI: I'll take the prerogative of the chair of moving on because the next two questions are very vital and require considerable input in my opinion.

Question D, are there other changes to the protocol entry criteria or monitoring procedures or study design which we would suggest, that is, staging of enrolling, stopping rules, monitoring of in-patient and out-patient contacts?

We've already strayed into the monitoring of in-patient and out-patient contacts, but we do need to give feedback on these other points, and we'll start with Dr. Adimora and then we'll go right down the line, Dr. Greenberg, Dr. Vanderpool, and back to Dr. Hall.

DR. ADIMORA: Well, as I said earlier, and I certainly agree that the information that's likely to be gained is highly useful, but I continue to have some discomfort with the idea of challenging people with live bacteria when there's any risk at all, and I would like -- I also understand that salmonella typhi is an infrequent endocarditis pathogen. I also understand that the level of bacteremia and perhaps even the frequency of bacteremia is likely to be relatively low, particularly the concentration of bacteria in the blood.

But I would still like to see some consideration for a performance of screening cardiac echoes because, you know, having treated people who

have no behavioral risk factors for endocarditis, who did not know that they had mild valvular preexisting abnormalities, I think that the benefits of doing a screening, transthoracic echocardiography, would probably outweigh the inconvenience and, yes, the expense of doing it.

CHAIRPERSON FERRIERI: Response from the sponsors?

DR. ADIMORA: I'm wondering about what other people --

CHAIRPERSON FERRIERI: I think this is a very valuable suggestion. I'd like to get input from the sponsors on this.

DR. LEVINE: Well, anything can be done, and we would want to do anything that increases the safety of the procedure and the model.

My only comment would be that let's consider risk. Let's ask the question: how common, how frequent is salmonella typhi endocarditis in endemic areas? How frequent was it in the pre-antibiotic era when there was persistent, continuing bacteremia going on for many weeks?

And the answer is that it was shockingly rare, extremely rare. If that's true, do we want to go to such -- do we want to add this when the risk

from that very specific complication is so rare? That would be my only question.

And perhaps I would ask the Committee to consider the literature. I left a chapter, Osler's chapter. Take a look at that. See the frequency of endocarditis in the pre-antibiotic era.

Steve Hoffman dealt with a lot of typhoid in adults in Indonesia. I can tell you what it was like in Chile: exceedingly, exceedingly rare.

That would be my only proviso in terms of a response.

DR. ADIMORA: Well, I understand that. That's why I prefaced my comment with I understand it's a rare event, and I understand that the level of bacteremia, from what I thought I heard you say, is likely to be quite low.

But nonetheless, I have some discomfort with giving people the organism in an experimental setting without that information, but I do certainly understand what you're saying, that it is a very rare event.

CHAIRPERSON FERRIERI: Would you consider as a substitute auscultation by a cardiologist?

DR. ADIMORA: Possibly, or perhaps -- I notice some people with murmurs could be included.

Perhaps doing echoes on those people who are going to participate who have murmurs.

CHAIRPERSON FERRIERI: Well, if someone had a murmur, you would follow that up, and they would have an echocardiogram, no?

DR. LEVINE: I would also suggest as information that there were almost 1,900 individuals previously exposed to salmonella typhi with more rigorous or less conservative criterion for the enter point of antibiotic intervention, and endocarditis was not seen.

Truly, it's an exceedingly, exceedingly rare event. It's just not considered a -- it's exceedingly rare, and therefore, without being pushed I think our response would be that would not be something that we'd consider worth the effort, time, money, et cetera.

CHAIRPERSON FERRIERI: Dr. Greenberg.

DR. GREENBERG: I would just add that identification of something that was never identified and has no potential clinical significance or might not have any also has risk, and so as you think about this, you have to think about what is the risk of taking this volunteer and for the rest of their life putting in their mind that they had something wrong

with their heart.

So I feel personally, given the amazingly low risk of endocarditis, I think if somebody has a murmur, you would investigate it just as you would do as a normal clinician, but to start looking all over in your patient for potential weaknesses opens up a box that I'd be worried about.

CHAIRPERSON FERRIERI: Dr. Vanderpool.

DR. VANDERPOOL: This is on a somewhat different subject, but --

CHAIRPERSON FERRIERI: Still pertaining to Question 4?

DR. VANDERPOOL: The same subject, but different than just this.

CHAIRPERSON FERRIERI: Right.

DR. VANDERPOOL: Are there other changes to the protocol entry criteria? Yes, I think there should be. I think this is the point at which the recruitment process needs to be -- it doesn't have to be elaborated, but certainly spelled out because there are social and ethical entry criteria that you're using, and I think that those need to be up front, and the more up front they are, the better it will be for this protocol, which I assume will be somewhat of a benchmark protocol for possibly others in the future

that deal with experimental vaccines.

So I really think that the entry criteria need to be set forth. The social and ethical criteria you'll be using. You don't have to nail everything down because those are judgment calls, but I think you need to accent that we will be making judgment calls about the social and ethical criteria that would enable those who are approached as recruiters to be recruited, for the payment not to be viewed as coercive, and so on.

I think you're going to have some criteria. We need to think about it and have them put down specifically.

CHAIRPERSON FERRIERI: Is there anything specific that you want to suggest though, Dr. Vanderpool, or do you just want to be sure that the general category is addressed of social, ethical issues?

DR. VANDERPOOL: I think something like social and ethical criteria will be followed -- entry criteria -- will be followed that will enable the respect for the subject's autonomy to be secured or to assure respect for the subject's autonomy.

I think we know -- you've already said that there are people for whom $2,500 even in an

isolation unit would be a hard thing to turn down, and you said, well, no, we're going to have people who are employable even if they've lost their job for a while.

So it may be left somewhat open, but I think if you outline briefly the recruitment steps about how they're contacted and how there'll be group meetings and discussion, that that will take care of part of it, but then I think the judgment call about who to exclude on the basis of social and ethical criteria are going to be things that are done.

CHAIRPERSON FERRIERI: Thank you.

Dr. Mintz, any other points or study design?

I would like us to address study design for sure. Dr. Greenberg and then Dr. Hall.

DR. GREENBERG: Yes. I remain --

CHAIRPERSON FERRIERI: The microphone, please.

DR. GREENBERG: I remain unconvinced that two separate inocula are used here, and it seems to me that in this initial study perhaps gaining more data with one, given the fact that I haven't heard a convincing reason that the two are very different, and also from a safety standpoint, I have a much higher level of safety with something that's been given to

1,600 people versus another agent that has never been given to people.

CHAIRPERSON FERRIERI: Are you talking about the Quailes strain with the two doses?

DR. GREENBERG: Yeah.

CHAIRPERSON FERRIERI: I would look at it differently. I would propose looking at two doses of the ISP, of the newer strain perhaps, but --

DR. GREENBERG: Well, actually, one, I don't like using two different strains, and I don't know why use a new strain if you have a lot of experience with an older strain unless somebody can say that the immune response may be different or you're going to learn something, but I haven't heard what we're going to learn.

CHAIRPERSON FERRIERI: Well, let's hear more on this because I think several of us probably have thoughts on it.

Dr. Hall first and then Dr. Fierer.

DR. HALL: The original point was not that I was going to make, but I agree with you that I would like to see all things equal, but more volunteers be in each group if possible, but at least a second group potentially with the Quailes if this is really important, and I don't know enough about the

background of this particular organism to know if it potentially has advantages.

But I think if it does, then I think it's really worth going at at this particular time.

The question though that I had was I wondered whether we could have clarification on the contact that the volunteers will have with each other, particularly if there are two strains. I have a number of question.

The, quote, potential for nosocomial spread in confined areas, and I have one anecdotal. We had a study which will remain unnamed a few years ago of a GI viral package in which the volunteers were isolated from each other, but a secondary case occurred, and actually we then traced that to find it occurred through the ice, common ice bin where they would go and help themselves, which was a great preservative.

So I was curious as to what kind of precautions against these contacts or spread from one to another would be, and can you be reinfected if you had one strain versus another or a mild infection?

CHAIRPERSON FERRIERI: Thank you.

Dr. Tacket, do you want to respond to that?

DR. TACKET: Yes, just very briefly. The volunteers are instructed very carefully in hygiene, hand washing primarily.

There is certainly an ice machine on the ward, but it's the type where you put a cup under a lever and the ice drips down, which actually I'm not sure we thought that true, but it's a good design.

(Laughter.)

DR. TACKET: We have some formal data about transmission of salmonella typhi on our research isolation ward to individuals who had not been inoculated with an attenuated strain and in every small numbers, like six volunteers who were not inoculated, living on a ward in a dormitory style with 12 or 18 volunteers who had been inoculated with an attenuated strain. There was no transmission among these adults using our good hygiene.

There's also similar data for toxigenic E. coli in the conditions of our ward. Very small numbers and certainly doesn't rule out the possibility.

DR. HALL: These then, they're on a ward situation. So they intermingle among each other; is that correct?

DR. TACKET: Oh, very much so. It's more

like a dormitory.

CHAIRPERSON FERRIERI: Separate bathrooms for each person?

DR. TACKET: Separate stalls, but not a separate bathroom, but yeah, and there are bunk beds, four volunteers to a room. So they're very closely in contact.

CHAIRPERSON FERRIERI: Dr. Fierer next, please.

DR. FIERER: I would just point out that we really don't know what the important antigens are for protection in typhoid. We do know that Vi protects, but the strains really don't give an antibody response to Vi and they still protect, and we have no idea how they protect, and I think the most important thing is that you have a challenge strain that's heterologous from your vaccine, that whatever you end up with, I think that's the most important criterion.

And, you know, whether the Quailes strain would be okay since none of the vaccines seem to be based on that or you need another one I don't know, but I think that's what you should be aiming for.

CHAIRPERSON FERRIERI: Yes. That's an important point. I want the group to respond to this

issue. This may be beyond what FDA wanted us to respond to, but we've talked about monitoring. We've talked about the monitoring procedures, that is, blood cultures, et cetera, the contacts, but the issue of the strains and the number of groups.

I'd like FDA to mention something on this point. Dr. Mittoon?

DR. MITTOON: Before we leave the monitoring, I wanted to ask whether there might be any consideration given to actually monitoring the study personnel who were on the ward at the time that the study was being conducted.

And the other question I wanted to raise would be how would one handle it in the event that a subject decided that they wanted to leave the ward, but was, indeed, positive?

CHAIRPERSON FERRIERI: I think there would be support here for monitoring the personnel that you indicate. There are lots of heads nodding, but what about the issue of someone who's positive who wants to leave the ward? Any thoughts on that?

DR. TACKET: Yeah, I mean, it's happened in other studies --

CHAIRPERSON FERRIERI: Right.

DR. TACKET: -- that we've done, frankly,

and it's a very difficult question. I think given the spirit of the discussions that we've had today and previous discussions, we would like very much to -- even though a volunteer leaves the study, in other words was no longer having ASEs drawn, for example, that they would remain on the ward and receive ciprofloxacin for 14 days. So that would be the goal if that happened.

CHAIRPERSON FERRIERI: Is that your question though, Dr. Mittoon?

DR. MITTOON: But that presupposes that they be willing to stay there. I guess that really was my question. What happens if someone says, "I don't want to stay"?

CHAIRPERSON FERRIERI: And how is this consonant with Dr. Vanderpool's issue of autonomy?

DR. TACKET: This happens very rarely. What they are told up front, that if they decide to leave the study, they can certainly leave the study at any time, but they would be required to remain to receive ciprofloxacin for 14 days. If they are required to remain on the ward for 14 days, they might as well remain in the study.

However, if a volunteer -- for example, what happens more often than just wanting to leave is

there's a family emergency, and in the course of 30 days that might well happen, in which case I think we would make the decision on a case-by-case basis, but I could imagine that we might discharge a volunteer on ciprofloxacin with the understanding that they would return to our out-patient area for directly observed therapy.

I'm not sure we would have a policy up front saying across the board, "Here's exactly what we would do," but that would be the goal, would be to have them come back for directly observed therapy as out-patients if we were not able to convince them to stay on the ward.

CHAIRPERSON FERRIERI: Could you incorporate at least a sketch of this so it's apparent that thought has been given to it, and that there is a direction?

DR. TACKET: Sure. Good idea.

CHAIRPERSON FERRIERI: I think that this would be important for the agency.

Other points from the table? Yes, Dr. Hoffman.

DR. HOFFMAN: Two questions. First has to do with the strains again. CVD 109 is derived from ISP 1820.

DR. LEVINE: Nine, oh, six; 906 is derived from 1820.

DR. HOFFMAN: So that do you believe that there would be some advantage -- you mentioned in your presentation there might be some advantage gained from further studies with this carrier strain by doing challenge studies with the parent; is that right?

DR. LEVINE: No, 906 has been abandoned as a vaccine strain.

DR. HOFFMAN: So there is no vaccine strain that's derived from the --

DR. LEVINE: At this point.

DR. HOFFMAN: -- this Chilean isolate?

DR. LEVINE: All of the --

DR. HOFFMAN: Just following up on Dr. Greenberg's point, what is the advantage of having this second strain as opposed to the Quailes strain, which seems perfectly adequate?

DR. LEVINE: There may be no advantage. We just don't know because we have not worked with it. There are several reasons for suggesting looking at it.

One is that when the vaccine challenge model was discussed at the Diarrheal Vaccine Steering Committee some years ago in Geneva, this question came

up. What is the validity of the Quailes strain, which is now quite an old strain? As far as we know it is still valid.

Be that as it may, the question was raised if one sets up a model, why not look at a more modern strain, and in setting up a modern strain, we need one with an appropriate history. We need one with complete sensitivity to antibiotics, and in that sense ISP 1820 fits the characteristics of a possible alternative strain.

We don't know how the two strains would behave. It is conceivable that ISP 1820 might have a high attack rate and be a bit less hot, if you will, than Quailes or vice versa. We just don't know without doing the comparison.

It's because this was a bit of a quandary for us that we put it on the table to the Committee. We don't feel strongly, but we thought we would share the situation: that the question had been raised about adding to the model a more modern strain, and so we put that on the table and put that in the protocol.

CHAIRPERSON FERRIERI: Would you be doing one group at a time? How do you envision the numbers on the ward at one time? So you would do Quaile low dose, high dose, and separately, and then you would

have the others?

This may seem very simplistic, but I wondered what your plans were so that in addition there's no chance of cross-transmission of the two strains.

And if you did low dose earlier, including for ISP 1820, then you'd know that you had to stop and couldn't go on to high dose; same for Quailes.

Could you address these two issues, both?

DR. TACKET: The intention at the moment was to do all 24 volunteers as a cohort, and they'd be randomized to one of the three groups, but I think your suggestion is perfectly valid in terms of the study design. It would add an element of safety that somebody else has also mentioned this morning.

It does add a doubling of the expense.

CHAIRPERSON FERRIERI: Does it? Yes, personnel and so on, trying to staff the ward, et cetera.

DR. TACKET: Yes.

CHAIRPERSON FERRIERI: Yes, of course.

Dr. Snider. Did I miss anyone? Dr. Snider, please.

DR. SNIDER: Well, I guess I have a different take on this, and that is with the numbers,

the sample size you're talking about, I don't think that it's very likely, although I may be wrong, but I don't think it's very likely that you're going to be able to tell much difference between the two, and so a larger sample size would be necessary if you wanted to really try to find -- because the confidence limits, I think, are just going to be so wide.

CHAIRPERSON FERRIERI: Agreed.

DR. SNIDER: But, on the other hand, it occurred to me when we were talking about monitoring the staff on the ward that if there is transmission on the ward, that it would be difficult to pick it up, you know, if people were getting more than the original dose you gave them, and one way to detect for that would be to have two different strains, and obviously you would have to characterize your isolates to determine that.

So I could see the -- the only real justification I could see for having more than one strain would be to detect transmission on the ward. Otherwise, I don't see a huge benefit in having just eight people with one of the strains. I don't think you're going to be able to do a meaningful comparison.

DR. LEVINE: One purely theoretical possible advantage of one strain over the other, if

attack rates were similar, were if there was a difference in incubation period such that with one of the strains one could achieve a high attack rate with an incubation that was shifted to the left by two days with a model. That's 30-some odd days. That actually would be quite attractive.

DR. SNIDER: But my question, Mike, is statistically how are you going to know that with your sample size.

DR. LEVINE: We won't be able to know that in the beginning, but --

CHAIRPERSON FERRIERI: Not at a statistically relevant level.

Dr. Clements-Mann and then Dr. Estes.

DR. CLEMENTS-MANN: I was just wondering with the other strain since there's just one dose, what would be your plan if the attack rate was maybe almost there, but not quite there. Would you also propose to go up a dose, to give a tenfold higher dose at some point?

I was just curious why just ten to the three.

DR. LEVINE: We're making the assumption that this is a guess based on our best guess, that ten to the three may very likely with buffer be the

inoculum that would serve for the model.

I think that if ISP 1820 did not give a comparable attack rate, I think we would probably abandon ISP 1820.

CHAIRPERSON FERRIERI: Dr. Estes and then Dr. Adimora.

DR. ESTES: Well, one of the questions that I had had early when I read the protocol was that one of the new things you're testing is giving this in buffer, and the only prior experience you have is with the Quailes strain, and you're not doing a direct test of that. I mean, you're going on your shigella data that says if I take a shigella and put it in milk or bicarb., it makes a difference to me.

To me that's another argument of why you should stay with the Quailes strain where you have a lot of data. Again, you're establishing a new model with current new technologies where you can get a tremendous amount of quantitative data from it. I just think you're -- I think you can get a lot of wonderful data if you stay with an organism you know a lot about. I think you may be confusing the issue if you put in a new strain.

And it's not clear. You said that the pulse gel electrophoresis patterns at this point are

similar. Unless there's some other reason why the new strain seems to be necessary to test.

CHAIRPERSON FERRIERI: Do you have any animal in vivo data? There's no animal in vivo data that you would have on these two strains?

DR. LEVINE: The only animal model that's used is the hog gastric MUS and IP challenge, which is absolutely irrelevant. There is no model other than the old chimpanzee model.

There is not a pressing special aspect of this newer strain. It had simply been raised amongst a group that was international, and they simply questioned Quailes, but I don't think there is any molecular genetic basis to question it. There's no immunologic basis to question it. There's really not a clinical bacteriologic reason or clinical reason to question it, and that's in great part why we're asking the Committee for guidance on this.

CHAIRPERSON FERRIERI: Well, let me get --

DR. LEVINE: But we're trying to please everyone in terms of recommendations.

CHAIRPERSON FERRIERI: Well, maybe you don't have to please us terribly. Let's get a sense of the Committee.

How many would be content with looking at

Quailes rather than both strains? Could I get a -- this is not a formal vote, and those of you who don't have an official vote can let me see a show of hands as well. How many would be content here? Put your hands up a little more.

(Show of hands.)

CHAIRPERSON FERRIERI: That's at least three quarters of the table would be content with going with Quailes, and so that might help you very much and help FDA as well.

How many people would be content with going -- continuing their looking at the two doses with Quailes strain?

DR. BREIMAN: Can I ask a point of information on that?

CHAIRPERSON FERRIERI: Yeah.

DR. BREIMAN: I mean is there not a question of whether or not a vaccine might not prevent disease due to one strain versus another? Is that one issue that you would end up wanting to study in a model?

DR. LEVINE: The only place that that issue has been raised was in a field trial in Indonesia where there's a major antigenic difference of the flagellar antigen. That's the only time that

that question had been raised, but differences amongst phage types from the field trials done, there is protection against a broad array of phage types.

The question about the zed 66 unusual flagellar type was never answered. That essentially exists only in Indonesia in a very small proportion.

CHAIRPERSON FERRIERI: Thank you.

I want to reask my question to test the objectivity again. How many would object to using both strains as this protocol moves forward?

So it's a different way of asking. How many would object? Hands up for objecting to using the --

DR. FIERER: I'd like to know whether you also include maintaining the same number of subjects. I mean if we lower the number of strains, would you increase the group size?

CHAIRPERSON FERRIERI: Well, we can make it a combination of questions if you would like.

Keeping both strains and increasing the numbers with or without both doses. Do you want to qualify it further Fierer?

DR. FIERER: No. I mean I think the important advantage of dropping one strain is that you can increase the group size.

CHAIRPERSON FERRIERI: Right. So how many would object to going with the protocol as given with two strains?

(Show of hands.)

CHAIRPERSON FERRIERI: So we have three object -- four objections to going with both strains. So --

DR. EDWARDS: Perhaps the word is "prefer" and not object. I guess I --

CHAIRPERSON FERRIERI: How many prefer; how many prefer to go with both strains?

DR. EDWARDS: With both?

CHAIRPERSON FERRIERI: Yeah.

DR. EDWARDS: Okay. Can I just mention one thing. No matter whether you drop or not a strain, your numbers are still too small to --

CHAIRPERSON FERRIERI: Well, we all acknowledge that Caroline.

DR. EDWARDS: -- achieve -- right. So that is the reason we're voting one versus another.

CHAIRPERSON FERRIERI: Yeah.

DR. EDWARDS: It's not --

CHAIRPERSON FERRIERI: Preferentially we would prefer the numbers to be greater, but we acknowledge the expense, all of the difficulties, et

cetera.

Dr. Mittoon first and then Dr. Hoffman.

DR. MITTOON: I'd just like to make the point that in likelihood, we don't have to solve everything with this one study, and so I just want to throw that out. I would think that if this study, you know, goes forth, likely there will be many more and that one would have opportunity to perhaps address these different issues in that context.

CHAIRPERSON FERRIERI: Well, that is an important point, and there is sentiment here that if you stayed with one, you could increase the numbers. You could go with one dose or two doses, but you would be able to balance things more and attribute some of these to Dr. Fierer.

Dr. Hoffman.

DR. HOFFMAN: I would just say one doesn't necessarily have to exclude a priori that one couldn't determine differences in incubation period or pre-patent (phonetic) period even with eight individuals in a group. Certainly with 12 it's quite likely that one could.

And we've had studies in malaria where with those kinds of numbers one has seen differences in pre-patent periods, which as Mike points out is

potentially very important in terms of the efficiency, economy of the mode.

CHAIRPERSON FERRIERI: Any other points before we move to the last question because we only have a few minutes left for our session today?

Yes, Dr. Hall.

DR. HALL: I just also want to offer as another potential that if -- it's been mentioned -- if you start with a low dose for both of those together, then if there is, say, no infectivity in one and there's infectivity in another, you still have an option of going to the higher dose.

Given the other way, if there's good infectivity in both of those strains at that time, the higher dose is not necessary. So you may be able to get for the same numbers more information.

CHAIRPERSON FERRIERI: Twelve and 12 is what you're proposing, the two different strains, same does?

DR. HALL: Right.

DR. CLEMENTS-MANN: Yes, I would just like to say with virulent organisms, too, I mean, if you imagine eventually doing a study with a vaccine group, you probably wouldn't have more than eight controls in the study. So that this will be the sample size that

probably will be realistic in the future, and usually with virulent organisms you can get a pretty good idea of what would be a good dose.

CHAIRPERSON FERRIERI: Dr. Breiman.

DR. CLEMENTS-MANN: With small numbers.

DR. BREIMAN: Is the numbers that we're talking about based on the practical limitation of the size of the ward or the amount of the budget for the study? Because it would be interesting to see sort of a statistical consideration with a few assumptions as to what you could observe with either eight or 12 or 16.

I'm not sure how we got those numbers.

DR. TACKET: Well, the most important assumption would be the attack rate, and that's what we're here to find out. So I would suggest that we not get too distracted about concern about statistics because we really are asking what is the attack rate, which would be the most important thing to determine sample sizes for other studies.

DR. BREIMAN: But I mean even for that it would be nice to have a level of precision. I mean with eight, can you really say very much about the attack rate with, you know, just eight observed cases?

I mean you can give a number, but, you

know, how precise is that number?

CHAIRPERSON FERRIERI: Thank you, Dr. Breiman.

If there are comments to be made, they should be made officially, recognized, and for the record, and so may I call upon someone here now who had his or her hand up? Yes, Dr. Snider.

DR. SNIDER: Well, I guess, you know, the answer to the question depends a lot on how likely you think it is that the two strains, you know, would have different clinical characteristics, and I guess I was basing my earlier comments on what I interpreted as an indication of extraordinarily high level of homology between the genomes of, you know, these two organisms and also measurements of their immunologic characteristics.

I think the more differences there are in those regards, the greater the likelihood that there may be some difference, and certainly then the greater the likelihood you could show, you know, a difference with a smaller study.

But I mean, it seems to me it depends to a large extent on how many, as was said, how many questions do you want to try to get the answer to in this first go-round, as pointed out by FDA, versus,

you know, establishing a model that it can even be used, you know, for the purposes you intend or it has to be changed in some way.

And so I guess my concern is also the track record of one strain with regard to its safety record being know and the importance of ethically, politically, socially and everything of establishing, you know, a model and doing it safely as opposed to trying to pile too many different things on it and perhaps take more chances, if you will.

CHAIRPERSON FERRIERI: I'm afraid we've spent too much time on this issue. We have to get to the last point, and there were no votes on these.

The last question: does the consent form adequately address the potential risks to the volunteers?

And I'd like to start the discussion by getting feedback from you all on whether you thought that the general statement in there that there may be other organs -- doing a translation, that all organ systems conceivably might be involved with side effects, but there's no elaboration of them.

Dr. Adimora.

DR. ADIMORA: Actually I like the consent form and the process a lot. I do have a couple of

questions.

One is a comment concerning the issue you just raised. I was wondering about the absence of a statement that people do, in fact, have a risk of death. I mean I think any time where there's a likelihood that people could become bacteremic, they probably should be aware that it's unlikely that they'll die, but they could, especially since I'm not sure that the general public really has a great understanding of what it really means to be bacteremic, and so that's a comment.

I wouldn't hard pedal it. It seems extremely unlikely, but I would think that people should be given an opportunity to weigh that risk for themselves even though it's quite small.

The question I had is given your past experience, who are the people that you feel are most likely to enroll in this study. I would assume that they are more likely to be university students, at least some of them, but I'm wondering who else is very likely to do this, given your past experience and your beliefs.

DR. TACKET: I don't think they'll be university students because they don't have 32 days to drop out of their lives and be in an isolation ward.

DR. ADIMORA: Well, they would in the summer or some Christmas vacations. I don't know exactly when you're planning to do it.

DR. TACKET: It's possible we might have some university students. I don't mean to discard that, but you're asking for the most likely volunteer. I think it's probably someone in the community who does not have a job, who has the time to participate in the study.

Now, I had mentioned earlier that in the screening process we are fairly picky about literacy, about people who have choices, and that sounds like kind of a vague concept, but when you interview a volunteer and they have never held a job, they can barely read the consent form, they're not able to read it and then respond to verbal questions about it, when they don't show up for consecutive appointments that they have said they would show up for, when there's a pattern of unemployment and irresponsibility, those folks don't get enrolled in our studies, but that's not written in black and white anywhere.

I think actually that's what was alluded to before. Why can't that be kind of codified somehow in a formal way? It would be hard to do.

So the short answer is there will be

people from the community who have 30 days. We've had people who take time off for two week studies who are on vacation. So it's conceivable there might be someone who's employed at another job who would come in on their vacation time, but most of the time's people who are between jobs.

CHAIRPERSON FERRIERI: Do you have any suggestions Dr. Adimora to the consent form? You say that you like it generally speaking. Are there any serious omissions from it?

And I recognize that all of you have your hands up, but we'll give her a chance.

DR. ADIMORA: To me the most obvious omission is the one that I stated. I think that it could be stated without being horrifying that occasionally --

CHAIRPERSON FERRIERI: Rarely.

DR. ADIMORA: -- rarely, very rarely --

DR. TACKET: No, we would be happy to add that. We have that in other consent forms. So this is not a big problem.

CHAIRPERSON FERRIERI: It doesn't inhibit every volunteer at all.

DR. ADIMORA: Right.

CHAIRPERSON FERRIERI: No, let's just do

this real systematically. Dr. Danis hasn't had a chance to say very much, and then Dr. Sears. Did you have your hand up as well?

Ms. Knowles, you haven't said anything if you care to add anything.

First Dr. Danis.

DR. DANIS: I think the consent process as you described it before verbally was excellent. I think the written consent form and the questionnaire have some issues that might be added.

I think there might be some more stated about the possible consequences of remaining a carrier even though the probability is low. The employability if one is a carrier; issues about insurability if one is a carrier or insurability if one has any medical sequelae from this need to be addressed.

I think the issue of the fact that they will have to be rehospitalized if they remain -- if they have to have a second course of IV antibiotics would be important.

And I think that in speaking with you, Dr. Tacket, about how one deals with financially backing the medical care following this care, it seems like there are options that one addresses that are not stated in here, and I think there should be some

statement about every effort would be made to deal with the contracting agency in providing -- however you need to deal with this in a way -- I think the ethics of taking a volunteer and making them sick and saying that there will be no option for taking care of their medical sequelae is very problematic, particularly because the folks that you suspect will be the most eligible candidates are likely to be uninsured medically.

DR. TACKET: I'd like to comment on that quite a bit. The second in the consent form in italics is a boilerplate. For all consent forms at the University of Maryland it requires this exact verbiage, and it's horrible if you're read it. This came down from our IRB about 15 months ago, and we were horrified by it, and our sponsor, our financial sponsors were horrified by these words.

It's actually probably equally problematic not to include those words because those words are the actual contractual facts, reality, and perhaps I should defer to Dr. Lang or others from the contracts from NIAID who might want to comment on reimbursement.

At the moment the wording is essentially that if you have a complication, that you are responsible for the costs of the medical care related

to that, you or your insurance carrier, and that's the contractual agreement.

CHAIRPERSON FERRIERI: Well, that doesn't surprise most of us who know about IRB activities. This is true all over the country. It's been true for years. This is standard boilerplate material. Substitute University of something else for the University of Maryland.

Dr. Vanderpool.

DR. VANDERPOOL: Well, the ethics of that are pretty clear though that in most foreign countries you have to reimburse subjects that are harmed in research. In the U.S. you don't have to reimburse, but you've got to tell them if they're not to be reimbursed.

So I think that whether it's a boiler plate or not, it needs to be in there if they're not going to be, in fact, reimbursed or covered in some more thorough way.

And I would think that one of the requirements I would see as necessary for approving this consent form would be that you just change that boilerplate section. Instead of "university statement," have something like university statement involving safety and limited medical coverage, and put

this in bold print.

Let me say a couple more things. That's not the only issue on this form. For one thing, I think it reaches unintelligibility for a lot of ordinary people. I mean you look at the first paragraph and see the wording. "This is to participate in a clinical trial to establish a human model of typhoid fever." I don't think ordinary people are going to know what that means, or in the next sentence down, "In addition, the experimental design of the clinical trial."

I don't know. I think if you had enough time in the recruitment session they might know that, but there are numerous instances of this.

Third, I think there are, pertinent to the question under discussion, there are risks that aren't mentioned here. Several of the articles mention, for example, the possibility of perforation of the intestine during the first few days.

DR. CLEMENTS-MANN: That's in here.

DR. VANDERPOOL: Is that in there?

CHAIRPERSON FERRIERI: Yes, it is.

DR. VANDERPOOL: The final thing then would be that I do think that the benefit section is -- and this is in keeping with the FDA, but I would go

beyond what the FDA recommends -- there are more benefits here than are mentioned, and you don't want to sell the protocol, but for a lot of people they're going to get a first rate physical exam and for nearly everyone they're going to be thinking about monetary compensation for the time.

So it seems to me you can say there are no physical benefits for you, but, and then mention the other benefits that are here.

CHAIRPERSON FERRIERI: That's a very good point, stressing more positive things, Dr. Vanderpool.

Okay. We have time for a couple more points to improvement of the consent form. We'll start down with Dr. Fierer and then work down the table here.

DR. FIERER: Yeah, I must say I really can't support this with the harm paragraph. I think, for one thing, the VA, in fact, does not have this policy. The VA is a health care system where they provide care to all eligible patients who are harmed in the course of a study free. So the only issue is money.

And when you're doing a study in which you're infecting people, it's quite different than doing a therapeutic study in which people might be

harmed, and I think that we bear an ethical responsibility to provide medical care to people in the highly unlikely event that they would be harmed, and I really think that that has to be our position here.

I don't care what the University of Maryland says.

CHAIRPERSON FERRIERI: The responsibility section, not the details of potential risk, are you objecting to?

DR. FIERER: That's right.

CHAIRPERSON FERRIERI: That our responsibility ethically, to care for those who are, quote, unquote, injured as a consequence of enrolling in this study.

Dr. Hall.

DR. HALL: I also found in reading that that this may actually lead to a bias in selection. Certainly those who have no insurance I would think would be unwilling to sign up if they read that and understood it.

By this format here of having questions and so on, I think, my assumption is that these are going to be very well informed people by the time they are enrolled. I think it's a very unusual --

CHAIRPERSON FERRIERI: If I could reemphasize the point of Dr. Vanderpool that one go through this protocol and clean up a lot of the language to make it understandable to the average person off the street.

Okay. Dr. Snider and then Dr. Clements-Mann.

DR. SNIDER: Several things. I agree with the latter statement. I don't know what the reading level of this is, but the reading level needs to be checked, and obviously at whatever reading level it is, then the subjects who are enrolled need to be matched up with the reading level. So generally you want to get it obviously down to an eighth grade level if at all possible.

Since it was mentioned that a psychological evaluation is going to be done during the 48 hours, that's not as far as I could see mentioned in the consent form. I would suggest that that be added. If I overlooked it, I'm sorry for bringing it up.

I think the benefits part should be strengthened, and I agree with what's been suggested, but also I think it should be made clearer what the benefits to society are because when you look at the

polls or the surveys that have been done of people, why they do or do not participate in research, one of the major reasons people participate in research is to contribute to society, and if you don't have that spelled out in there, you're at a disadvantage. So I would encourage you to do that.

And finally, you mentioned your policy about how you deal with the economic incentives to participation, and it probably would be a good idea to just state your policy in that regard so that people who are reading that understand what your policy is.

CHAIRPERSON FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yeah, I agree that we all have this language in our consent form, but I just wondered if you could tell this Committee what would happen if someone had to be admitted for IV therapy. I mean could that be covered under your current system, taking care of -- I mean, you're not going to leave then or say, "If you can afford it, we want you to come in for 14 days."

DR. TACKET: Yeah, there are other precedents in other VTEUs, as you well know, of contracts paying for adverse events, so that I assume -- oh, Gina is here. Perhaps she can address this with more authority.

CHAIRPERSON FERRIERI: Could you give your name, please?

DR. RABINOVICH: Gina Rabinovich, National Institute of Allergy and Infectious Diseases.

The issue of indemnification from clinical trials is one that has been continuously discussed in depth with the VTEUs, as well as with our other systems. It is a difficult one for any federal agency outside of Department of Defense because we don't have the authority to indemnify.

We are able and have handled on a case-by-case basis payment for any -- for acute care costs, and the problem then becomes how does one define acute care costs.

Realistically speaking, something like a hospitalization that would be required because of exposure during a trial with something that could be covered under the contract, and we have done that in other situations on a case-by-case basis.

What we are unable to do, and that's what the word "indemnification" really means, is to provide funding for health care costs that go beyond the extension of the contract period because there is no -- it's really an OMB requirement that you have the funding which you would need to actually provide

indemnification.

So in terms of anything that would be relatively short term that would be a health care burden incurred because of participation in the trial, that can be handled, and generally we work with the investigator, their sense of what kind of insurance the subject has and assuring that the patient is provided for.

CHAIRPERSON FERRIERI: Thank you.

Would this satisfy you, Dr. Fierer?

DR. FIERER: Well, yes, depending on what that time limit was. I mean what I'm really concerned about is supposing somebody has a bowel perforation, you know, a month after they leave the study that's related to this. That's going to be a very expensive hospitalization, and you know, would wipe somebody out.

It's highly unlikely, but I'd certainly want reassurances that it was covered.

DR. RABINOVICH: Right. What we're unable to cover are things that extend beyond the contract period, which, Mike, is like the year 2001. Is that it?

Yes, so it's short term in the sense of indemnification a la the Vaccine Injury Compensation

Program, which will compensate for lifetime care costs of specific adverse events, like vaccine associated paralytic polio. It's short in that sense.

CHAIRPERSON FERRIERI: Well, then the form would have to be modified to incorporate the specifics of this, and can you accept that, Dr. Levine, Dr. Tacket, FDA? I mean can you do that?

DR. RABINOVICH: It's really up to the IRB. I mean this is their language.

CHAIRPERSON FERRIERI: Right.

DR. RABINOVICH: It's something that we have attempted to clarify in the past. We would welcome working with them to do that.

CHAIRPERSON FERRIERI: You'll have to work with them on this point.

Now, I realize that time has run out more than ten minutes ago, but I'd like anyone else at the table who has not had a chance to suggest revisions to the consent form to speak now if you will.

Dr. Sears.

DR. SEARS: I just want to reiterate what Dr. Danis said in that of all the adverse outcomes that could occur, the only one in my mind that may occur is that someone could become a chronic carrier because it's not clear that each person will be able

to get through day 14 days of ciprofloxacin, and if you go to alternative therapies, the chance of a chronic carrier state will go up.

So in that regard, I would just like to back up her comment that a sentence in the consent form to make the individual understand the economic implications of that in terms of employment, I think, is critical for the group of individuals who are likely to volunteer for this study, who although they may have choices, I staunchly believe have fewer choices than any individual in this room.

CHAIRPERSON FERRIERI: Any other precise points on the form? Yes, Dr. Hoffman.

DR. HOFFMAN: In response to that, my take on it, if someone didn't have gall bladder disease, that almost you could eventually eradicate salmonella from everybody.

DR. SEARS: I think it's very unlikely. I agree with you. If you go to two weeks of IV ampicillin, I think it's very unlikely, but it has such a long term economic impact on an individual.

DR. HOFFMAN: I have one comment under potential risks. I would like to see the words, verbiage changed from in terms of the severe complications from "these occur rarely and almost

exclusively" to "these occur infrequently in natural disease and most commonly in persons" because it's not exclusively or even close to exclusively in person who haven't had antibiotics.

CHAIRPERSON FERRIERI: Okay.

DR. HOFFMAN: Which is what it says here. So just changing "rarely" to infrequently and "almost exclusively" to "most commonly," it would be a fairer statement.

DR. VANDERPOOL: Could I say a word about that?

CHAIRPERSON FERRIERI: One last point, Dr. Vanderpool.

DR. VANDERPOOL: There are two ways to go ethically with this. One is to be benevolent and to accept the articulate defense of Joshua Fierer in terms of how coverage needs to be supplied.

The other is to go for freedom and choice, which would say if you don't have coverage -- and this is one of the virtues I see in the consent form -- if you don't have coverage, you say it, but you say it in bold so that they know exactly what they're getting into and they make informed consent.

So there are two ways we could go. If the Committee wants to go with the benevolent model, then

great, but it can go -- if it goes with the freedom model, which is "take your chances; you won't get coverage at the University of Maryland," then at least we should really put it out there in a very clear, strong way so that they know exactly what they're doing.

I suspect most of us are not going to want the freedom model, but that's one way to go with it, and that's the federal regulation model.

CHAIRPERSON FERRIERI: Thank you.

Ms. Knowles.

MS. KNOWLES: Yeah, I would agree with the concern expressed in terms of addressing treating medical conditions if needed beyond the initial study period of time, and I think we have to remember Tuskeegee in this particular situation.

I know the next comment I'm going to have is probably something that is a huge albatross, but while I have done clinical research, I do understand consent forms, I do agree that there probably are a lot of people that, you know, look at this and they understand, you know, maybe a tenth, if that, and perhaps maybe it might be a general thing to suggest that IRBs review their consents for literacy levels.

There are actually software programs that

can do that now.

CHAIRPERSON FERRIERI: Thank you.

We'll have to conclude. I'll sum up very, very briefly that the Committee certainly is supportive of proceeding with the model and believes that the benefits outweigh any of the potential risks to the volunteers, and that we've made very specific responses to FDA questions where we could.

The area that we were vaguest on deals with the study design, the number of strains, but I think there would be support for proceeding with Quailes under conditions that we elaborated, consideration of increasing somewhat the size in the groups, and then most importantly, that many suggestions have bee made regarding other aspects, ethical, moral issues, as well as the consent form.

So I hope this will be valuable to you, Dr. Pratt, Dr. Mittoon, as well as the sponsors.

I want to thank the Committee and guests here for a most invigorating discussion. Thank you.

We'll reconvene at 1:45 from lunch.

(Whereupon, at 12:49 p.m., the meeting was recessed for lunch, to reconvene at 1:45 p.m., the same day.)

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

(1:49 p.m.)

CHAIRPERSON FERRIERI: If people could join us at the table who are supposed to be at the table, we can begin the afternoon session.

I thought since the composition of the table is slightly different, that we would do introductions again. So if you could all take a seat, please? Could we start with you, Dr. Webster? And could you give your affiliation?

DR. WEBSTER: Rob Webster, St. Jude's Children's Research Hospital.

CHAIRPERSON FERRIERI: We're doing introductions again.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

MEMBER HALL: Caroline Hall, Infectious Disease, University of Rochester.

MEMBER GREENBERG: Harry Greenberg, Stanford University and the Palo Alta VA Hospital.

DR. COX: Nancy Cox, Centers for Disease Control and Prevention.

DR. LEVANDOWSKI: Roland Levandowski, Center for Biologics.

MEMBER EDWARDS: Cathy Edwards, Vanderbilt

University.

MEMBER CLEMENTS-MANN: Mary Lou Clements-Mann, Johns Hopkins University.

DR. SNIDER: Dixie Snider, Associate Director for Science, CDC.

MEMBER ESTES: Mary Estes, Molecular Virology, Baylor College of Medicine.

DR. KILBOURNE: Edwin Kilbourne, New York Medical College.

DR. BREIMAN: Rob Breiman, National Vaccine Program Office.

CHAIRPERSON FERRIERI: Pat Ferrieri, University of Minnesota Medical School. Everyone knows Mrs. Cherry, who is sitting to my left.

Well, this is an important afternoon. The past several years I recollect we've done a good deal of this on the phone after our January meeting, but we have the rare opportunity and pleasure of discussing this here with everyone face to face. And that's completion of decisions on the formulation of influenza virus vaccine for '98-'99. And the introduction and review will be done by Dr. Levandowski.

DR. LEVANDOWSKI: Thank you.

SESSION 2 - OPEN SESSION

COMPLETION OF FORMULATION OF

INFLUENZA VIRUS VACCINE FOR 1998-1999

INTRODUCTION AND REVIEW

DR. LEVANDOWSKI: As has been already stated, we're here today to finalize recommendations for the influenza strains to be used to manufacture vaccines for the 1998-1999 season.

The Committee previously met on January 30th to begin the process of selecting strains. And at that time, information was presented on surveillance of new strains, on spread of those strains in human populations, the antibody responses to new strains after immunization with current vaccines, and availability of candidate strains for manufacturing.

Based on the then current information, the Committee recommended that the influenza vaccine for 1998-1998 be trivalent and that it contain an influenza B/Harvin/07/94 component. Final decisions on the remaining two strains were deferred for the accumulation of additional information.

For the H3N2 influenza A strain, a recommendation for a change from the current vaccine was made with a provisional recommendation than A/Sydney/05/97-like component seemed to be needed

because of the increasing proportion of A/Sydney/05/97-like strains everywhere in the world, including the United States.

However, the provisional recommendation was made to permit review of more recent A/Sydney-like strains since it was not clear whether other more recent strains might demonstrate additional antigenic drift.

For the H1N1 viruses, the picture was less clear. Strains referred to as HI deletion mutants, which have been represented by A/Beijing/262/95 and characterized by significant alterations in antigenic characteristics as a result of amino acid sequence changes, including the deletion of an amino acid at position 134 of the hemagglutinin, these strains have been known for the past two to three years, but they have recently been increasing in number, particularly in Asia. In addition, these strains had been isolated in Africa at the time of our previous meeting.

A clinical trial using an experimental vaccine containing the A/Beijing/262/95 strain was shown to produce antibody responses in people that reacted with the H1 deletion viruses better than current vaccines and also produced antibodies to non-deletion strains that were similar to current

vaccines.

That decision was deferred because the epidemiology of spread was unclear and it was uncertain whether the clinical trials results were representative for H1 deletion strains which have been more recently identified.

In February, the WHO recommendations for influenza vaccines were made using data available here and also additional data that were collected between the two meetings.

Based on all of the information available at that time, the WHO recommended, as has been published already in the February 27th Weekly Epidemiological Record, which has been made available to the Committee, that the vaccines be trivalent and they contain an A/Sydney/05/97-like H3N2 component, an A/Beijing/262/95-like H1N1 component, and a B/Harvin/07/94-like component.

WHO did not recommend commercial production of an H5N1 vaccine but indicated its support of continued development of experimental vaccines and indicated that it will continue to monitor the situation with H5 influenza viruses.

We're going to take up the H5 part of the discussion in a later session this afternoon. Right

now we're going to present some additional data to help complete the vaccine recommendations. And for that, I'd like to invite Dr. Nancy Cox from CDC to present information on characterization of additional strains and surveillance.

And also I have asked Nancy if she would just go ahead when she is finished with that information after taking questions from the Committee with what we view as the options for selection.

DR. COX: Thanks, Roland.

ADDITIONAL SURVEILLANCE AND STRAIN CHARACTERIZATION

DR. COX: If everyone would just grab the package, if the Committee members would grab the package, of information from CDC, I think it will be easy to follow along.

On Page 2, there's a summary of the influenza season in the United States. And I think we'll go ahead and start with the first overhead. And I'll very briefly summarize the information that's on Page 2.

In this overhead, you can see that there are three of the four systems that we use to monitor influenza activity. First of all, in the top panel, you see the number of isolates of influenza that had been reported by the WHO collaborating labs in the

United States.

In the middle panel, there are the weekly estimates of influenza activity from the state epidemiologists. And here we're just showing the number of states that report widespread and regional activity.

In the bottom panel, you see influenza-like illness reported by our sentinel physicians. And what you can see is that influenza activity actually peaked overall according to all three systems during weeks three through five of 1998.

Now, there were a total of approximately 68,000 specimens which were tested by the WHO collaborating labs for influenza. And nearly 10,900 of these were positive for influenza. This is an increase over the number that we normally have reported to us at this time of the year.

Of the influenza-positive specimens, 99.8 percent are influenza Type A. And though only 20 percent-24 percent of these viruses have been subtyped, of these, 99.8 percent are influenza A(H3N2) viruses.

Next overhead, please. Now, the peak of influenza activity as reported by state and territorial epidemiologists occurred during the week

ending February 7th. During that week, a total of 47 states reported regional or widespread activity.

And in the bottom panel, you see the activity was reported for the most current reporting week ending March 14th. And here we have a total of only 17 states reporting regional or widespread activity. So clearly influenza activity has been dropping quite markedly.

Now, the third overhead shows the percentage of deaths attributable to pneumonia and influenza as reported by the Vital Statistics Offices of 122 cities. Pneumonia and mortality levels increased above the epidemic threshold during early January and have remained above the threshold for the past ten weeks.

So, in summary, this season's influenza epidemic has been characterized by a predominance of influenza A(H3N2) viruses and by excess influenza and pneumonia-related mortality.

Now we're going to move on and talk about the viruses. On Page 7 of your handout, you'll see a frequency table for influenza A(H1N1) isolates characterized by our WHO collaborating lab at CDC. We'll concentrate on the panel down below.

While we really haven't had a great number

of H1N1 viruses to examine, I would like to point out that we have one Beijing/262 deletion mutant-like virus from the United States and we have five from Asia.

If we look at the time period before this, I want just to remind you that we had a large number of Beijing/262-like strains from Asia. And during that same time period, we had no Bayern-like strains.

Next overhead, please. Well, I don't have any HI tables for the H1N1 viruses. So I hope you can remember the patterns that you saw last year, last January, and then the year before as well. And I'll just remind you that the Beijing/262/95 and Bayern-like viruses have greater than eight-fold reciprocal differences in Hi titers between them.

Now we see that the Beijing/262-like viruses have been detected in Japan, in Taiwan. Of course, last year we knew that they were detected throughout China and in Hong Kong and Singapore, but now we have added Taiwan and Japan to the list. We have talked about the isolation in Senegal in August of '97 and in South Africa in November of '97.

In addition, since we last met, two isolates have been obtained in France during January of 1998. And a single travel-related isolation of

virus occurred in California in February.

So, in summary, we now have these viruses detected on four continents. And given the fact that influenza surveillance really isn't particularly good in Africa, the number of isolated we have probably reflects a reasonable amount of activity there.

Next overhead, please. Now, the last time we met, you will remember that it appeared that in experimental trials conducted by SmithKline Beecham in Germany, the A/Beijing/262 experimental vaccine inducted bitter cross-protective immunity against the Bayern-like strains, then vice versa. In fact, the antibody titers induced by the Beijing/262 vaccine were higher against the Bayern-like strains than against the homologous strain.

Therefore, we retested the sera that we had from the experimental trial with several Bayern-like and several Beijing/262-like viruses to confirm our earlier data. And the results are shown in the coming overhead.

So for the adult population, we can see that the post-vaccine geometric mean titers are indeed a bit higher for the Bayern-like strains, which are listed here, as opposed to the Beijing/262 or vaccine-like strains listed here.

We're not really sure why the titers against the Hong Kong/408 strain are so low. Perhaps it's just one of those observations that we make from time to time, but we don't put any particular significance on this observation.

So both of these populations, first the population that was not previously vaccinated and the population that had been vaccinated the previous year, showed this difference.

Next overhead, please. This was also reflected in results for the elderly population, where you see that in individuals who received the Beijing/262-like experimental vaccine. They were slightly higher geometric mean titers, post-vaccination against the Bayern-like strains than for the Beijing/262-like strains. So we see that we get better reciprocal cross-protection by using the Beijing/262 vaccine.

Now, I hope you can recall that in January, we saw that when we used the Bayern-like vaccine-like candidate, Johannesburg, we got very low levels of antibody against the Beijing/262-like candidates. So this is an asymmetric cross that we're seeing here.

Next overhead, please. Now we're going to

be moving on to the HI reactions of H3N2 strains. And I'm not going to show you an overhead of the HI table on page 12. We're going to skip right on to Page 13, which is representative of what we're seeing now.

It's a fairly recent test that was conducted on the 5th of March. And you can see that here we have Wuhan-like titers, titers against Wuhan-like strains that are high in this column, where we're using the Wuhan vaccine, and titers that are high against the Sydney-like viruses when we're using the Sydney antiserum here.

And so you can very easily pick out the Wuhan-like and the Sydney-like strains, and you can see that we have in this table two strains from the United States that are Wuhan-like and a larger number of strains that are Sydney-like.

Likewise, we can see that there are two strains from France which are Wuhan-like and then a larger number of strains from Japan, Guam, Korea, the U.K., and France which are all Sydney-like.

Next, please. So when we look at the frequency of Sydney-like strain that have been isolated since October of 1997, we see that in the United States, we have a total of 188 H3N2 strains which have been antigenically characterized. And 144

of those are Sydney-like while only 44 are Wuhan-like.

And also you can see if you follow along here, no matter what the geographic location is, we have more Sydney-like strains than we have Wuhan-like strains circulating. And this is shown even more clearly on the next overhead.

This is the geographic distribution, which we have updated since the end of January. And what is on this map that wasn't apparent before because we didn't know about it before is that, actually, there were Sydney-like isolates that occurred in Japan in January of 1997. And we just found out about those rather recently.

You can see that there are Sydney-like strains all over the United States. And, actually, although we don't have any that we have analyzed from Africa, I'm not sure whether other centers have any or not. But basically Sydney-like viruses have been isolated from all continents from except perhaps Africa.

Next overhead. Here is where you can clearly see that the proportion of Sydney-like strains has increased dramatically since September of 1997. So that now of the strains that we have characterized worldwide, the majority, approximately 80 percent, are

Sydney-like.

If we look at the distribution in the United States -- and here the numbers are slightly higher than they are for those that are antigenically characterized because we have been running a bit ahead in terms of the genetic characterization that we're doing. You can see that we have about 78 percent of strains which are Sydney-like isolated from the United States.

Okay. Next, please. I decided to keep the summary very, very simple. Clearly for H3N2 viruses, Sydney-like strains are predominating worldwide. And they constitute approximately 80 percent of U.S. H3N2 strains. Beijing/262/95-like strains have spread and now have been isolated in Asia, Africa, Europe, and North America.

Are there any questions now?

CHAIRPERSON FERRIERI: Does the Committee have any questions for Dr. Cox? Dr. Webster?

DR. WEBSTER: Nancy, could we go back to Page 9 and the Hong Kong/408/97? This is the serological responses. I wasn't clear what the 14 percent or 14 in the post-vaccination --

DR. COX: I'm sorry?

DR. WEBSTER: On Page 9, --

DR. COX: Yes.

DR. WEBSTER: -- the clinical trial serological responses to Hong Kong/408/97, that rather strange response. What does it mean?

DR. COX: Yes. We've looked at the sequence of the strain and so on. And I'm not really sure why that particular strain is so low, but we have seen this occasionally in the past. We're dealing with an MDCK isolate. And sometimes we get lower responses to MDCK-grown viruses than to a grown counterpart.

So we really haven't attached very much significance to that. We have looked at the sequence. We don't see anything unusual about the sequence of BHA. So I think it's some kind of a reflection of the technical matter in the test, rather than anything that we really have to worry about in terms of the virus characteristics.

DR. KILBOURNE: Nancy?

DR. COX: Yes?

DR. KILBOURNE: Do you have any database that would allow you to estimate the number of vaccine failures in terms of the H3N2 components?

DR. COX: No, no. I don't think there's any database that exists in the United States at all.

DR. KILBOURNE: Well, at some point post-epidemic can you make that estimate from any source?

DR. COX: No. We don't get vaccination status for most of the isolates that we receive. So we have no idea if the person was vaccinated or not.

Now, there have been some observational studies of vaccine effectiveness, and there was a publication in last week's MMWR concerning vaccine failures, if you will, in nursing homes. And there was also an outbreak in a vaccinated military population.

So vaccine effectiveness was calculated, to the best of our ability. And it appeared that vaccine effectiveness was quite low this year. All of the four outbreaks that we reported in the MMWR were Sydney-like outbreaks.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Nancy, how many more isolates do you have to characterize in detail? And do you have some sense of whether you have more H1N1s that you need to do additional work on?

DR. COX: We've tested all the H1N1s that we have received so far. Our big backlog is really with the H3N2 strains.

CHAIRPERSON FERRIERI: If there are no further questions, we'll proceed with the program, then.

OPTIONS FOR STRAIN SELECTION

DR. COX: Again, I've kept this overhead very, very simple. I think that we for the H3N2 vaccine component clearly need to change. And the Sydney-like, Sydney/05/97-like, strain really appears to be the option that we have at this time.

We don't have an indication that there are new variants of H3N2 that are antigenically distinct and genetically distinct. So it seems that the Sydney-like vaccine candidate is our only clear option.

For the H1N1 vaccine component, we have two options. One is to retain the current vaccine component. and then the other option is to change the H1 vaccine component to an A/Beijing/262-like strain.

I think that given the fact that we have seen this major antigenic difference between the Beijing/262 and Bayern-like strains and given that we have detected the Beijing/262 strains on four continents now, this option must be carefully considered and considered in the light that when you have a vaccine that's based on the Beijing/262 virus,

you get better reciprocal, actually much better reciprocal, cross-protection against the Bayern than you do if you use the Bayern-like candidate. And in that case, you get very low levels of antibody against the Beijing/262-like virus.

Are there any questions or comments?

CHAIRPERSON FERRIERI: Everyone is burned out from the morning session? I think the data is so familiar, Nancy, that we don't find it too surprising. Dr. Estes?

DISCUSSION AND RECOMMENDATIONS

MEMBER ESTES: One of the questions we discussed at the end of January, I guess, was the growth properties of the viruses. So if you make the recommendation to change the second recommendation, are there good lots of virus available to do that?

DR. COX: Roland may want to comment on that because he has more information from the vaccine manufacturers.

DR. LEVANDOWSKI: Right. There are vaccine candidate strains that are available. And we do have information from manufacturers are how they grow. It's very clear that in the case of the H1N1 strains, that the A/Johannesburg/82/96 strain, the nib 39 reassortant, is vastly superior. It's one of the

best growing reassortant viruses that has been made in a long time.

The Beijing/262/95-lie reassortants grow better than the wild type, but the description that we have from manufacturers is that they're not growing as well, certainly not as well as the nib 39 reassortant and more consistent with what was seen or maybe even a little but lower than what was seen with the A/Texas reassortant from previous years.

So there are reassortant viruses that are available for manufacturing. There are certainly differences between these two strains, as we often see.

CHAIRPERSON FERRIERI: Other questions? Dr. Kilbourne?

DR. KILBOURNE: One of the reassortants that Roland is talking about is our X-127, which is the prototype for the Beijing/262. We'd have to call it a medium-high yield and reassortant. We know it's not a 62 reassortant.

We dropped it a year ago on the advice of all concerned because at that point the epidemiologic faith of that strain wasn't very obvious. And it was restricted to one or two continents at that point.

There's no reason why we can't exhume that

and do better with it by incorporating further genes, but at the moment, as Roland points out, it's only a medium yielder, still better than wild type.

CHAIRPERSON FERRIERI: Are there other presentations, Roland, or is that it?

DR. LEVANDOWSKI: Other did you say hesitations or --

CHAIRPERSON FERRIERI: Presentations. Not presents. Presentations.

DR. LEVANDOWSKI: We don't have the additional information to present at this point except along the lines of strains and reagents, the question that just came up.

There are also now two reassortants that are available for the A/Sydney strain. The one that, of course, has the most experience is the IVR108, which has been used in manufacturing for Australia and in Australia.

And our laboratory this past week has come up with a strain that looks like it's possibly a little bit better growing than the IVR108, but it's at the point where there's not a lot of characterization and it may not be something that will be useful just because of the timing of the development.

For all of the strains that are out there,

we have reagents that are available for the current vaccine strains that can be sent to manufacturers now and can be used for interim testing if there are new strains that are selected.

We're about to start production of sheep antisera for both the A/Sydney/597-like strain and also the Beijing/262-like strain pending the outcome here. Those reagents would not be available for use until sometime in May because it takes several weeks to produce them and qualify them.

So, as in previous years, the new reagents would not be available until later in the season.

CHAIRPERSON FERRIERI: Dr. Eickhoff?

DR. EICKHOFF: I would just like to ask Dr. Kilbourne: Did your comments suggest that if you are asked to work further with the X-127 reassortant that that could be polished, if you will, in time for this year's production?

DR. KILBOURNE: Whether in time or not, I can't guess, but from past experience, we should be able to get the other genes in. We have been concentrating, really, on trying to make a better Sydney reassortant, and we have not made one better than the one that now exists, and also starting to work on the Hong Kong reassortant, the H5.

DR. EICKHOFF: Yes, right.

DR. KILBOURNE: But if there's any indication of acceptance, we'll go back to X-127.

CHAIRPERSON FERRIERI: Is there anyone here from industry who would like to make some spontaneous remarks or any information you would like to share with us at this time? Now is the opportunity.

(No response.)

CHAIRPERSON FERRIERI: Well, this is all that we're going to hear about the two remaining decisions we have to make, then. So why don't we -- you might remember at the end of January that we made the decision on B. And we leaned in the direction of choosing A/Sydney/05/97 but felt we wanted to hear more information a bit later. And then, according to one of the throw-away newspapers, I said that H1N1 was more problematic. That is indeed the case.

I would entertain a motion for the composition of the choice of the H3N2 strain. We'll have a formal vote on it, then. Anyone care to make a motion that we will then vote on? Dr. Edwards?

MEMBER EDWARDS: Scientifically it looks like the Beijing is a good choice.

CHAIRPERSON FERRIERI: For the H3N2?

MEMBER EDWARDS: Sydney.

CHAIRPERSON FERRIERI: Oh, Sydney.

MEMBER EDWARDS: A/Sydney for the H3N2 and Beijing for the --

CHAIRPERSON FERRIERI: Yes. So we have a motion. Anyone second it?

MEMBER GREENBERG: Second.

CHAIRPERSON FERRIERI: So we have a motion on the floor to accept A/Sydney/05/97 as the H3N2 choice for '98-'99 vaccine. Unless there's further discussion, we'll start voting with Dr. Edwards. Yes or no?

MEMBER EDWARDS: I agree with the motion.

CHAIRPERSON FERRIERI: Dr. Clements-Mann? Mary Lou? Dr. Clements?

MEMBER CLEMENTS-MANN: Yes, I agree.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: I agree.

CHAIRPERSON FERRIERI: Dr. Estes?

MEMBER ESTES: I agree.

CHAIRPERSON FERRIERI: Dr. Kilbourne?

DR. KILBOURNE: I agree. I think we have to realize that we're picking the wrong strain because with the penetration of the Sydney this year, something else is going to evolve. But I think we can

rely on enough heterovariant immunity to get through.

CHAIRPERSON FERRIERI: Yes.

DR. KILBOURNE: And also it should be a light H3N2 year next year.

CHAIRPERSON FERRIERI: Yes. That's prophetic but hopefully true.

Dr. Breiman?

DR. BREIMAN: I agree.

CHAIRPERSON FERRIERI: Dr. Webster?

DR. WEBSTER: I agree.

CHAIRPERSON FERRIERI: Dr. Eickhoff?

DR. EICKHOFF: Agree.

CHAIRPERSON FERRIERI: Dr. Hall.

MEMBER HALL: I agree, but can I ask Dr. Kilbourne: Do you have a soothsaying prediction for which strain will come next year, then, if it's not going to be Sydney, since this is unusual?

DR. KILBOURNE: That's a prediction. Did I get your question?

MEMBER HALL: Yes. I mean, which of the strains have you decided should be it next year? Do you have any yet?

DR. KILBOURNE: Will I put that on the record?

MEMBER HALL: Sure.

DR. KILBOURNE: Why not? Am I missing your question still? Well, I would guess that we will have less H3N2 than we've had the last two years --

CHAIRPERSON FERRIERI: And so he's not predicting --

DR. BREIMAN: So what is coming?

DR. KILBOURNE: -- based on the pervasiveness and penetrance of the virus this year because there is an old, old pattern that doesn't always repeat at the biennial periodicity of these strains.

MEMBER HALL: I was wondering whether you thought the H3N2 that would be coming, even if it's not the prominent one, will replace Sydney and which one that would be, if you have any predictions in that.

DR. KILBOURNE: Well, I wouldn't dare predict that, but I think it's going to be different.

CHAIRPERSON FERRIERI: Thank you.

Dr. Adimora?

DR. KILBOURNE: How efficient I don't know.

MEMBER ADIMORA: I agree.

CHAIRPERSON FERRIERI: Dr. Greenberg?

MEMBER GREENBERG: I agree.

CHAIRPERSON FERRIERI: For the record, I vote yes as well. I know how boring this might be to some of you to vote like this, but this is very important for FDA and industry, CDC as well.

So we'll move to the other issue, and this will require a little bit of discussion, then, or using a crystal ball. This is the choice of the H1N1 strain and whether we retain the current A/Bayern/07/95 or switch to the A/Beijing/262/95-like, keeping in mind the immunologic data showing the excellent cross-protection of the A/Bayern by the A/Beijing/262/95, all the other uncertainties about the epidemiologic shifts that could take place.

And so is there further elucidation of this point before we consider making a recommendation to vote on? Dr. Webster, would you like to lead the discussion on this point?

DR. WEBSTER: Well, based on what we have heard from Dr. Cox on the cross-protection between these strains induced by the Beijing/262 and the cross-protection, it would look as though a change is merited. And if we look at the distribution, the worldwide distribution would also indicate that a change should be made.

There is some little concern about the

Hong Kong/408/97 and that information that's not clear. But overall the cross-protection in the adult population convinces me that the change is indicated.

CHAIRPERSON FERRIERI: Can I ask for a point of clarification, then? The numbers are very small on Page 7 of the handout, Dr. Cox. And the prevalence of the A/Beijing was greater in the immediate quarter, from April through September.

The shift to a/Bayern is a more recent one but, again, based on relatively small numbers. And it seems like there's been a flip-flop of this type before in October through March a year ago.

We had the flip Bayern and then Bayern decreased in April through September. And now Bayern has flipped up again the small number that's probably due to immunity that's been induced to the other strains.

But do you have anything else to add to this data at all?

DR. COX: I think that one of the problems for us has been that we really haven't received viruses from China in a very timely manner over the past six months.

CHAIRPERSON FERRIERI: That's what I'm worried about, that most of the influences have been

from China. And we don't see that in the data you presented.

DR. COX: But because we only have five strains from Asia. We very recently received a large group of viruses from China. And, according to the information that we have so far, we believe the H1s that were in that package will be Beijing/262-like.

CHAIRPERSON FERRIERI: Okay. That's --

DR. COX: This table does not reflect information from the other WHO collaborating centers. So this information does not reflect the data from Japan or the data from Europe either because we didn't receive the viruses from France.

So they're not listed here, but we know that they appear on the map because we know that they were isolated.

CHAIRPERSON FERRIERI: And they're Beijing-like?

DR. COX: They're Beijing-like, yes.

CHAIRPERSON FERRIERI: This is very helpful. We always need a constant refreshing of this.

Other points on this? Would anyone care to make a motion based on the discussion, Dr. Webster's thoughts? Dr. Kilbourne, do you have an

opinion? Dr. Kilbourne, do you have a strong opinion about the choice of the H1N1 strain for the vaccine?

DR. KILBOURNE: Not any strong opinion, but I do note that the baseline pre-immunization titers are lowest to that strain. I think that's worrisome, particularly that there has been the seeding of the five continents, --

CHAIRPERSON FERRIERI: Right, with the Beijing.

DR. KILBOURNE: -- even though the data are very meager.

CHAIRPERSON FERRIERI: Yes. Well, would anyone care to make a motion about the H1N1 strain, then? Dr. Estes?

MEMBER ESTES: I move that we change the strain to the A/Beijing/262.

CHAIRPERSON FERRIERI: Very good. A second to that? Dr. Greenberg?

MEMBER GREENBERG: Second.

CHAIRPERSON FERRIERI: Okay. We'll start the voting, then, at this end. Dr. Webster?

DR. WEBSTER: I recommend that we change to the Beijing/262 strain.

CHAIRPERSON FERRIERI: Dr. Eickhoff?

DR. EICKHOFF: Yes.

CHAIRPERSON FERRIERI: Dr. Hall?

MEMBER HALL: Yes.

CHAIRPERSON FERRIERI: Dr. Adimora?

MEMBER ADIMORA: I agree.

CHAIRPERSON FERRIERI: Dr. Greenberg?

MEMBER GREENBERG: Yes.

CHAIRPERSON FERRIERI: Dr. Edwards?

MEMBER EDWARDS: Yes.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

MEMBER CLEMENTS-MANN: Yes.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Yes.

CHAIRPERSON FERRIERI: Dr. Estes?

MEMBER CLEMENTS-MANN: Yes.

CHAIRPERSON FERRIERI: Dr. Kilbourne?

DR. KILBOURNE: Yes.

CHAIRPERSON FERRIERI: Dr. Breiman?

DR. BREIMAN: Yes but with the proviso the one question I wanted to ask Nancy is: Is the lack of, what appears to be a lack of, a homologous response on Page 10 in the elderly group that has not been vaccinated meaningful at all? I mean, there's only 33 percent or something like that that had elevated titers with the X-127 strain.

DR. COX: I think that these sera have

been tested in a variety of labs. And our titers always tend to be somewhat lower than those obtained by other investigators. And it was true in this case as well that our titers were somewhat lower.

But we do, in fact, often see that the elderly do not respond as well as we would like, even to the homologous strain. So I wouldn't say that this is really different from what we have often seen in the past.

CHAIRPERSON FERRIERI: The official vote of mine is to endorse the adoption of the A/Beijing/262/95.

That's the end of the formal discussion here. Very final points, Dr. Kilbourne?

DR. KILBOURNE: Well, yes. With reference to the elderly, I think that may reflect original antigenic sin. If you measure their antibodies to earlier H1s going way back, they might have been going up considerably. So we often have this problem with the elderly, as Nancy was saying.

CHAIRPERSON FERRIERI: Thank you. We always bringing up Biblical issues here.

(Laughter.)

CHAIRPERSON FERRIERI: Roland, I can't believe this, but it's about 2:33 and we're ready to

start the open session on the H5N1 virus. Are you ready?

DR. LEVANDOWSKI: Sure. If you're ready, we're ready.

CHAIRPERSON FERRIERI: We're ready. We've been waiting eagerly all day. We were so tremendously impressed at the end of January with all of the data presented on the H5N1 strain, so-called Hong Kong flu, and want to again give credit to all of the different agencies who educated us with FDA, CDC, and NIH. Dr. Levandowski will start off.

DR. LEVANDOWSKI: Okay. Thank you.

SESSION 3 - OPEN SESSION

UPDATE ON H5N1 INFLUENZA

INTRODUCTION

DR. LEVANDOWSKI: Again, we'll try to be brief on this session, as we have been on the previous one. During this session, what we hope to do is to provide an update for the Committee on H5N1 influenza A viruses.

To date, no cases have been identified outside Hong Kong. And the onset of the last confirmed case of H5N1 infection in man occurred in Hong Kong. And the date of that last onset was still December 28th. That's in the face of continued

heightened surveillance in that area of the world.

Altogether there were 18 cases of H5N1 infection confirmed in adults and children. There were eight cases of pneumonia. And there were six deaths among those patients. So clearly the H5N1 strains have demonstrated significant potential for morbidity and mortality in man.

The new cases in Hong Kong, of course, ceased coincidentally with the removal of the chickens that were infected with H5N1 viruses from live poultry markets.

Chickens have now been reintroduced into Hong Kong markets as of February, and they have been coming in under intense scrutiny and screening for H5N1. That strategy seems to be successful at this time.

What remains unclear is whether the cases in Hong Kong represent an isolated event that's related to the high concentration of infection in domestic poultry or whether it's the opening gambit of introduction of a new influenza A subtype, which we talk about as antigenic shift in man. And, of course, I'll remind you we haven't seen an antigenic shift for several decades now, a true antigenic shift.

At the previous meeting, the Committee

gave a very strong recommendation to us to proceed with activities to develop and test experimental vaccines for influenza A(H5N1) viruses. We got that message loud and clear.

And the national and the international influenza community is proceeding in the developmental efforts. And I think that's reflected in the WHO recommendations, indicating that they, too, agree that these vaccines need to be developed and experimented with.

Our presentations in this particular session will focus on the continuing activities that are relate to surveillance and to vaccine development since those things go hand in hand.

Not everyone involved in the efforts that we'll be discussing are represented here today, although in some sense maybe there are representatives from most of the different groups involved.

But we're trying to keep it brief. And so we will attempt to give a comprehensive summary by a few of us on the activities that are being undertaken by many.

To start off, I've asked Dr. Nancy Cox from CDC if she would again give us an update on surveillance activities.

UPDATE ON EPIDEMIOLOGICAL DATA

DR. COX: Today I'm going to confine my remarks to some of the lab data that we have generated. I'm really not going to talk very much about the epidemiologic situation in Hong Kong because I think you had a very good update by K. G. Fakuda at the end of January and I don't think I can really add very much to that as we have not finished testing all the sera that we have received from Hong Kong.

What we plan to do is complete all of the testing of the cohort sera and then release the results at one time. And we're having to test those sera using a variety of tests, including microneutralization, Western blot, and ELISA, so that we know how the results correlate for these different tests. So it's taking us a bit longer than we had originally anticipated.

First overhead. We have been collecting chicken jokes. So in case anyone in the audience has a chicken joke they would like to donate to the Hong Kong investigation team, please let us know.

We see that this incident in Hong Kong has given new meaning to: Why did the chicken cross the road? This one obviously was getting out of Hong Kong.

Next overhead, please. You probably remember from our January discussion that we have observed that there are really two genetic and antigenic groups among the strains isolated from humans in Hong Kong.

One group is represented by Hong Kong/156, shown in this column here. And the virus, the antiserum is along this column here and the antigen that's along this row here.

And we can see that antiserum to the Hong Kong/156 covers the Hong Kong virus itself quite well but really doesn't cover viruses in Group 2 particularly well.

We have continued to make antisera to a variety of viruses in Group 1 and Group 2. And this observation has pretty well held up. Antisera and this particular antiserum to Hong Kong/483, in contrast, covers viruses in both groups quite well.

So, once again, we're seeing a kind of asymmetric reaction in the hemagglutinin inhibition test so that serum to viruses from the second group seem to cover viruses in both groups better than antiserum to viruses in Group 1 do.

Next overhead, please. The other thing I should point out here is that -- and I could have

pointed it out in the previous HI table as well -- is that we had hoped that the duck/Singapore/97 strain might provide a good apathogenic surrogate virus which could be used instead of these highly pathogenic viruses. That is, they're highly pathogenic for chickens as well as for people. And so we had hoped that this duck/Singapore strain could be used perhaps as a vaccine candidate.

But, unfortunately, you can see the homologous titer is 120 here. And, unfortunately, viruses in this group are not terribly well-covered by the antiserum to the Singapore strain. And so we see that it's behaving similarly to the Hong Kong/156 antiserum.

The other antisera that we have here tend to cover the viruses in both groups better. And, in particular, we see that the antiserum to Isolate 491 actually covers viruses in both groups particularly well.

We have looked at the sequence of this, at the hemagglutinin of this strain carefully. And it has a very good match to the consensus sequence. So the sequence of 491 has a very good match to the consensus sequence for the Hong Kong strains.

And we have observed this in the past,

that when we have a virus that matches, that has an HA sequence that matches, well with the consensus HA sequence, antiserum to that virus tends to cover most of the strains that are circulating quite well.

Next, please. I'm just repeating an overhead that you had seen in January because I think it's quite interesting and just reminding you is worthwhile, I think.

We have color-coded the isolates as either Hong Kong/156-like or Hong Kong/483-like. And we see that we have three isolates from fatal cases in each group so that there isn't a difference in the severity of disease caused by these two different antigenic and genetic variants.

Next overhead, please. Sorry. On Page 21 of your handout, there is a dendrogram for the HA genes of the 16 human isolates that we have now sequenced. And I somehow didn't get an overhead of this in my package today. So we'll just look at this.

It's not quite as obvious in this dendrogram as it was on the dendrogram we had presented earlier, but there are two groups. If you draw a line right above the Hong Kong/481, this is the division between the two groups of viruses. And the antigenic profile of these strains actually matches

quite well the genetic differences that we're seeing.

We do know that there is one particular change that appears to be correlated with the antigenic change we see. And that is a difference in potential glycosylation site at amino acid 154 to 156 in the HA and viruses with the glycosylation site, those that match with the antigenic profile of the Hong Kong/483. So those are the viruses that cover -- antiserum to those viruses cover both groups better.

On Page 22, you'll see a dendrogram showing the evolutionary relationships among the N1 neuraminidase genes of these Hong Kong strains. And if you look carefully, you'll see that in general the pattern that's shown for the hemagglutinin gene is also reflected in the pattern that we see for the neuraminidase gene. We have I think 14 of the 16 neuraminidase genes sequenced at the present time.

So, in summary, in the next overhead, we can say that all of the viruses that were isolated from humans in Hong Kong have multiple basic amino acids at the cleavage site between the HA1 and HA2 domains of the hemagglutinin.

And, of course, we know that this feature is associated with highly pathogenic avian strains. We also know that these strains are highly pathogenic

for chickens.

All of the 14 isolates that we have sequenced the neuraminidase genes for have 19 amino acid deletion in the stalk region of the neuraminidase. And we can say that for all of the isolates that we have examined in detail, they contain all eight gene segments of avian origin. And there has not been reassortment between human and avian strains.

Okay. I think I'll just stop very briefly now and see if there are any questions. If there aren't, I'll just go on and make a few comments, more specific comments, about vaccine candidate development.

CHAIRPERSON FERRIERI: Why don't you proceed, Nancy? And people may think of other things to ask, then.

DR. COX: Okay.

UPDATE ON VACCINE DEVELOPMENT

DR. COX: I think vaccine candidate development is just a bit harder to get one's mind around if you're not thinking about this all of the time. And so I thought I would show some of the same overheads that I showed in January.

Just to remind you that one of the big

issues for us is safety, in working with these particular strains, we're concerned not only about the safety of our laboratory personnel but also about the fear that these viruses might escape and get into the poultry populations in the United States.

USDA regulations require that these viruses be worked with under P3+ containment, which means that, in addition to regular P3+ P3 conditions, you must be able to shower out of the facility.

I had mentioned in my presentation that we had hoped that the Singapore '97 strain would be a good surrogate apathogenic virus. We have been looking at that strain. And others have been looking at other strains to try to find a suitable one.

The second approach that we were considering was to remove the multiple basic amino acid cleavage site from the hemagglutinin and then rescue the genetically altered HA gene back into a suitable background.

Unlike other situations where influenza vaccine candidates are being developed, we realized early on that it would be necessary to test these particular H5N1 vaccine candidates for pathogenicity in chickens, mice, and in ferrets as well before any human trials could be done.

And then I just wanted to mention that we realized that all the normal characteristics that are required for a good vaccine candidate would be required for this one. It would have to have proper growth and processing characteristics for the vaccine manufacturers.

Next, please. I had mentioned that the duck sampler virus was examined in detail and doesn't appear to be ideal. It could work in an emergency situation, but, as we feel we have a bit more breathing room, we realize that this is not an ideal candidate. Some additional strains are being examined. And I think Roland may have a few comments later on.

And then, as I mentioned before, we were looking at the possibility of obtaining a human-avian transfectant, which would have the altered HA rescued into it. And the potential genetic backgrounds that the H5N1 could reside in were A/PR/8 and A/Ann Arbor/6/60.

We have been pursuing the A/PR/8 approach in our laboratory. And the folks at Aviron have been pursuing this avenue. And I'll mention a bit more about that later.

In addition, it would be possible to have

the modified HA rescued into an avian background. The researchers at the National Institute for Infectious Diseases in Japan are pursuing that, as are we. And this is the background that we are using at CDC.

Next, please. Now, there are a variety of strategies that one can take to alter the virulent multiple basic amino acid cleavage site that is associated with virulence.

And both at CDC and at Aviron, we have taken similar approaches to altering that site so that we will have an avirulent avian sequence or the human sequence itself.

Next, please. And where we are at the moment is that 7:1 reassortants that have H3N1 antigens have been made for use as helper viruses for the rescue of the altered HA genes. And these reassortants have either a human A/PR/8 or Ann Arbor genetic background. So this step has been reached in the U.S., the U.K., and Japan.

But, even better, now there are 6:2 reassortants available, both in Japan in an avian background and Aviron has also produced a 6:2 reassortant with the human Ann Arbor 660 cold adapted background.

Now, these strains are being tested for

pathogenicity. I believe Aviron is testing first in chickens. And those studies are ongoing now. I'm not sure of the status of the studies in Japan, but I know that they are proceeding as quickly as possible.

So, as I mentioned, candidates generated both with the Hong Kong/156 and with Hong Kong/483 are being tested in animal models. And then work is continuing in the U.S. and the U.K. to identify additional surrogate apathogenic strains and to generate additional transfectant viruses that might be suitable.

Okay.

CHAIRPERSON FERRIERI: Thank you, Dr. Cox.

Are there questions for Nancy? Yes, Dr. Kilbourne?

DISCUSSION

DR. KILBOURNE: Nancy, going back a bit, is this 19 amino acid deletion of neuraminidase, is that unique to these Hong Kong strains?

DR. COX: Yes, as far as we know. Now, there aren't a lot of neuraminidase sequences in Gen Bank, but, as far as we have been able to ascertain, it is unique to these strains.

DR. WEBSTER: Let me just add something. The chicken/Pennsylvania/N2 also had a deletion. And

some of the early human PR/8s, late PR/8s, also had deletion in that site. So they're not unique, but we see quite a lot of viruses.

DR. COX: But this is not the same. It's not an identical deletion.

DR. WEBSTER: No, it's not an identical deletion.

DR. KILBOURNE: No. I'm aware of that, Rob, but I just wonder whether this unique 19 amino acid stretch was sort of an identifier for these strains.

DR. WEBSTER: Not just for these strains.

DR. KILBOURNE: There are stalk mutants and deletion mutants.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Nancy, I wonder if you could just briefly summarize what's going on with regard to surveillance for H5N1.

DR. COX: There's really quite a bit going on. In Hong Kong itself, enhanced surveillance has been in place for some time. And the laboratories there have really been overwhelmed with the number of viruses that they have been processing. Of course, most of them had been H3N2 strains. But their surveillance is really excellent in Hong Kong itself.

In addition, efforts have been put in place to enhance surveillance in Guangdong Province in China. And we really have not a lot of information about what's going on currently there, but we do know that training has occurred, reagents have been distributed some time ago. And so the labs are fully capable of identifying H5N1 viruses should they be isolated.

We also know that they have stepped up surveillance in hospitals. So they're looking for cases that would be similar to those that had occurred in Hong Kong.

And then what is going on beyond that varies quite a bit from country to country. There were some things that were put into place in the U.K., for example, that were fairly similar to what was put in place in the United States, which is enhanced surveillance in emergency rooms again trying to focus on patients who were seriously ill with respiratory disease and from whom it might be most likely to isolate influenza viruses, particularly if they had been traveling in Asia recently.

So we're trying really to focus the surveillance as much as possible on those patients who would be most likely to be infected with the H5N1

viruses so as not to overwhelm the laboratory staff at the state and local levels.

I don't know if that tells you enough.

CHAIRPERSON FERRIERI: Yes, Dr. Hall?

MEMBER HALL: Can I just say: How about the surveillance in chickens, too? What does that consist of at this point?

DR. COX: Again, in Hong Kong, we believe that it's very thorough, particularly for chickens that are being imported. They're looking very, very closely at whether the animals have any antibody to any avian influenza viruses.

We don't really know how much surveillance has been stepped up in Guangdong Province in China, but they probably have increased surveillance in birds.

In the United States, I really can't say whether surveillance has been increased. I don't know if there's someone in the audience. If Rob could make a comment?

DR. WEBSTER: To my knowledge, there has been no increased surveillance, but there is basic surveillance still going on.

CHAIRPERSON FERRIERI: At the breeders, Dr. Webster? Where is the surveillance taking place,

then?

DR. WEBSTER: The surveillance goes on at the Ames Institute in Ames by Dennis Senney and others. And there is market surveillance going on in New York every two or three months. And, to my knowledge, there's no peptance for H5N1.

CHAIRPERSON FERRIERI: That's reassuring. Everyone is taught all the other dangers of chickens, which will be eradicated.

Other questions for Dr. Cox?

(No response.)

CHAIRPERSON FERRIERI: Otherwise, Dr. Levandowski may want to announce the ongoing aspects of the program this afternoon.

DR. LEVANDOWSKI: Okay. Sure. I'd be happy to do that. Next on the program, continuing with updates as to activities going on for vaccine development, Dr. Dominick Iacuzio from NIAID has some information to present on clinical trials and other activities.

DR. IACUZIO: Thank you for giving me an opportunity to update you on what I reviewed back in January. The first few slides actually I will review a few of the basics of what we were trying to do in response to at that time back in December and January

was what we thought of as sort of an urgent need to do something with preparing a vaccine.

We went ahead and prepared a recombinant HA, which is a purified recombinant protein. It's a hemagglutinin monovalent Type A. The HA sequence genes were cloned from the CDC material. This was done by Protein Sciences. And this is a recombinant HA. And it's produced in the baclovirus expression vector system in the spotofrida Fugiperida insect cells.

Next slide. Just to review, the recombinant HA protein has a lot of characteristics which are like the typical HA protein that is isolated or characterized from the traditionally grown HA. This, however, is uncleaved. And a lot of the other characteristics on this slide, Trypsin-resistant, glutenates, red blood cells, are characteristics typical of an HA.

Next slide, please. Protein Sciences prepared a vaccine for clinical use and this through a contract with NIAID. And the material is sterile for injection through the IM route. This particular material was at a ten-microgram per half a mil dose in single-dose vials.

And we had some preclinical challenge data

that was conducted by Mike Purdue at the USDA. And I believe he presented some data at the last January Council meeting.

We are continuing in this Phase I multi-center trial. And, just to review, it's ten micrograms per half a mil dose. There were two doses at a three-week interval. Again, this is a compromise, but we wanted to move quickly.

The subjects are adults or laboratory workers who are at increased risk since they are busily preparing or trying to prepare recombinant candidates for the traditional vaccine.

Primary endpoints here, we thought we would have the opportunity to collect safety and immunogenicity data on this recombinant H5. And we have right now seven sites lined up. Two international sites have contacted us. There are one or two that were interested, but I could talk more about that later.

Next slide. In the chronology of events, we are moving quickly here of when the first case was isolated and when I guess there is more of an intense need to move ahead.

The response of preparing the reagent-grade HA, the vaccine was prepared in January

when I talked last. And since that time, we have had an NIH IRB approval of the protocol.

In February, the first laboratory, five laboratory workers were immunized with the recombinant HA vaccine. And since that time, actually, in March, additional laboratory workers have been immunized. I have some more specifics about that in the additional slides.

The national time frame, just to give you an idea of how quickly things did move, the protocol was prepared for the IRB in January. I think we are now even better prepared if we had to go through this again.

FDA approval moved rapidly also in allowing us to proceed with the clinical study in February. The first laboratory workers, like I said, were actually immunized February 23rd.

Additional immunizations occurred on March 9th. The second site started vaccinating, actually, about a week ago. And Dose 2 was administered to the first five subjects last week. And additional sites, there are five domestic and international sites. But there have been several delays.

Next slide. We are learning through this experience to be better prepared in case we really

have to respond with the next in case of a pandemic. The actual numbers here are for Dose 1, we have 13 immunized just at the NIH Clinical Center. Dose 2, like I say, five were immunized last week.

The other site that is ongoing or up and running, I should say, is the St. Jude's site. In talking to my colleagues, another eight additional laboratory workers will be immunized this week, I believe.

We have run into some delays with the other U.S. sites. That includes CDC; the USDA, both Athens, Georgia and Ames, Iowa; additional workers at Protein Sciences who are going to be immunized through this GCRC at the University of Connecticut; and also laboratory workers at New York Medical College who are preparing high-growth reassortants.

Some of the delays that we have run into in trying to facilitate this whole process were identifying a principal investigator in a clinical site at a typical site that does research work. Sometimes that wasn't logistically easy.

We did do this for the FDA, for example, by using the NIH Clinical Center. And in the case of the University of Connecticut, the GCRC will work.

We have had problems with health clinics

at various agencies because recently a lot of these agencies have contracts with the health clinic. And to administer an experimental vaccine is problematic. We have run into hurdles where we didn't expect these. Local IRBs to review have at times been maybe unresponsive to what we thought was an urgent need, period.

The single products assurances have also induced delays. These are needed for NIH-sponsored studies, IRB approval of protocols and consents, of course, there's always a time lag.

And, like I said, there are liabilities for contract health clinics which are at these particular agencies. And the "i" word keeps coming up, the indemnification. Those involved with pandemic planning have been very much aware in the past, and also currently the indemnification is a real issue.

Next slide, please. We recognize that there are other H5N1 vaccine approaches. We would like to participate in a license-inactivated vaccine. There have been ongoing discussions. Maybe Roland might be able to talk a little bit about that.

There needs first to get the pilot lot production of a candidate. And, of course, we would be interested in a Phase I type of safety

immunogenicity study.

As Nancy mentioned, there are various or there are other approaches, not only the inactivated license vaccine, but Aviron has successfully made an Ann Arbor backbone of the cold adapted vaccine with the H5N1. And your exploring the possibilities or the concerns that would need to proceed to both prepare a pilot lot and to do safety testing.

In the meeting last week with a group in D.C. on vaccines, we came across the safety and containment issues for conducting a study like this.

I think that's it.

CHAIRPERSON FERRIERI: Thank you, Dr. Iacuzio.

Questions from the panel? Dr. Greenberg?

MEMBER GREENBERG: This is just for my own benefit. Baclovirus-expressed hemagglutinin for traditional hemagglutinins is a reasonable vaccine? I just don't know the --

DR. IACUZIO: We have in the past conducted -- I believe I had a slide, actually, for about seven studies or small studies of other recombinant HA. And we have shown in these studies -- and a few of these studies have been published -- to be safe and immunogenic.

In one study, -- it's a very small study -- there has been a hint of some type of efficacy. But it wasn't designed or powered to be an efficacy study.

CHAIRPERSON FERRIERI: Do you have an immunologic data on your vaccinees?

DR. IACUZIO: Not yet. According to the protocol, we plan to do the first bleed after the second dose two weeks post-dose. So that will be an additional week. And then we would do that first subset of subjects and to do exactly that.

We plan to do both the virus neutralization assays at CDC. Nancy Cox offered three times to do these additional assays for us together with a few other assays.

CHAIRPERSON FERRIERI: We're fine here at the table. Anyone else who would like to pursue further discussion on the vaccine or we will have Dr. Levandowski continue on, then, with his part of the program?

(No response.)

CHAIRPERSON FERRIERI: I think we should proceed, then, Ron.

DR. LEVANDOWSKI: Okay. Thank you. I just have a few brief comments on activities that

haven't been touched on before, both here at FDA and at other institutions.

Of course, our efforts are predominantly directed toward trying to support the inactivated influenza vaccines, which are the ones that are licensed now and the ones that we would have to rely on in the event of a pandemic for the widespread use. So I think it is natural that we would be concentrating in that area.

As you have heard, there are vaccine strains and reagents that are being produced in many places. And we haven't emphasized it. And I guess, even as I'm saying this, I'm not sure now because I think Nancy would have said something if it were so. But my understanding was that work is going on in Australia as well for some of this. No? Okay. I'd better not say much more than that.

But there are quite a few different centers that are involved. And the first thing I guess that I could comment on that we've done that we have something very positive on is the production of a sheep antiserum that can be used for standardizing vaccines.

As Dominick mentioned, from the Hong Kong/156/97 prototype strain, Protein Sciences has the

baclovirus-produced recombinant hemagglutinin. That was made available to us and also to the National Institute of Biological Standards and Control in the United Kingdom.

Both of us have now produced a sheep antiserum which could be used as a preliminary reagent for standardization of vaccines. This material we have in fairly good quantity. And it can also be made available for research purposes, for other types of purposes that might require a specific antiserum.

These antisera are particularly useful because the sheep, for some reason, does make a very clean antibody. And we would be happy to make that available.

In saying that we have this reagent, it's not the only reagent that we're likely to need. It's a reagent and not the reagent because, as Nancy was pointing out, there may be differences between strands.

So the specific reagent that we would want to have for experimental vaccines might be somewhat different or it might be a different hemagglutinin and that we need to use immediately, but, as with statements that we make every year about the utility of antisera that were not produced specifically for a

strand, these could be used as an interim reagent, even for strains that are not directly related.

We and others have received permits now to start and funding, I would say gratefully, to start work on some of the nonpathogenic strains. And a number of us have been working with the duck/Singapore strain, which Nancy also talked about at some length.

As she pointed out, it may again not be the ideal strain for work, but it is a strain for us to begin to get some experience with making reassortants. And we think that there could be other kinds of useful information we get out of that, whether that particular strain gets used for production or not.

I should mention that John Wood's lab at National Institute of Biological Standards and Control has been working with the duck/Singapore strain and has some experience with that.

And also Dr. Kilbourne's laboratory has begun some work. He may want to have some comments of his own in regard to production of some high-growth reassortants.

Our particular plans for the duck/Singapore strain are to just do some very basic reassorting to begin with. And we plan to make an H5

avian N1 PR/8 reassortant and also an H5 avian N2 Johannesburg neuraminidase reassortant as our first approximation. And we have some rationale for wanting to do that. And I would like to be a little bit provocative to the Committee and ask for some discussion on this point perhaps.

We have found in our laboratory in the past that strains that have the PR/8 neuraminidase tend to be among the best-growing viruses that we see. We don't use those for reassortant viruses for production today because we like to have the neuraminidase as close as possible.

But inactivated influenza vaccines are immunogenic and protective predominantly on the basis of their hemagglutinin, which is what we standardize the vaccines for. And I would ask if maybe either there would be some discussion about how it would be perceived if there were a vaccine that were made with the wrong neuraminidase; that is, a neuraminidase that wasn't the one from the prototype strain, understanding that if we use such a strain, it might permit larger-scale production of inactivated vaccines. It would be a trade-off between quantity versus quality in this sense.

There are some additional strains that we

have learned about. Nancy Cox alluded to that also. There has been an outbreak of an H5, pathogenic H5, infection in chickens in Italy, in poultry in Italy. And Dr. Webster may know some more about this as well.

Those strains, I guess serendipitously there was a strain that was isolated that's an H5 which is not among the pathogenic strains. This strain was isolated sometime earlier this year, I think January or February. And it's been sent to Waybridge, where it's being looked over now. And it is another strain which potentially could be useful as a surrogate strain for production of high-growth reassortants.

I don't know how closely related it is to the Italian pathogenic strain. And maybe Nancy Cox would have to confirm this, but my understanding of the pathogenic strain is that it's in the Eurasian lineage and it is antigenically quite similar to the Hong Kong strain.

Would you want to comment on that right now?

DR. COX: I don't know anything about its antigenic properties, but genetically it's closely related.

DR. LEVANDOWSKI: Okay. So genetically it

looks similar. Thank you.

Whatever we do, we're not sure how any of these strains are going to behave in manufacturing because it's not something that we've had experience with previously. And, as has been expressed, there are concerns about protection of the environment, both for us and for the manufacturers.

We have been looking into ways that we can collaborate with our colleagues at the Department of Defense. And I don't believe there's anybody representing DOD here in the audience to comment on what I'm about to say. But we have been in discussions with them as to a role that they could play in terms of producing experimental vaccine batches.

They have facilities where it may be possible for a somewhat higher level of containment for making vaccine than our regular manufacturers and could perhaps help us to get some early information about the strains that have already been discussed that are already in the pipeline.

And along those same lines, as a form of reassurance -- and maybe this is something else I would like to hear some discussion from the Committee on.

In terms of the strains themselves, as we're concerned about safety for the environment, of course, the initial studies would be to look in animals to see virulence properties. And I don't know whether we can do transmissibility but perhaps that.

But we have some ongoing discussions again with the Department of Defense about the potential for some studies in people to try to answer some questions about virulence and transmissibility of these strains that we anticipate may be used in real life for producing vaccines.

And I think I'll stop there and ask for some discussion.

CHAIRPERSON FERRIERI: Thank you, Roland.

You've heard Dr. Levandowski's comments and some of the questions he's posed for us. Would anyone like to address at least the first one on how you would perceive a vaccine that would have a different neuraminidase in it? Dr. Greenberg?

MEMBER GREENBERG: Can I get a clarification of how advantageous the PR/8 neuraminidase would be? Are you talking logs different? I thought that because if it's not substantially advantageous, I would assume that most people would want to have the homologous neuraminidase

candidate for what would be perceived as a totally new pandemic strain.

DR. LEVANDOWSKI: Okay. In terms of how much better than a reassortant that had the correct neuraminidase, generally the highest-yielding strains we see are always those that have PR/8 neuraminidase in our reassorting process. And we sometimes select against those.

They're not always that much higher. They're maybe twofold higher, but sometimes it's more than that. It may be fourfold or higher than that.

MEMBER GREENBERG: Is that a limitation for production? I mean, you don't normally need that for production; right? I mean, you always have the right neuraminidase traditionally with inactivated vaccines.

DR. LEVANDOWSKI: Yes. We have traditionally aimed to have the right neuraminidase because, in spite of not standardizing the vaccine for neuraminidase, the expectation is that neuraminidase might add something to the protection of the vaccine. But, again, we don't standardize for that. We don't always measure antibodies against neuraminidase.

In terms of the production, when we say a strain is two or fourfold higher by hemagglutination,

for the manufacturers, it doesn't always end up being two to fourfold higher in terms of their recovery of hemagglutinin for the vaccine at the end. There are steps in the process that have an effect on whatever their starting mass of hemagglutinin might be.

DR. SNIDER: I was going to ask: I mean, since we seem to have plateaued off at somewhere around 80 million doses, would this make a difference in the bottom line or would there have to be other changes made in the production process in order to get substantially more doses? Because here we're talking about trying to cover the entire population. And how far would that get us, could you guess?

CHAIRPERSON FERRIERI: Dr. Kilbourne?

DR. SNIDER: Do you have an idea or do any of the manufacturers have an idea?

DR. LEVANDOWSKI: You know, I think that's unknown. I don't really think I can answer directly. Would it, in reality, add something to the overall production of vaccine?

I can't say yes or no. I think we would have to see. It would have to be something that probably needs to be studied and some way to understand whether that would be beneficial or not.

CHAIRPERSON FERRIERI: Thank you.

Dr. Kilbourne, then Dr. Estes.

DR. KILBOURNE: Yes. A couple of things. As a lifelong proponent of neuraminidase, I would hate to see this happen, although I would accept Ronald's statement that probably the primary immunogen in our conventional vaccination procedure is the hemagglutinin.

I also disagree with his fundamental premise here. And I don't think we have sufficient systematic observations on reassortants to be able to make the statement that the addition of the N1 neuraminidase is necessarily equatable with high yield.

As a matter of fact, you can't do any better than X-31, which is a 6:2. And, even though we have a 7:1 reassortant in the lab to compare it with. It's no better.

I think that the question might be held in reserve for specific instances, but in general I couldn't quite go along with that.

CHAIRPERSON FERRIERI: Dr. Estes?

MEMBER ESTES: Well, I had the question about what studies have really been done looking at the effect of a heterologous neuraminidase. And if we don't have good data, maybe that's something that

someone should do those studies.

CHAIRPERSON FERRIERI: Any response to that, Dr. Webster?

DR. WEBSTER: No. I wasn't going to respond to it.

CHAIRPERSON FERRIERI: Well, I think that's a reasonable suggestion. And maybe Dr. Levandowski would like to respond to that or Dr. Iacuzio, one of you.

DR. KILBOURNE: I'd just like to add specifically in this instance, Ronald's position may be quite defensible because I don't think we yet know what the antigenic relationship of the PR/8 N1 is to the Hong Kong H5N1. And there may be sufficient heterovariant cross-immunity there. So it would not be a simple matter of just giving the HI antigen. I think there are all things that had to be explored in much more detail.

CHAIRPERSON FERRIERI: That sounds reasonable. Do you have any reasonable, Ronald or Dr. Iacuzio?

DR. LEVANDOWSKI: No. My response is that this is the sort of discussion I was hoping we would have.

CHAIRPERSON FERRIERI: Terrific. Okay.

Dr. Webster?

DR. WEBSTER: I think in principle in the face of a pandemic, that a vaccine that is not matched in the neuraminidase would be acceptable in an emergency situation. But when there's time, we should match the neuraminidase.

And at the moment, there isn't time to look at the other N1s that are available and avian species out there and make a double reassortant, put on one of the best matching avian neuraminidases. There are viruses N1 neuraminidases from swine from Europe and Asia that match quite well with this Hong Kong.

So I would, in essence, agree in an emergency situation use just the hemagglutinin.

CHAIRPERSON FERRIERI: Any other points? Any other further thoughts on the Committee's part regarding studies in people, transmission among people, in safety strains in the environment?

DR. WEBSTER: The other question that Roland raised was the wisdom of having a PR/8 donor for the high growth or an avian donor for the high growth, what is preferential.

I think we have to keep in mind that we have to be careful if we're putting a human genome

into an avian code. And we have to be careful with this, especially if we think using it as a live vaccine, even during production. This raises potential problems.

DR. KILBOURNE: Well, I would maintain PR/8 is no longer a human virus, as Bayer showed in his human volunteer experiments. I think we can be a little bit reassured by that. I'd be more concerned with perhaps putting this in the form of a live virus vaccine of any sort.

DR. WEBSTER: That's my main concern.

CHAIRPERSON FERRIERI: Other ideas or thoughts around the table? Are there any other issues that the three of you, Roland, wish to bring up that might help you as you move forward? Nancy Cox?

DR. COX: Just one question. I would like to get the opinion of the Committee on using this N1 which has the 19 amino acid deletion in it, in the reassortants. Are there concerns about using that particular neuraminidase to produce a vaccine candidate?

CHAIRPERSON FERRIERI: Very good question. Well, we have two experts here at the table. Dr. Webster?

DR. WEBSTER: There is some evidence from

Dr. Ayers' work years ago of the so-called stubbing neuraminidases being slightly less immunogenic than the more recent work of Dr. Cojuoca and Pelesi and others for very short neuraminidase stalks influencing both the immunogenicity and the viruses.

So it is something that has to be taken into account. In emergency situation, use it, but if it's possible, find one with a long stalk.

DR. KILBOURNE: I think most of the evidence would indicate that I know about that whether it's a short or long stalk doesn't make much difference in terms of antigenicity or immunogenicity. It makes a great deal of difference perhaps in terms of viral function, but I think you could expect good antigenicity from such a virus.

CHAIRPERSON FERRIERI: These are highly complex issues. And there may be representatives from news agencies, the media here. And we're talking about great potential differences in the structure of these viruses or antigenicity, immunogenicity, genetics.

If you can't have an answer to your question from what you have heard, then I suggest you not call me, as you may be prone to do, but to call the agency in order to feel that you are receiving the

absolutely recorded answers here that are in the public domain.

What is your number, Roland?

(Laughter.)

DR. LEVANDOWSKI: I'm in the book, at least for at work.

CHAIRPERSON FERRIERI: I always say, "Call CBER." And people say, "Spell that for me."

Are there other issues that anyone would like to bring up? We have the time to do it and the leisure today that we didn't have this morning. Dr. Snider?

DR. SNIDER: I'd just like to just a little bit more about the issue of the human transmission studies and under what circumstance you think or you were suggesting they might be important to do. I think you raised that, Roland, earlier.

DR. LEVANDOWSKI: Yes. Well, we have had feedback about concerns about manufacturing, in particular. Just as we're concerned about the laboratory workers who are getting these experimental vaccines, the manufacturers, too, have real concerns about their manufacturing workers.

I guess whatever can be done to try to get some reassurance that strains that we're making, which

whatever background they're on are not likely to be virulent or easily transmissible in people would be very useful or if it turns out that they are, to know that in advance so that measures could be taken to try to deal with that.

DR. SNIDER: So this primarily has to do with the safety of the laboratory workers who are working with the candidate vaccines?

DR. LEVANDOWSKI: Predominantly it would be protection of the environment, yes.

CHAIRPERSON FERRIERI: Any other thoughts?

(No response.)

CHAIRPERSON FERRIERI: Then I suggest we bring this session to a close. And I'll turn this over to Mrs. Cherry now.

OPEN PUBLIC HEARING

EXECUTIVE SECRETARY CHERRY: At this time we put additional time on the agenda for anyone who wishes to make a statement during an open public hearing session.

I've not been notified of anyone who wishes to speak, but this is your opportunity. Going? Going?

(No response.)

EXECUTIVE SECRETARY CHERRY: I guess

there's no one who wishes to speak, then. We'll call the open public hearing session closed for the day.

CHAIRPERSON FERRIERI: Thank you, Nancy.

We're not going to take a break now. We'll move on to Session 4, which is an open session on the Laboratory of DNA Viruses and Laboratory of Hepatitis Viruses. And an overview of the laboratory will be presented by Dr. Peter Patriarca from FDA.

DR. PATRIARCA: All right. One second.

CHAIRPERSON FERRIERI: No. Take your time.

(Pause.)

SESSION 4 - OPEN SESSION

LABORATORY OF DNA VIRUSES AND

LABORATORY OF HEPATITIS VIRUSES

OVERVIEW OF THE LABORATORIES

DR. PATRIARCA: I'm going to take about five minutes this afternoon to actually give a preview of what will be discussed later this afternoon. This presentation will be in two parts. I'll handle the first part for our products. And then Carl Frasch will follow me talking about bacterial products.

Just very briefly, what I'd like to do very quickly is give you an overview of our division, Division of Viral Products, which is responsible for

the regulation, review, and research related to viral vaccines and related products.

Our division at the present time is divided up into five laboratories, which are shown here. Two of these laboratories, namely the Laboratory of Hepatitis Viruses, headed by Dr. Steve Feinstone; and the Laboratory of DNA Viruses, headed by Dr. Andrew Lewis, were recently reviewed in December. And you will hear more about that a little bit later this afternoon.

What I have depicted here are the main disease areas that these laboratories are primarily interested in. But, again, I'll focus my comments very briefly on these two laboratories.

Beginning with the Laboratory of DNA Viruses, this laboratory has two main functions. The first is the review and evaluation of DNA virus vaccines and related products; secondly, recombinant gene delivery systems; and, finally, cell substrates and adventitious agent issues. This laboratory also, as you will hear, conducts research related to the regulation and use of DNA virus bioproducts.

Now, an important component of this laboratory is the Unit on Gene Expression headed by Dr. Jerry Weir. Jerry is in the audience. And if I

could just ask him to stand up now so that everyone could see him? Jerry was one of the people who was reviewed in December.

Jerry's research activities focus on three primary areas: first, to determine the cis-acting DNA elements regulating the expression of herpes simplex virus genes; secondly, to investigate the regulation of foreign gene expression and HSV vectors designed for gene therapy; and, then, finally, to evaluate the feasibility of DNA vaccination as a strategy for HSV vaccine development and at the same time to identify critical antigens that might be included in subunit vaccines.

Now, another important component of the laboratory is the Unit on Poxvirus Biology headed by Dr. Mike Merchlinsky. Mike is also here. And if I could ask him to stand up so that everyone can see him?

Mike's research program focuses in on two primary areas. The first involves the development and evaluation of vectors for the generation of poxvirus recombinants. And I would mention that Mike and his coworkers have pioneered a very extraordinary and innovative method that you'll hear about a little bit later on this afternoon.

And then, secondly, Mike and his colleagues identify and characterize viral genes that participate in the resolution of intermediates of viral DNA replication. This also is a very complicated process and line of investigation that you'll hear more about later this afternoon.

Now, the other laboratory in my division that was reviewed in December was the Laboratory of Hepatitis Viruses, which has three primary functions. First, the laboratory reviews, evaluates, and regulates hepatitis A and B vaccines, other hepatitis vaccines, and other related biologic products.

Secondly and perhaps equally importantly, the laboratory provides expert consultation to other CBER offices and especially the Office of Blood on hepatitis therapeutics and blood safety issues.

And, then, finally, the laboratory also conducts research related to the immunology, molecular biology, and pathogenesis of hepatitis A and C viruses.

Now, the person whose laboratory was reviewed is December is Gerardo Kaplan, who I don't think could be here today because of a conflict. No. I don't see him.

Gerardo's work has focused on four areas:

first, to identify non-primate cells that support the replication of HAV; secondly, to identify and characterize the cellular receptor for HAV. And this actually is something that he was actually able to do. It's an extremely important breakthrough that you'll hear more about this afternoon.

Thirdly, he's working on identifying internal factors required for HAV replication or blocking of that replication. This is very important in vaccine development and also for the creation of various diagnostics for HAV.

And, then, finally, he's developed a program looking at various small animal models to study HAV replication and pathogenesis.

So that's all I have this afternoon in the way of an overview. You'll hear more details later on this afternoon. And if there are no questions, we can proceed to Dr. Frasch.

CHAIRPERSON FERRIERI: Are there any questions? Are there any questions for Dr. Patriarca?

(No response.)

CHAIRPERSON FERRIERI: You can continue to speak if you wish, but what we're trying to accomplish is that before Dr. Frasch presents, that we're getting Dr. Apicella on the line. He was on my site visit

team when we did the visit.

(Pause.)

EXECUTIVE SECRETARY CHERRY: Hi, Dr. Apicella. This is Nancy. We're just ready to start. Dr. Frasch is going to give his little overview of the lab in open session.

DR. APICELLA: Okay.

CHAIRPERSON FERRIERI: Hello, Mike. This is Pat Ferrieri. Thank you so much for being able to join us today. We'll now do the overview of the Laboratory of Bacterial Polysaccharides by Dr. Carl Frasch. Again, this is open session.

You can hear us, Mike?

DR. APICELLA: Yes, I can hear you fine.

CHAIRPERSON FERRIERI: Thank you.

SESSION 5 - OPEN SESSION

LABORATORY OF BACTERIAL POLYSACCHARIDES

OVERVIEW OF THE LIBRARY

DR. FRASCH: Okay. First of all, I'm going to tell you that this will be one of the laboratories within the Division of Bacterial Products. The Division of Bacterial Products, as the name denotes, deals with all bacterial-related vaccines, such as DTP, the toxoid vaccines, and then also the polysaccharide vaccines. So my laboratory

obviously has all the polysaccharide vaccines.

I'd like to start off to tell you that together encapsulated bacterial pathogens are a leading cause of morbidity and mortality in both pediatric and elderly populations. Therefore, the scope of studies within the Laboratory of Bacterial Polysaccharides encompasses all non-enteric encapsulated bacterial pathogens. And this is reflected by the organization within the laboratory.

We have four different sections within the laboratory. The first section is headed by Dr. Margaret Bash. And that section is Molecular Epidemiology and Vaccine Section. She has --

DR. APICELLA: Excuse me. This is Dr. Apicella.

CHAIRPERSON FERRIERI: Yes?

DR. APICELLA: I can hardly hear Carl. Maybe he can speak a little louder or get the mike closer.

CHAIRPERSON FERRIERI: We have a microphone right over this gizmo here that is permitting us to hear you, but we'll try to do better. You can hear me fine?

DR. APICELLA: I can hear you fine.

CHAIRPERSON FERRIERI: Carl, we might have

to have you present from the table perhaps. If you come, Carl, and sit here where Nancy had been sitting and use her microphone, I think then Dr. Apicella can hear you.

DR. FRASCH: Mike?

DR. APICELLA: Yes?

DR. FRASCH: This is Carl.

DR. APICELLA: Yes, Carl. I can hear you now.

DR. FRASCH: Great. All right. I'm sitting at the table, rather than the podium.

DR. APICELLA: Okay.

DR. FRASCH: All right. So basically the Laboratory of Bacterial Polysaccharides has four sections due to the breadth of the kinds of studies that we're involved in.

The first section is headed by Dr. Margaret Bash. And she has now a staff fellow, a pediatric intern, and a technician working with her on meningococcal and now a gonococcal-related project due to a grant from Women's Health.

The second section is the Lipopolysaccharide Section headed by Dr. Chao-Ming Tsai concerning principally meningococcal lipopolysaccharides but also other

lipopolysaccharides. And I'll get into some of the studies that he has done in a moment.

The next section is the Pneumococcal Vaccine Section headed by Dr. Chi-Jen Lee. He has a visiting scientist with him and a technician. He is studying pneumococcal conjugate vaccines and pneumococcal conjugate vaccines as they relate to maternal immunization.

The last section of our laboratory is headed by myself. And we're interested in looking at the immune response to different bacterial polysaccharide vaccines. These involve immune response to meningococcal polysaccharides, pneumococcal polysaccharides, *H. flu* polysaccharides, and now more recently the Group G streptococcal, or GBS, polysaccharides.

So there are two ORISE fellows working with me and a technician on these studies. And these studies involve also distribution of U.S. reference materials for *Haemophilus* and *Pneumococcus*.

Let me show up a few slides very briefly highlighting some of the accomplishments of the laboratory. Okay. The first is we work on a better understanding of the protective immunity to encapsulate pathogens. We're working on --

CHAIRPERSON FERRIERI: We're just rearranging some seating here, Mike, so Carl can see the screen.

DR. FRASCH: I have to see the screen and talk, too.

CHAIRPERSON FERRIERI:Can you hear him now?

DR. APICELLA: Yes, yes.

CHAIRPERSON FERRIERI: Thank you.

DR. FRASCH: Sorry for the confusion.

So, anyway, we're working on a better understanding of protective immunity encapsulated pathogens. We're working on improved Group B meningococcal vaccines. This is a study we're doing in collaboration with some laboratories in Brazil.

We're working on pneumolysin as a protein carrier for more broadly specific pneumococcal vaccines. We're concerned that the present conjugate vaccines may need to provide somewhat broader protection. So we think if we use a common pneumococcal antigen, then we may be able to increase the specificity.

Then we're working on immuno assay development and standardization for comparative devaluation of conjugate vaccines. As I mentioned, we helped develop the standard *Haemophilus* assay. And we

distribute a reference serum throughout the world for *Haemophilus*.

We have done similarly for several of the pneumococcal types. And we distribute a reference serum internationally for measuring pneumococcal antibodies. This is particularly important now that there are several efficacy trials going on for pneumococcal conjugate vaccines.

Not on this slide is our work, more recent work, with the Group B streptococcal assay standardization. And we'll actually be presenting, having a workshop on some of our results in about two months.

Okay. Other people in our laboratory are working on improved identification of meningococcal disease. We have developed a number of PCR probes for identification of meningococcal meningitis using from either the blood or the CSF.

This has become important because we're collaborating with the Government of New Zealand because they're having an epidemic of Group B meningococcal disease. And we hope to help them when they apply a vaccine to try to prevent a disease.

We're working on studies for prevention of gram-negative septic shock. And we're trying to

understand better the *in vivo* biological activities of meningococcal LOS. And we have been trying to work on some anti-endotoxin peptides.

Another area is we're working on better methods for control of licensed vaccines. For example, Dr. Tsai in our group has developed a highly sensitive and specific quantitation method for *Haemophilus* polysaccharide in combination vaccines using a Dionex HPLC method.

This is particularly important with the combination vaccines that may contain whole cell pertussis and other components which essentially prevent the chemical identification of the *Haemophilus* polysaccharide, but Dr. Tsai has developed a method where one looks at the unique *Haemophilus* subunit and can quantitate that polysaccharide in all vaccines that we have looked at.

We are now extending these studies to try to look at some of the meningococcal Group A and Group C, see if we can apply the same method for that because these polysaccharides are only in clinical studies and may end up being in combination vaccines.

And, lastly, we're working on new methods for construction of lipopolysaccharide-based conjugate vaccines.

Okay. This slide is to illustrate that members of our laboratory have international recognition or at least recognition outside of FDA because our members participate with ad hoc reviews for NIH; CDC; MRC; Canada, for example; American Cancer Society.

We have worked with the WHO to draft requirements for *Haemophilus* conjugate vaccines, Vi polysaccharide vaccines. We have been consultants to CDC, PAHO, WHO. And some of our people have been scientific advisers to the Japanese and Taiwan governments. So the last slide simply shows some of the things, in conclusion, where we think our laboratory has had an impact on CBER research and medical science in general.

We have identified new conjugate vaccine antigens. We have improved case identification for clinical trials of meningococcal vaccines, developed better methods for characterization of the Hib conjugate vaccines -- and, as I say, we're trying to extend those to other conjugate vaccines -- develop standardized methods for measurement of anti-polysaccharide antibodies to *Pneumococcus*, *Meningococcus*, Group B strep, and so on.

Thank you.

CHAIRPERSON FERRIERI: Thank you, Carl.

Are there questions for Dr. Frasch in the Lab of Bacterial Polysaccharides? Last chance.

It looks like there are no questions, Carl. Thank you so much.

EXECUTIVE SECRETARY CHERRY: We have to take a break now.

CHAIRPERSON FERRIERI: We have to take a break now so that we will clear the room of those who are not validated by the FDA leadership. Dr. Goldberg is in the audience. Dr. Hardegree is here, Dr. Egan. Dr. Patriarca can stay. Dr. Burns I believe can stay as well.

I hope I'm not losing members of the Committee. We will be voting on the reports that we conducted.

EXECUTIVE SECRETARY CHERRY: I would ask all the members of the Committee to try to stay. We need these votes.

CHAIRPERSON FERRIERI: If anyone is leaving, could you please let me know? We have an official break here while we're getting the room cleared.

(Whereupon, the foregoing matter was concluded at 3:55 p.m.)