FOOD AND DRUG ADMINISTRATION

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE

AND

VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE

+ + + + +

JOINT MEETING

+ + + + +

THURSDAY
JULY 27, 2000

The joint committee met in open session at 9:23 a.m. in the Versailles Ballrooms I, II and III of the Holiday Inn, Bethesda, Maryland, Dr. Paul Brown, Chairman of the TSEAC, and Dr. Harry Greenberg, Chair of VRBPAC, presiding.

PRESENT:

PAUL W. BROWN, M.D.	Joint Committee Chair
HARRY B. GREENBERG, M.D.	Joint Committee Co-Chair
ERMIAS D. BELAY, M.D.	TSEAC
DAVID C. BOLTON, Ph.D.	TSEAC
DONALD S. BURKE, M.D.	TSEAC
DEAN O. CLIVER, Ph.D.	TSEAC
ROBERT S. DAUM, M.D.	VRBPAC
MARY K. ESTES, Ph.D.	VRBPAC
BRUCE EWENSTEIN, M.D., PhD	TSEAC
LISA A. FERGUSON, D.V.M.	TSEAC
PATRICIA FERRIERI, M.D.	Temporary Voting Member
BARBARA LOE FISHER	VRBPAC Consumer Rep
DIANE E. GRIFFIN, M.D., PhD	VRBPAC
ALICE S. HUANG	VRBPAC
KWANG SIK KIM, M.D.	VRBPAC
STEVE KOHL, M.D.	VRBPAC
PETER G. LURIE, M.D.	TSEAC
JOHN F. MODLIN, M.D.	Temporary Voting Member

PRESENT: (continued)

MARTIN MYERS, M.D.	Temporary Voting Member
PEDRO PICCARDO, M.D.	TSEAC
RAYMOND P. ROOS, M.D.	TSEAC
DIXIE SNIDER, JR., M.D.,PhD	VRBPAC
DAVID S. STEPHENS, M.D.	VRBPAC
SHIRLEY JEAN WALKER	TSEAC Consumer Rep
ELIZABETH WILLIAMS, DVM,PhD	TSEAC

I-N-D-E-X

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

(9:23 a.m.)

DR. FREAS: Could I ask you to take your seats, please. We will begin. We are behind on the time schedule. If you take your seats, we are going to go ahead and resume this committee meeting.

I would like to welcome the public to the open session of this joint meeting of the Transmissible Spongiform Encephalopathies Advisory Committee and the Vaccines and Related Biological Products Advisory Committee.

At this time, for the members of the public, I would like to go around and introduce the members of the committees seated at the tables. I will start on the righthand side of the room. The first nine individuals are members of the Vaccines and Related Biological Products Advisory Committee, and if they would raise their hands when I call their name, I would appreciate it.

At the end of the table is Dr. Dixie Snider, who is Associate Director for Science, Centers for Disease Control and Prevention.

In the next chair is Dr. Mary Estes, the Professor of Molecular Virology, Baylor College of Medicine.

In the next chair Dr. Steve Kohl, Adjunct Professor, Department of Pediatrics, Oregon Health Sciences University.

In the next is Dr. Alice Huang, Senior Counselor for External Relations, California Institute of Technology.

Next is Dr. Robert Daum, Professor of Pediatrics, University of Chicago Children's Hospital.

in the next chair is our Consumer Representative for the Vaccines Advisory Committee. That is Ms. Barbara Low Fisher, Co-founder and President, National Vaccine Information Center, Vienna, Virginia.

In the next chair is Dr. David Stephens, Professor of Medicine, Microbiology and Immunology, Emory University School of Medicine.

Next is Dr. Diane Griffin, Professor and Chair, Molecular, Microbiology and Immunology, Johns Hopkins University.

Next is Dr. Kwang Sik Kim, Division Chief, Pediatric Infectious Disease Division, Johns Hopkins University.

Next is a temporary member for today's meeting, and that is Dr. John Modlin, Professor of Pediatrics and Medicine, Dartmouth-Hitchcock medical

Center.

Around the corner of the table is another temporary voting member for today, Dr. Patricia Ferrieri, Professor, Departments of Laboratory Medicine, Pathology and Pediatrics, University of Minnesota.

Next is another temporary voting member for today, Dr. Martin Myers, Acting Director, National Vaccine Program Office, Centers for Disease Control and Prevention.

Next is the Chairman of the Vaccines and Related biological Products Advisory Committee who is acting as Co-Chair for today's meeting, and that is Dr. Harry Greenberg, the Grant Professor of Medicine, Microbiology and Immunology, Senior Associate Dean for Research, Stanford University Medical School.

In the next chair is the Chairman of the TSE Advisory Committee and the Chairman of today's meeting. That is Dr. Paul Brown, Medical Director, Laboratory of the Central Nervous System Studies, National Institute of Neurological Disorders and Stroke.

In the next chair is Dr. Raymond Roos, Chairman, Department of Neurology, University of Chicago.

At the corner of the table is Dr. Peter Lurie, Medical Researcher for Public Citizen's Health Resource Group, Washington, D.C.

Next is the Consumer Representative for the TSE Advisory Committee. That is Ms. Shirley Walker, Vice President of Health and Human Services, Dallas Urban League.

Next is Dr. Bruce Ewenstein, Clinical Director, Hematology Division, Brigham and Women's Hospital.

Next is Dr. Ermias Belay, Medical Epidemiologist, Centers for Disease Control and Prevention.

Next is Dr. David Bolton, head of the Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

Next is Dr. Pedro Piccardo, Associate Professor, Indiana University Hospital.

Next is Dr. Lisa Ferguson, Senior Staff Veterinarian, U.S. Department of Agriculture.

Next is Dr. Donald Burke, Director, Center for Immunization Research, Johns Hopkins University.

Next is Dr. Dean Cliver, Professor, School of Veterinary Medicine, University of California, Davis.

At the end of the table, Dr. Elizabeth Williams, Professor, Department of Veterinary Service, University of Wyoming.

There are three standing members that are not attending today. They are Dr. Stan Prusiner, Dr. Jeffrey McCullough, and Dr. Walter Faggett.

I would now like to read into the record the official conflict of interest statement for this meeting.

The following announcement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting. Pursuant to the authority granted under the committee charter, the Director, Center for Biologics Evaluation and Research has appointed Doctors Linda Detwiler, Patricia Ferrieri, and Martin Myers as temporary voting members.

In addition, the Senior Associate Commissioner of FDA has appointed Dr. John Modlin as a temporary voting member.

Based on the agenda made available, it has been determined that the agenda addresses general matters issues only. General matters waivers have been approved by the agency for all special government employees participating for this meeting.

The general nature of the matters to be discussed by the committee will not have a unique and distinct effect on any of the participants' personal or imputed financial interests. In regards to FDA's invited guests, the agency has determined that the services of these guests are essential.

The following reported interests are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by these guests:

Dr. Ronald Dobbelaer is employed by the Biological Standardization Scientific Institute of Public Health, Louis Pasteur, in Brussels, Belgium.

Dr. Walter Orenstein is employed as the Director of the National Immunization Program at the Centers for Disease Control and Prevention.

Dr. Suzette Priola is employed at the Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, NIH.

Dr. Jean-Hugues Trouvin is employed by the Department of Biologics, APSS, APS, in France.

Dr. Gerald Wells is employed at the Veterinary Laboratories Agency in Weybridge, United Kingdom.

Dr. John Wilesmith is employed at the

Veterinary Laboratories Agency in Weybridge, United Kingdom.

in the event that discussions involve specific products or specific firms for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted on the public record.

A copy of the waivers 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 previous financial involvement with any firm whose products you may wish to comment upon.

So ends the reading of the conflict of interest statement. Dr. Brown, I turn the microphone over to you.

CHAIRMAN BROWN: Thank you, Bill. Welcome, everyone, to this meeting. I thought I would open by telling you a little story that might have consequences for the members of my committee.

I sent a little review of the whole BSE new variant CJD problem to the journal Neurology about two months ago, and I'd like to read the committee the one paragraph review by a reviewer of this submission.

"I feel that the amount of novel information is equal to zero and that this short paper does nothing more, in addition to providing some questionable justification for the arbitrary decision made by the panel of which Paul Brown was president of the Federal Drug Administration to defer blood donations from donors that have resided in Great Britain for more than six months. That particular decision rested and continues to rest on a very weak scientific background, and the attempts by Dr. Brown to defend that position in the present paper remain rather unconvincing."

So you can see that the participation on these committees is not without its own risk.

The background information which was supplied as a summary for the present meeting is a very lucid and concise document, and I'd like to read three or four paragraphs that seem to me to have generated this meeting at this time, and they are extracted from this background summary information. But I think the chronology is important.

In a letter to manufacturers in December of 1993, the FDA recommended that bovine materials from BSE countries should not be used in biological products.

Second statement: Uncertainties about BSE-free status of certain countries led to the inclusion of all of Europe in the list maintained by the USDA. There has been no general guidance issued advising manufacturers on how to proceed in the event that a country used as a source of bovine derived materials is subsequently added to the USDA list.

Third statement in April 2000: CBER sent a letter to manufacturers including the recommendation that bovine derived materials from countries in which BSE is known to exist or from countries whose BSE status is unknown not be used in the manufacture of biological products.

The last statement: The FDA has recommended that bovine derived materials from countries in which BSE is known to exist or from countries whose BSE status is unknown not be used in the manufacture of biological products. The agency has learned that this recommendation for U.S. licensed biological products has not been universally followed by vaccine manufacturers.

I think the chronology of those four statements will set the scene for why this particular meeting exists.

We have a number of presentations from

speakers invited by the FDA this morning. They will be followed by comments and presentations by two of the manufacturers, and these are not the manufacturers implied in the last statement that I mentioned. Finally, we will have an open public hearing and discussion and presentation of a number of questions which the FDA would like discussed by this committee.

Today there will be no formal voting on any of the questions. There will be discussion only, and we will be sure and cover specifically two or three items which the FDA is particularly interested in having opinions about.

I now invite as the first presentation this morning introductory remarks by Dr. Egan from the FDA. Dr. Egan.

DR. EGAN: Thank you very much. Good morning. On behalf of the Office of Vaccines Research and Review, I'd like to welcome the members of the Transmissible Spongiform Encephalopathy and the Vaccines and Related Biological Products Advisory Committees to this joint meeting and to express my gratitude to all of you for being here, and in many cases rearranging your schedules to do so.

I'd like to take a few minutes to provide the background and history for this meeting and an

outline of what we hope to accomplish today. I will also go over the questions for discussion. There are no issues, however, on which we have asked for a formal vote.

The potential for contamination of biological products with the agent of bovine spongiform encephalopathy, BSE, has been a concern of the Center for Biologics Evaluation and Research and the Office of Vaccines Research and Review for many years.

CBER has recommended that bovine derived materials from countries in which BSE is known to exist or whose BSE status is unknown but suspect not be used in the manufacture of biological products. Manufacturers have been referred to the USDA listing for the BSE status of a particular country. Recommendations, however, were not offered by FDA on how to respond to changes in the USDA list that would affect existing vaccines as new countries are added.

The appearance of new variant Creutzfeldt-Jakob Disease in the United Kingdom and its attribution to oral exposure to the infectious agent of BSE have raised concerns regarding the potential for human exposure to the BSE agent that might result from the use of bovine derived materials in the

manufacture of vaccines.

No evidence exists that any case of variant CJD has resulted from the administration of a vaccine product. However, the theoretical risk of disease that might result from contaminated vaccines needs to be considered.

Earlier this year during the review of a regulatory submission, we learned that CBER's aforementioned policy on the sourcing of bovine products has not been universally followed. This finding prompted the Office of Vaccines to conduct a general review of all licensed vaccines.

The requested in depth review of sourcing of bovine materials for vaccines has been completed by nearly all manufacturers and submitted to the Office of Vaccines. Personnel within the Office of Vaccines have been reviewing these responses, and that review is essentially complete. A few uncertainties remain, and these are being looked into further. The uncertainties that remain, however, do not present any new type of issue.

Let me be more specific now about the nature of the issues regarding the sourcing and use of bovine materials. Fetal calf serum sourced from the United Kingdom prepared during the mid-1980s has been

used in the preparation of certain cell and viral seed banks.

Beef broths prepared from skeletal muscle or skeletal muscle plus pancreatic tissue that were sourced from Europe, specifically Germany, Denmark, the Netherlands and Poland, have been used in bacterial fermentations.

Polygeline prepared from bovine bones sourced from Germany, Italy, Austria, and Switzerland has been used in the preparation of a master bacterial seed bank.

Bovine hemin has been used as a component of a bacterial culture medium.

Several other bovine derived materials of European source have been used in the preparation of bacterial seeds.

This listing that I've just given fairly well covers the range of all issues. We have not considered milk derived products such as amino acids or lactose or tallow derivatives such as glycerol to be problematic, now have we considered bovine materials sourced prior to 1980 to be problematic.

The affected bovine materials would be classified as Category III and IV materials in the European Union scheme. That is, materials having low

or no demonstrated infectivity. The European categorization scheme is based on scrapie infectivity in sheep and goats, and the European Union has noted that infectivity in BSE infected cattle appears to be much more restrictive.

The experimental data on BSE infectivity that we would really like to have is, to our knowledge, not in the literature. There are a number of assumptions that must be made in making estimates of risk for these issues.

Moreover, the experimental data that does exist, in many cases, only establishes a boundary, for example, that the infectivity of a particular material is less than a certain number of units, although that material's infectivity could be orders of magnitude less than the experimentally demonstrated limit.

There are limits to how much material can be injected into animals. We recognize that one cannot prove absolutely no infectivity, but we certainly would have desired lower limits to have been determined.

In the presentations by Doctors Vann and Berkower later this morning, we will be presenting risk calculations that incorporate a number of these assumptions and that reflect these boundaries. They

are very, to us, conservative estimates.

Differing risk evaluation, depending on the assumptions that are made, will lead to differing conclusions, and your own evaluations may differ markedly from ours. That is why we are here today. We seek your expert opinion in defining potential risk.

For a number of these issues, manufacturers have agreed to and have begun to take corrective actions. For example, manufacturers have committed to changing beef sources for bacterial fermentation broths and culture medium components. Additionally, several manufacturers have indicated a willingness to re-derive cell or seed banks as necessary.

Now since manufacturers are taking these corrective actions, why are we then here? The answer is primarily that corrective actions take time. New materials such as beef broths need to be made and qualified, and following qualification new batches of vaccines need to be manufactured, formulated, and tested. For some products, this will take on the order of one year. Realistically then, we do not expect new products to be able to reach the market until the fall of next year.

Additionally, we are seeking guidance from the committee on the need to re-derive master seeds, not working seeds but the master seeds. We are requesting an estimate of risk, if any, that these products might pose, and your expert opinions for forming an interim policy for the use of the existing vaccines.

We are, moreover, requesting your opinions on dealing with investigational products that have similar issues regarding bovine sourcing, and in this context we need to consider both new vaccines as well as currently licensed vaccines that are components of an investigational product -- for example, a new combination vaccine.

Let me now go over the questions that we would like you to consider. I will clarify these questions, if needed, so that discussions on the following presentations can be appropriately focused.

In the first question we are asking the committee to please discuss the potential risk presented by the use of bovine derived materials sourced from Europe, including the United Kingdom, in currently licensed vaccines.

In this discussion we would like you to please comment on the various risk estimates that have

been presented to the committee, and in this discussion to please include: Preparation of bacterial and viral, master and working seeds, preparation of master and working cell banks -- for example, the use of fetal calf serum; to consider to include fermentation processes -- for example, the use of bovine derived media components; the formulation of the final products -- for example, the use of gelatin in their formulation; and additionally in this discussion, please include some risk assessment for bovine materials sourced at differing times from differing European countries, U.K., Germany, France, etcetera.

As a second question for discussion or point for discussion, we would like the following: The following item pertains to currently licensed U.S. vaccines that contain bovine derived material obtained from Europe, including the United Kingdom. We would like the committee to please discuss those circumstances, if any, under which FDA should take specific regulatory actions regarding these vaccines.

Some examples of regulatory actions which are available to the FDA include product recall, modification of the package insert or issuance of a "Dear Doctor", "Dear Health Care Provider" letter or

some combination.

Finally, question 3: This item pertains to investigational -- that is, non-U.S. licensed -- vaccines that contain bovine derived materials obtained from Europe, including the United Kingdom. This includes certain investigational vaccines used under IND that contain currently licensed vaccines as components, such as components of a new combination vaccine. In addition, this includes the usual investigational vaccines without previous U.S. licensed components.

In the presentations by CBER personnel this morning, Dr. Asher will provide an overview of BSE epidemiology and FDA policy, and Doctors Vann and Berkower will provide overviews of the manufacturing process for bacterial and viral vaccines respectively, indicating points in the process where bovine source materials have been used and approximate amounts of these materials.

Estimates of risk from bovine source materials will also be presented by Doctors Vann and Berkower for these viral -- for these bacterial and viral vaccines.

I'll try to answer any questions that you might have at this time.

CHAIRMAN BROWN: Does the committee have any questions for Dr. Egan? Thank you, Dr. Egan.

DR. LURIE: Can you explain as far as possible when it was that the problem that we are here addressing came to the attention of the FDA, and how it was that -- Well, why don't you answer that question first.

DR. EGAN: It first came to our attention or to our attention within OVRR of these issues around March of 2000. So a few months ago.

DR. LURIE: I wonder if you can just react to my concern about this. My concern is that it's taken some four months to put together a meeting to discuss this issue, which I think is risky on the part of FDA in that it invites a period of percolating of sometimes not accurate scientific information in the general public.

So I'm wondering why it took quite so long to call this meeting.

DR. EGAN: I think there were a number of issues that were involved. First, we were trying to get some initial assessments for risk on our own from the manufacturers and evaluate those, and then to work on trying to get a review of all vaccines, having all the manufacturers go over all vaccines so that we

could present a comprehensive list of issues to the committee.

Then there are some times that it takes to prepare materials for the committee, our own presentations and other materials to get to the committee, and there is some time that it takes to announce the committee meeting in the Federal Register and have sufficient time for the public.

I understand that you do regard that as lengthy.

DR. LURIE: I guess my reaction to that is -- I mean, among the list of options, perhaps not a likely one but among the options that you listed was the option of recall. It sort of seems somehow contradictory to be having the meeting four months later where the subject is recall.

It seems to me that a clear message from taking as long as it took to put the meeting together is that, you know, there is little risk. Now that may be true, but I guess that's the point that I'd like to drive home. It seems that it's taken a wile.

Let me ask you another question. In the very important December 17, 1993, document -- I don't know if you were at the agency at the time in which FDA wrote to the manufacturers of FDA regulated

products -- the statement is we request that bovine derived materials from cattle which resided or originated from countries where BSE has been diagnosed, etcetera, etcetera, not be used in the manufacturer of FDA regulated products intended for administration to humans.

What about that statement, if anything, seems unclear to you?

DR. EGAN: I think the statement is clear.

DR. LURIE: Yeah. So do I. And my next question is: Later in the same letter comes the following statement: The agency is considering rulemaking to restrict the use of bovine derived materials from BSE countries. This is in December of 1993.

Can you tell us what the fate of that consideration was?

DR. EGAN: I don't believe -- There was not rulemaking by the agency.

DR. LURIE: Can you explain why?

DR. EGAN: No, I cannot.

DR. LURIE: Does that seem to you, in retrospect, to have been a mistake?

DR. EGAN: You know, I think that's probably an issue that we could debate a lot about

whether rulemaking is required or whether the existing flexibilities that exist with the agency to deal with it are sufficient. I could probably give you personal opinions.

CHAIRMAN BROWN: Can we come back to this perhaps in the open discussion rather than linger on with Dr. Egan? I think these are kinds of questions that would be equally appropriate in the discussion.

DR. LURIE: It's only that he's at the microphone.

DR. EGAN: Yes. To answer your first question, yes, I was at the agency in 1993, but in a different capacity.

CHAIRMAN BROWN: Thank you very much, Dr. Egan. We now will have an overview of the U.S. vaccination program presented by Dr. Orenstein from the Centers for Disease Control. Dr. Orenstein.

DR. ORENSTEIN: Thank you very much. I don't know whether -- I guess it's through a computer presentation rather than slides. Okay, we have both here.

DR. FREAS: It's your choice.

DR. ORENSTEIN: Okay. Well, if somebody will run the computer, I'll just talk about next slides.

The title of my talk is an Overview of the U.S. Vaccination Program, and I've been asked by the FDA to review the benefits of and, hence, needs for vaccines in the U.S. As you review potential risks of vaccines today, it's important to place any risk evaluation in context with the benefits in order to formulate the most appropriate policies. Can I have the next slide, please.

Last year as we came to the end of the Twentieth Century, CDC looked back on what it considered were ten great public health achievements. Among those ten great public health achievements of the Twentieth Century, vaccination was listed and, in fact, was the first of a series of ten articles on major public health triumphs during the Twentieth Century. Next slide, please.

Vaccines are considered one of the most cost effective measures of preventive health. In 1995 Tengs, et al. published an analysis of 310 life saving health care sector interventions. of those 310 publications, six involved vaccines -- Six of the 45 identified were cost savings that were vaccine related. All published childhood cost/benefit or cost effectiveness analyses showed society saved money for childhood vaccination, and this doesn't include some

unpublished information or later evaluations. Next slide, please.

We have achieved some of the highest immunization rates in this country for routine childhood immunization. For most of our vaccines among 19- to 35-month-old children, a median age of 27 months, we have coverage rates of 90 percent or higher. For hepatitis B we are approaching 90 percent, at 88 percent, and varicella vaccine, which is a newly licensed vaccine in '95 recommended for universal use in '96, we are beginning to see exponential increases in coverage with approaching 60 percent in our last measurements. Next slide, please.

This is a slide updated from an April 1999 MMWR article that looks at, for eight vaccine preventable diseases or, in the case of congenital rubella, a complication, what their representative annual Twentieth Century morbidity taken from data or estimates during the early to the mid-Twentieth Century and what happened in 1999.

What we've achieved is 95.9 percent or greater reductions in all of these diseases, and for many of them through rounding we get to minus-100 percent. To highlight a few, diphtheria as a disease is virtually gone in this country, although the

organism persists, and we do run risks if vaccination levels fall of a return of diphtheria.

Measles, which I'll cover in more detail, we believe, is no longer circulating in the United States. Rubella is essentially gone in the United States. It is now primarily a disease of Hispanic populations, Hispanic populations who grew up in countries that at the time were not practicing rubella vaccination. And hemophilus influenza Type B, which at one point is estimated to have caused 12,000 cases of meningitis and 20,000 cases of invasive disease, is now, when it occurs, often a grand rounds case. People are brought around to see such a rare illness. Next slide, please.

This is to remind us of what used to occur in this country. This is a slide form the Rancho de los Amigos Hospital in Los Angelos during the 1950s showing a ward full of persons on iron lungs or Drinker respirators. During the 1950s, we had an average of about 16,000 paralytic cases a year in the United States, and over 1800 deaths. Next slide, please.

This slide shows what has happened with polio in the United States, first with the introduction of inactivated vaccine and then oral

vaccine. Polio has been eliminated in the United States. The last indigenously acquired cases of polio in the U.S. occurred in 1979. There have been no wild virus induced polio cases since 1979 acquired within the U.S.

Nevertheless, we continue to be at risk of polio. While there is a worldwide eradication effort underway, we still have about 30 countries in the world that are endemic for polio, and the World Health Organization estimates that roughly 20 will still be endemic by the end of this year. Hence, if polio vaccinations drop, we run the risk of a return of epidemics of polio. Next slide, please.

This is a slide classically taken from Krugman and Sam Katz and others showing the clinical course of measles. I put this in here to show that measles is not a trivial disease. A typical case often had fever between 103 to 105 degrees, multiple systemic symptoms including conjunctivitis or photophobia, coryza, and often a severe, intense cough. Next slide, please.

To further emphasize that measles is not a trivial disease, these are cases reported to CDC between 1985 and 1992, showing that 29 percent had at least one complication, including diarrhea, ear

infections, pneumonia, about one in 1,000 with severe encephalitis, and about one in 500 who died.

About 18 percent of the cases were hospitalized, and we learned during a resurgence how young physicians who had not seen measles were really misled by the toxicity, and we heard anecdote after anecdote of kids without complications being admitted to hospitals, because the kids looked so toxic, and they were suspecting something else was going on. Next slide, please.

This shows you what has happened with measles in the United States. Vaccine was licensed in 1963. We've seen a dramatic reduction, but we've had three major outbreaks of measles in the United States, the last between 1989 and 1991 in which we had over 55,000 cases, over 11,000 hospitalizations, and officially reported 102 deaths from measles during that period.

We have now achieved substantially higher vaccination coverage than we had at that time, and we believe all measles in the U.S. today is not endemic circulating measles but measles from foreign importations with limited domestic spread. Next slide, please.

This slide doesn't show up. It would show

in the slides. But let me put it -- We still run the threat of reintroduction of measles and, if coverage falls, of measles epidemics. During the three-year period 1997 to 1999, there were 116 international importations of measles into the U.S. They infected 32 states and the District of Columbia, and infected 78 counties. There's a clear need and a clear threat for measles vaccine, and a clear threat for the reintroduction of measles. Next slide, please.

We often give statistics and numbers, and I'd like to, with your forbearance, read a clinical description. This was put together by Lloyd Olson from Indiana University in 1975 of pertussis to put in perspective, I think, one of the best clinical descriptions:

"The child possessed of a coughing fit is a pitiful sight, all the more so as the observer is helpless to alleviate or terminate the attack. Each attack consists of ten to 30 forceful coughs per spasm, and into each cough the patient appears to concentrate all his energy. He leans forward or, if standing, stands with legs spread grasping the nearest object and leaning far forward, tongue protruded to the utmost, saliva and mucous streaming from nose and mouth, eyes bulging with tears streaming, his entire

body racked with the total exertion of each cough." Next slide, please.

"The coughing continues in a staccato series. The face becomes more and more cyanotic. The neck bulges with venous congestion, and still the attack continues. Finally, when it seems certain that death is imminent, a final cough appears to clear offending secretions and mucous from the upper airway, and the first opportunity to inspire is offered. With a massive effort, inspiration ensues. Air rushes into the lungs against a still narrowed glottis, and a characteristic whoop is produced." Next slide, please.

Apart from the complicating conditions which occur in some patients with pertussis, the major danger from the disease is during severe coughing paroxysms during which prolonged hypoxia may lead to irreversible changes in the CNS or even death. The greatest mortality via this mechanism occurs in infants.

This shows you what has happened with pertussis in the United States, first with whole cell pertussis vaccines, showing a major acceleration in the decline of pertussis, and now in cellular vaccines. We've seen pertussis increasing recently in

the United States, and this involves particularly young adults and adolescents who are a reservoir of continuing transmission.

If immunization levels fall, I think we can be certain that we will again see epidemics of pertussis without the need for international importations. Next slide, please.

To put it perspective the concerns about pertussis, this is data from Japan, but it was seen in the United Kingdom and Sweden. In Japan there was extreme concern about the safety of the whole cell vaccines after two deaths followed whole cell vaccination. The pertussis vaccination program was suspended for a time, then reinstituted at two years of age, but not very effectively.

Again, this was after two deaths following vaccine. There was a major epidemic of pertussis in which 41 deaths were reported, and it was only through reintroduction of a cellular vaccine, first at two years of age and then at younger ages, that have led to major control of pertussis in Japan. Next slide, please.

I'd like to move now to varicella. The CDC has estimated that roughly everybody got varicella in the pre-vaccine era. That's about 4 million cases

per year, about 11,000 hospitalizations per year, about 105 deaths per year, about one on average per week in children. The majority of deaths and hospitalizations did not occur in persons with risk factors, but in those who were healthy children and healthy adults. Next slide, please.

These are data from a sentinel surveillance project CDC funded in Antelope Valley, California, West Philadelphia, and Travis County, Texas, where immunization coverage, as best we can measure it in the trial population, varies from about six to 80 percent or so.

What you can see here, if you look at the bottom line, is an overall reduction in reported cases of varicella, ranging from 77.5 percent to 84.3 percent. The other thing of interest is that a program targeted toward children is having a major impact on circulation of varicella in all age groups, including older adolescents and adults. Next slide, please.

What's gratifying is we're not only seeing a decrease in reported cases, but we're seeing a major decrease in hospitalizations, shown here by the blue bars, and on the rates of hospitalizations, shown here in red. Next slide, please.

The last disease I want to talk about is hepatitis A. Hepatitis A is again not a trivial disease. It consists generally of a pro-germ of fever, malaise, loss of appetite, nausea, abdominal discomfort, and jaundice. Next slide, please.

The CDC estimates that approximately 100 persons die each year in the absence of a vaccination program from fulminant hepatitis A. While the usual illness resolves within two months, about ten to 15 percent have relapsing illness up to six months. About 11 to 22 percent are hospitalized, and the cost per case, even for children, is not insubstantial, in children ranging, from CDC estimates from our hepatitis group, from $433 to $1492 per case.

The total cost estimated and published in the ACIP statement on hepatitis A was approximately $100 million. Next slide, please.

What you can see here with hepatitis A in the Indian population where coverage rates for hepatitis A vaccine in children have ranged from about 60 to 80 percent is a marked drop in hepatitis A to the point that hepatitis A in the American Indian population is now similar to the overall U.S. population. Next slide, please.

The last point I want to make deals with

the immunization schedule. At the present time, we routinely vaccinate children in the United States against 11 vaccine-preventable diseases in a number of areas at high risk for hepatitis A, 12 areas.

What this means is a substantial number of injections and a substantial number of doses of vaccines that are needed for young children. In fact, if you cut off at 18 months of age, it now requires 16 to 20 injections, 16 to 20 doses, to fully immunize a child by 18 months of age.

This is a major challenge for parents, for health care providers. In some cases, five injections are being given at a single visit, and clearly, combination vaccines, if deemed to be safe and effective, would be very, very important in trying to assure everybody benefits from these vaccines. Next slide, which is the last.

So in summary then, vaccines are one of the greatest achievements of public health. Most vaccine-preventable diseases are at or near record low levels. There is an ever present threat of vaccine-preventable diseases, both within this country and from abroad, and therefore, there is a need for maintaining high vaccination coverage levels. Thank you.

CHAIRMAN BROWN: Than you very much, Dr. Orenstein, for this very upbeat presentation on the utility of vaccines, which many of us, I think, probably were not fully aware of.

Any questions for Dr. Orenstein? Yes, Dr. Modlin?

DR. KIM: Kwang Sik Kim. In the context of what we are discussing today, can you somehow elaborate whether indeed vaccine safety, the safety of vaccines per se, has been any contributing factor to achieving or maintaining high vaccine coverage?

DR. ORENSTEIN: I think the issue of vaccine safety is critical, and I think there's a critical need to assure the public and the physicians and nurses and others who give vaccines that vaccines are safe. I think there has been a substantial commitment to improving of what we already consider a very safe schedule.

This includes the move from oral polio vaccine to inactivated polio vaccine, from whole cell pertussis vaccines to acellular vaccines, and a variety of others. So, yes, I agree. It's critical that vaccines need to be safe and have a special standard for safety.

CHAIRMAN BROWN: Sorry, Dr. Kim. Dr.

Modlin's sign is in my sight line right in front of you. So forgive me. Any other questions? Yes?

DR. STEPHENS: Walt, to you on the spot a little bit more, does NIP have an opinion about the issue directly for this committee?

DR. ORENSTEIN: I think not at this point. Clearly, I think we're here to hear the information and learn more about it.

CHAIRMAN BROWN: Thanks very much, Dr. Orenstein. The last -- One more question. All right.

DR. HUANG: Alice Huang. I have both a specific and a general question, the specific one being whether the varicella vaccine protects against shingles, with what we know about that.

The second general question is would you talk a little bit about herd immunity and the importance of that in vaccination.

DR. ORENSTEIN: In terms of shingles, the available data that we have show that the incidence rate of shingles following vaccination is substantially lower than what would be expected from natural virus.

Clearly, we haven't had the extreme long term follow-up, but at least in the childhood population I think the data are quite good that the

risk is extremely small. It's not zero, and there have been vaccine viruses isolated from patients with shingles. The Japanese also are seeing a decrease.

I don't know, John, if you wanted to comment more on it. I'm not as familiar with the Japanese data. Then I'll come back to the herd immunity.

DR. MODLIN: Just very quickly, Alice, the Japanese, who have been using the Yoka strain for the longest, I think, have the longest experience. They recently have published data on that now is about a 20-year follow-up for some vaccinees that suggests -- that substantiate just what Walt said, that the incidence of Zostra amongst the vaccinees has been lower than one would have otherwise expected.

DR. GREENBERG: Greenberg. There is a large cooperative study in the VA system currently evaluating whether vaccination of people over the age of 60 or 65, people who would have been exposed to wild type varicella, would benefit and are likely to be protected by vaccination, which might have been your question.

So that -- The answer to that is unknown at the present.

DR. ORENSTEIN: The data I was quoting is

really some estimates of risk of zostra, particularly in the childhood population and what we've seen and experienced in reports of cases.

In terms of herd immunity, we feel it's absolutely critical in terms of protecting the population. We know that there are populations that cannot be vaccinated, such as those with immune deficiency disorders or, if vaccinated, do not make adequate immune response, and they are protected through herd immunity.

We have achieved our measles successes without having to have 100 percent immunity in the population. I think that a number of groups derive benefit from vaccination that may not be vaccinated. They include one -- I mentioned those who medically cannot receive vaccines, for whatever reason or cannot mount an adequate immune response.

There are people with religious beliefs who do not desire immunization or do not feel -- feel immunization goes against their religious beliefs. They are benefitting by herd immunity, and those that refuse vaccination at the present time benefitting by herd immunity.

CHAIRMAN BROWN: Last question from Ms. Fisher.

MS. FISHER: Dr. Orenstein, as the head of the immunization program for the CDC, do you support strict guidelines for manufacturers to make sure that there is no transmission of BSE to American babies through vaccines using bovine sources for production?

DR. ORENSTEIN: I think that there should be guidelines for manufacturers, and I think that, to the extent possible, that risk needs to be as close to zero as possible, hopefully zero. But I think, with all of these things, we're going to have to weigh risks and benefits.

My hope is it's zero, and I think that we ought to try and go for zero, but with other vaccines we have to weigh the risks and benefits, and I think we need to understand what the magnitude of risk would be in order to put that into the equation of a risk-benefit evaluation.

CHAIRMAN BROWN: A postscript from Dr. Ewenstein.

DR. EWENSTEIN: Thanks. Have you tried to -- Well, I guess there are two parts to this. One, for the many vaccines that we've talked about, are there multiple sources, (~~a~~)? (b) Have you tried to project, without trying to infer anything from the question, what the impact would be on various, let's

say, periods of time when a vaccine was not available what the impact would be on the resurgence of diseases that you've described?

DR. ORENSTEIN: If we could go back -- I don't know if you can go back to the schedules, because you have to go vaccine by vaccine. There are four suppliers right now of DTAP vaccine. There is a single supplier of inactivated polio vaccine. There are three suppliers, I believe, of Hib vaccine. There is one supplier of MMR vaccine, one supplier of varicella vaccine, two suppliers of hepatitis A, one supplier of pneumococcal conjugate vaccine. Did I leave any out? I think that covers them all.

In terms of the impact, it's very difficult to project. It would depend, clearly, on how soon vaccine could be reinstituted. The longer we go, the more the risk.

I would presume there would need to be some accumulation of susceptibles. How long that would have to be and in which populations is very difficult, because these are sort of stochastic kinds of things. It's difficult to know when or whom is going to introduce disease in which population.

CHAIRMAN BROWN: Please?

DR. DAUM: Bob Daum from the University of

Chicago. As an infectitious disease practitioner, with many older, less expensive antimicrobials, we are now experiencing severe shortages because manufacturers just don't seem to be willing to make them anymore.

I'm sort of wondering whether you would be willing to comment on potential strain in this system where we as a practicing community, a medical community, need manufacturers to make these vaccines, because the government really isn't in that business right now, and what the impacts would be of actual threatened or perceived shortages of vaccines, in your view, on the vaccination program in this country.

DR. ORENSTEIN: Well, I think -- Thanks, Bob. I think, in my opinion, if we lose some of these vaccines, for whatever reason, I think we are going to see a return of some of these epidemic diseases. So I think we do need to weigh risks and benefits when we make any decisions about this.

I think it's not to maximize the benefits or minimize the risks, but I think they need to be weighed as fairly as possible in an overall policy decision. I think that I've tried to demonstrate that doing without vaccines is not without cost. There is a cost to society and a cost to the health of the

public, and I think we just need to balance those to make sure we derive the maximum health and the maximum benefit.

CHAIRMAN BROWN: Well, I don't think I'll thank Dr. Orenstein anymore. We'll just have continuing questions. So go ahead.

DR. KOHL: I'm going to push you, Walt, a little harder. If this committee or the FDA agrees on a product recall of specific vaccines, has the CDC prepared any scenarios of what the impact would be?

DR. ORENSTEIN: We have not. We'd need to know which vaccines, and we would need to know the magnitude of that in order to do that. So we have not.

CHAIRMAN BROWN: Dr. Orenstein, you'll be here the whole day, won't you?

DR. ORENSTEIN: Yes, I will.

CHAIRMAN BROWN: So in general discussion, if any of these questions come up that Dr. Orenstein can answer, he will still be here, and we can continue to ask him. Thank you.

The next presentation and the last one before our morning break will be given by Dr. David Asher from the FDA.

DR. ASHER: Thank you, Dr. Brown. Good

morning. I'd just like to add here that, in addition to other duties, I'm CBER's representative on the FDA TSE Intercenter Working Group, and one of the issues that we are concerned about is the development of an appropriate regulation concerning TSEs.

I will review FDA policies concerning BSE and the safety of regulated products, beginning with the first expressions of concern in 1991, soon followed by recommendations that manufacturers not use most bovine derived materials from countries with BSE, which remains today the policy of the FDA as well as of our sister agency, the U.S. Department of Agriculture.

Since we know that those recommendations were not always followed, I will also address briefly several factors affecting the risk that the use of bovine derived materials from various countries in manufacturing vaccines might result in transmission of BSE to recipients, an event that has not been demonstrated and the likelihood of which seems quite remote, but which might be catastrophic, should it occur.

Of course, there are precedents for accidental transmission of TSEs by veterinary vaccines and by human peptide hormones, though both products

are quite unlike those to be discussed today.

Several factors to consider in estimates to risk are related to the source of bovine materials: The temporal risk, that is, the years when cattle in a country were infected; the geographic risk, that a country has BSE in its native cattle and the BSE rates in that country; and the tissue risk, the likelihood that various tissues of an infected animal contain the BSE agent.

I'm very grateful to the SSC, the Scientific Steering Committee, of the European Commission's Health and Consumer Protection Directorate General for recently issuing a number of valuable opinions addressing those issues.

Also to consider in evaluating the theoretical risks are details of manufacturing and end use of vaccines that I can discuss only very briefly.

We are concerned only with bovine derived materials, those from other ruminants being negligible in CBER regulated vaccines, and of the animal TSEs, only BSE has been convincingly associated with a human disease, new variant CJD with its unique constellation of findings, listed here, several of which are BSE-like. FDA's concern about the potential transmissibility of animal TSEs to humans predates the

first description of VCJD in 1996.

Today we are mainly concerned about four bovine components used to manufacture vaccines: Serum collected from fetal and older animals in a high prevalence country during years when many cattle were infected; a derivative of gelatin prepared from the bones of cattle in several low prevalence countries; and bovine pancreatic extracts in meat broth, also from cattle in low prevalence countries.

For many years, FDA regulations have required that cultures used to manufacture biologics be free from extraneous organisms. Except for the so called ruminant feed ban of 1997, the FDA has issued no additional rule specifically regulating TSE safety. However, beginning in 1991 the agency has sent a number of letters to manufacturers of regulated products and issued published guidance expressing concern about the potential danger of ruminant TSEs for humans.

In May of 1991 the CBER Director first articulated concern for the safety of biologics and asked manufacturers to review sources of bovine and ovine materials that they used not only as active ingredients and excipients, but also as in-process reagents, including enzymes and cell culture

components like serum and its derivatives.

In July 1993, CBER provided manufacturers with a recently revised "Points to Consider" document specifically recommending that bovine serum and other additives in cell culture media used for production of biologics be free of the BSE agent.

Later in 1993, CBER and other FDA centers sent letters published the following year recommending that most bovine components in regulated products not be sourced from animals in BSE countries, and noting that the USDA maintains a list of such countries.

I must add here that the FDA did not consider the possibility that a product prepared with components derived from cattle in a country not on the BSE list might still be in inventory when the country was added to the list later.

In 1996 following the recognition of VCJD, the Deputy Commissioner of Food and Drugs sent letters to manufacturers of regulated drugs, devices and biologics requesting that they take whatever steps are necessary to assure all concerned that they were not using bovine materials from BSE countries in the manufacture of products for humans, and stating again that the USDA maintains the list of BSE countries.

Finally, in April of this year, the CBER

Director repeated that recommendation, clarifying that manufacture of biologics includes preparation of master and working seeds and cell banks, and pointing out that the USDA BSE list includes not only countries that have actually recognized BSE in native cattle, but also countries where the USDA has been unable to assure the FDA that BSE does not exist, the so called BSE suspect countries or status unknown countries, and reiterating the steps that CBER expects manufacturers to take.

As some members of the TSE Advisory Committee will recall, in 1994 bovine gelatin was temporarily excluded from FDA's recommendation against sourcing from BSE countries, but after process validation attempts failed to eliminate TSE agent during scaled down production of gelatin, and FDA learned that some brain, spinal cord and dorsal ganglia probably contaminated the starting material for bovine bone gelatin, the agency, endorsed by advice from the committee, again recommended against the use of bovine gelatin from BSE countries in injectable, implantable and ophthalmic products, and suggested increased precautions for oral and topical gelatin.

The TSE Advisory committee also has

reviewed bovine tallow derivatives, and was generally reassured about the safety of such reagents from any source. Revised FDA policies concerning tallow derivatives are in development now.

Besides gelatin and tallow, all other bovine components are either covered by FDA's general BSE guidance or have been considered case by case.

USDA regulations, intended to protect animal health and only indirectly protecting human health, prohibit the importation not only of ruminant meat and meat products from BSE countries but also offal, glands and blood. Bovine gelatin not for human consumption or industrial use is similarly restricted.

Bovine serum -- next slide, please -- Ruminant serum from BSE countries can be imported under USDA permit so long as the Administrator of the Animal and Plant Health Inspection Service determines that it will only be used under circumstances that will prevent introduction of BSE into animals, and the USDA permit does not authorize exposing any animal to that ruminant serum, even species not known to be susceptible to TSEs. The capitalization here is the USDA's, not mine, and it indicates their level of concern about the safety of the material.

Most important, in December of 1997,

published the following month, the USDA, having learned about earlier widespread exports of cattle and meat and bonemeal from the U.K. into many parts of Europe, prohibited the importation of ruminants and most ruminant products from all of Europe as a precaution, expanding the BSE list.

Now I will briefly review some information useful to estimate the theoretical risk posed by the bovine materials of concern today, starting with temporal risk.

To date BSE has been recognized only in cattle born in ten European countries, listed here in approximate order of the earliest birth cohort affected. The vast majority of recognized cases have been, and still are, in the U.K., which has reported over 176,000 to date, almost 2300 last year.

In the U.K. diseases affected some cattle born as early as the 1970s, peaking in cohorts born in the late 1980s when the USDA estimates that as many as .5 percent of all cattle there may have been infected.

The disease then appeared in cohorts of cattle born in France, Ireland, Portugal and Switzerland in the mid-1980s, and those born a decade later in the Benelux countries and in Liechtenstein and Denmark. The EC's SSC now suspects that there

must also be some native cattle infected with BSE in Germany, Italy and Spain, although those countries have not recognized the disease.

BSE cases peaked in the U.K. near the end of 1992. They may have peaked in Switzerland more recently. The situation in other countries is not yet clear.

The SSC recently released a helpful estimate of the probability that cattle in a given country have been infected with the BSE agent and the probable current incidence in each of 25 countries that provided information, the geographic BSE risk estimate or GBR.

The GBR depends on a number of factors, including numbers of cattle in a country, imports and feeding of meat and bonemeal, rendering and recycling of meat and bonemeal within the country, elimination of specified risk materials, so called SRM, from carcasses, surveillance for BSE, and cattle culling practices.

The quality of TSE surveillance is especially important, since passive confirmation of disease in sick animals alone misses at least 50 percent of infected animals, while active examination of brains of apparently healthy older animals provides

a more realistic estimate of incidence.

Both the intensity of BSE challenge -- that is, the exposure of animals to imported contaminated meat and bonemeal and to recycled meat and bone meal -- and stability, the effectiveness of national control efforts to remove infected animals, and contaminated products from the environment influence the risk that cattle are infected.

The overall SSC assessments were based not only on information provided by national authorities, but also on results of EC inspections, U.K. trade figures, and realistic worst case assumptions.

The current GBR, which seems inevitably destined for modification, recognizes four risk categories of country, from the highest, Roman Numeral IV which includes only the U.K. and Portugal, and a lower risk category III, probably to be further stratified, which includes all other countries known to have BSE in native cattle, plus the three suspect European countries.

Nine countries, including the USA, are considered to be in Category II. They are probably free of BSE, but have a history of importing cattle from the U.K., rendering some carcass into meat and bonemeal, and possibly feeding it to native cattle.

The U.S. feed ban was put into effect only in August of 1997.

Four countries in Category I are considered BSE-free, although one may be reconsidered because of its imports from a category III country. Of course, many countries did not provide information to the SSC, but all those of concern to the FDA today except one did respond.

The third element of risk associated with source is the tissue risk, which will be reviewed in detail by later speakers today. Thus far, only neural tissues and intestines of cattle have been convincingly demonstrated to contain BSE agent. However, in the U.K. and in some other parts of Europe, lymphoid tissues are also removed from beef carcasses as a precaution, because those tissues are consistently infectitious in sheep and goats with scrapie.

The EC has a system to estimate the risk that a given tissue of a ruminant with a TSE, including cattle with BSE, may be infectitious. Unfortunately, this system, in contrast to the GBR, assigns the lowest number, most recently an Arabic numeral, to the highest risk tissue. Tissues in the two highest risk categories are listed here.

Note that the four bovine materials of concern today, shown here bolded, are all derived form tissues in either low risk Category III or in the no-detectable infectivity category IV, which we prefer to call minimal risk tissues.

Just a warning: Experience looking for infectivity in a variety of tissues form human CJD patients assayed by intracerebral inoculation of monkeys illustrates that small sample sizes can yield misleading results. Note here that CJD infectivity was found in only a modest fraction of kidneys, livers and spleens tested. Those would be tissue risk categories III and IV in the European system for cattle.

Testing of a small number of specimens with the use of less sensitive animal models might have failed to detect infectivity in those tissues. I hope that today's more recent information from the U.K. Ministry of Agriculture, Fisheries and Foods BSE pathogenesis study may serve to increase our confidence in the EC BSE tissue risk estimates.

Now for a short digression. What has led regulatory authorities to recommend taking such apparently extravagant precautionary steps for sourcing -- for example, the U.K.'s including lymphoid

tissues among the specified risk material to be removed from older calves, the U.K.'s decision not to use its own blood donors' plasma for fractionation, and the FDA's repeated requests not to use most bovine materials from BSE countries?

The precautions may seem excessive, considering that there are, as we have heard, no actual scientific data showing that any of those materials is infected. However, those decisions reflect the uncertainty of the risk involved.

The basis for such decisions has been codified in the European Union as the "Precautionary Principle," which asserts the right of a society to respond preemptively to an uncertain risk while awaiting better scientific information.

In that regard, a recent opinion by the SSC expresses well FDA's thinking about minimal BSE risk tissues, noting that there is little doubt that under certain circumstances humans or animals could be exposed to the BSE agent by consuming ruminant blood products, and that this risk may be reduced or eliminated by a combination of various strategies, including source bovine blood from BSE-free areas or closed herds.

The SSC noted further that potential

infectivity in bovine blood, and presumably in other minimal risk tissues, might result not only from some as yet undetected intrinsic infectivity to the tissue, presumably at low levels and perhaps infrequent, but also from potential extrinsic infectivity due to contamination of the blood with high risk tissue, either by slaughter or blood collection techniques.

There are a number of factors that should serve to mitigate greatly the risk of transmitting BSE, even if the country of origin had the disease in some cattle: all material from health, inspected animals, especially animals from well controlled and documented herds; a documented history that the animals had never been fed meat and bonemeal; source animals for the material too young to be in the later stages of the BSE incubation period, as in the United Kingdom's 30-month scheme; and potential cross-contamination of low and minimal risk tissues with specified risk materials reduced by using slaughter techniques unlikely to embolize brain tissue or to allow its leakage; and by careful removal and disposal of risk material at the point of slaughter.

Risk is also affected by the manufacturing process, although often to an uncertain degree, and you will hear more today about the potential effects

of dilution, partition, and possible reduction of infectivity by heat in various production steps.

Additional, Sue Priola of the NIH is here today and available to comment on the theoretical, albeit unlikely, possibility that the BSE agent might replicate in some cell cultures.

The last element of risk to be considered in a traditional analysis is the end use of the product. Here we must recognize that vaccines at issue are all administered by intramuscular injection, a route that's more effective in transmitting most infections, including TSEs, than is the oral route to which transmission of new variant CJD has already been attributed.

I need not remind you that vaccinated children pose special concerns for caregivers, manufacturers, and for regulators. Children have a whole lifetime to incubate a slow infection. They are generally healthy, and they are especially vulnerable in that they are legally unable to give informed consent for treatments that they receive as much to protect others as themselves.

Their parents' continued confidence in the safety of vaccines will be necessary if our nation is to achieve universal immunization. Vulnerable people

undergoing non-voluntary preventive treatments that contribute to the general welfare are entitled to receive the highest level of fiduciary protection.

The public might reasonably understand that protection to include the most careful possible sourcing of all components of vaccines at all stages of production.

When, due to misunderstandings, FDA precautionary recommendations concerning that subsourcing were not followed in the manufacture of vaccines, the obvious great benefit afforded by the product may outweigh any remote theoretical risk of harm to the recipients. However, the agency would generally expect deviations from these recommendations to be corrected as soon as feasible, and for the situation to be disclosed to the public. Thank you.

CHAIRMAN BROWN: Are there any questions for Dr. Asher? Yes?

DR. BELAY: David, can you expand a little bit on what you call extrinsic infectivity, where that infectivity comes from and whether or not there have been any measures taken in European countries to mitigate that infectivity that could end up in low infectivity?

DR. ASHER: The two possible sources of

extrinsic infectivity in a low risk tissue come from the slaughter technique used and the tissue collection technique. The slaughter technique of greatest concern of those in which air is introduced into the cranial vault which is known to produce embolization of brain tissue, not only into lung, but it's now been documented into other tissues as well, though not specifically into muscle.

Less invasive pithing -- that is, the procedure of putting a rod through an entry wound into the skull and disrupting brain -- is also known to produce embolization. Less damaging slaughter techniques are less likely to produce embolization.

Information on slaughter techniques in the European Union may be available to the USDA. Perhaps Lisa Ferguson would like to comment on that.

CHAIRMAN BROWN: Well, before we have other comments, there is a document which has just been completed by the European Community with extraordinarily graphic descriptions of slaughter processes, and Dr. Bradley this afternoon, who is speaking, might want to -- if you have further questions about it -- give you more details, because he and I and a number of other people participated on the committee that drew up this document.

In general, slaughtering is done by captive bolt, which basically is a bullet on the end of a -- a bullet that never leaves permanently the pistol, and it's traumatic, but it has been relatively infrequently associated with any cerebral emboli.

The use of air injection and of pithing are both currently being discouraged, if not banned -- air injection -- as a guideline by the European Community. So this method of slaughter is on the way out, but has been used in some countries of the Western world during the period at which BSE was occurring.

DR. ASHER: The answer to the second question was during the collection of blood, particularly not fetal blood but from older animals, there is an opportunity for brain tissue exiting from a cranial wound to enter the blood.

The point I was making was that, if such techniques are avoided, the chance of extrinsic contamination is much reduced, and those would be mitigating factors.

DR. GREENBERG: Do you have some estimate of the likelihood that a country like the United States actually has BSE circulating and just below the level of detectability? What should be the level of

assurance that BSE is geographically restricted to various areas?

DR. ASHER: The U.S. Department of Agriculture has an active surveillance program, and I gave up counting when they reached more than 7,000 brains from suspect animals, all of which had been negative. Perhaps Lisa has the latest figure on that, and estimate of the probability for this country.

It seems quite remote at the moment.

DR. FERGUSON: Yes. I would agree that it does seem quite remote. We've had a fairly strong surveillance program in place since 1990, including what we would term both passive and active surveillance. We're not looking strictly at central nervous system cases that are presented, although those, obviously, are included, but we are also sampling what we call downer cows. In Europe they are more often referred to as fallen stock.

These are animals that are -- and they can't stand, for whatever reason. In many cases, it's not a CNS type reason, but we are sampling from both of those populations all animals.

Over the ten years that we've been doing the surveillance -- I looked at our figures yesterday, and through May of this year it was over 10,700. At

one point in time we did an estimate of essentially our confidence interval that we would find a one in a million case. I think it was like a 95 percent confidence interval, with our targeting in the adult population.

CHAIRMAN BROWN: Yes, and that one in a million figure, Dr. Greenberg, is one to keep in mind. It's entirely possible that cattle, sheep, pigs, chickens, fish and every other species known has a sporadic occurrence of CJD at the same rate that occurs in humans, one in a million.

What we can say is -- What we can't say is we don't know if that occurs. What we can say is that, if it does occur, it doesn't seem to cause a problem. Dave?

DR. ASHER: I would only want to comment. Regardless of whether one subscribes to the theory of spontaneous generation of the disease agent, the ruminant feed band is specifically designed to reduce or eliminate the recycling of any infective material, which is what clearly caused, as we'll hear later in the morning -- clearly caused the epidemic of BSE in the United Kingdom.

DR. ROOS: Ray Roos. David, you presented the SSC data regarding BSE in European countries. Now

there is also a USDA list that you commented on.

DR. ASHER: Yes.

DR. ROOS: I'm wondering about the relationship of those two, since we are going to be asked to comment later about countries and origins of bovine material.

DR. ASHER: The USDA has what I would consider a more conservative list in that all of Europe, including the low risk countries, at the moment are prohibited, and it's on the USDA list that the FDA relies.

Now the USDA has allowed for the possibility of European countries being reinstated by the provision to the USDA of reassuring information. To my knowledge, since January 1998 when the interim regulation was published, no European country has actually been reinstated, and it's on that USDA position that the FDA, obviously, relies.

CHAIRMAN BROWN: Let me clarify that. I think the question was: Is the FDA using the USDA list as its list of BSE-free, possible BSE occurring countries?

DR. ASHER: Yes.

CHAIRMAN BROWN: And has that information been included -- that is, specifically included -- to

the most recent letters to the manufacturer, so that there's no question that, if the FDA list currently might not include Country X but the USDA list does include Country X that it's been specifically communicated to the manufacturers that the USDA list essentially supersedes dated FDA lists?

DR. ASHER: The USDA -- The FDA has repeatedly noted that we rely on the USDA list. For the purposes of these discussions, though, there really is no difference, since all countries of concern today with the exception of one are Categories III or IV or "status unknown" in the European system. So it's really not a major discrepancy.

DR. ROOS: And the USDA list corresponds to the SSC tables that you have presented and, if not, which do we follow, David?

DR. ASHER: USDA is the agency to which the FDA since the beginning of this outbreak has turned for authoritative advice on BSE. The requirements of Europe are quite different, because they already have BSE in a number of countries, and in North America, so far as we known with the exception of one imported case in Canada, we do not.

So that the criteria for being listed in

this country are much stricter than they would be in Europe, and the way the list was developed is different. In this country the list was developed as a precaution to protect animals and us. In Europe it was an attempt to estimate how much disease is present in a given country.

CHAIRMAN BROWN: So FDA guidance, which is what we're here to consider, is based on the USDA list, current. Yes?

DR. SNIDER: With regard to that issue, it seems to me the EU SSC list, as you stated, is more conservative as it relates to European countries, but then I guess part of the disconnect is that in Category II the SSC includes not only countries like Austria which USDA prohibits imports, but also countries like USA and Canada and would only include in Category I Argentina, New Zealand, Paraguay and Norway.

So one of the things we would have to struggle with is again, if we wanted -- if the principle is to try to be as conservative and protective as possible, are we talking about excluding USA and Canada as well?

DR. ASHER: No, we are not. Of course, the SSC list I cited for information and because

today's issue is a European issue, not because we have any obligatory reliance upon that list, which we do not.

Let me point out that the USDA list is a "yes or no" list.

DR. SNIDER: Well, today's issue, but as it was pointed out by Bill Freas earlier, we are supposed to be talking about this from a very generic standpoint, not from particular manufacturers' sources of products, you know, today, but from now on.

I guess part of the concern is -- Now if for a variety of reasons, whether they are scientific, whether they are economic, whether they are political, countries start jumping around from one list to another, that's going to create some havoc, both for those of us trying to advise FDA and for FDA and for manufacturers.

So I think it's important to try to understand the basis for classifying countries as being places where we can obtain safe products, and I'm not questioning the U.S. being safe. I'm just having trouble trying to understand why we ban from Austria and don't ban from the U.S. because what's the USDA's basis for saying that when the SSC comes up with similar classification for those two countries.

That's all.

DR. FERGUSON: Could I clarify -- I think it might be helpful -- some of USDA's actions and what we did in the interim rule that was published at that time, what we have done in the intervening time and probably what is predicted in the future.

When we initially published our interim rule where we extended the restrictions to all of Europe, that was a very conservative action, and we took that because we did not know exactly what the status was in Europe. There were publications out at that point in time that really made allegations about severe underreporting of BSE in Europe.

So we took that action. At the time we took the action, we also provided for any country to give us information that addressed various factors, and we would consider that information. If, through that evaluation, we decided that country was not a risk, then we would go through further regulatory processes and take them back off the list.

So we did get information from various countries, and we went through some evaluation processes with those. About the time we got that done, there were several other factors that intervened.

We contracted with Harvard to do a risk assessment internally, which is still in process, but also about the same time the Scientific Steering Committee decided to go through their similar process. Actually, the factors that they were looking at were very similar to the factors that we were looking at.

You know, obviously, with this disease you're going to have the same things come into play. So even though we had initially done some evaluation, once we knew that the SSC was going through this, and we were somewhat familiar with the SSC's process, we decided we would sit back and wait and see what their final determination was.

Actually, as it turns out, they were getting more information than we were. Obviously, they had a bit more access. So we were very interested to see if there was additional information that showed up in their reports that we were not privy to.

As it turns out, probably our risk estimations were very close. They were very similar, you know, the large groups of countries falling into different categories, yeah. So even though at this point in time our list has not changed on a regulatory basis, it very likely will change, because we've made

that obligation initially, is if we estimate the risk of a country to be acceptable, then we will go ahead and take them off the list.

CHAIRMAN BROWN: Yes. And let me just add to this discussion and perhaps terminate it. This committee is not being charged with validating the decisions made by USDA and a variety of other organizations as to the relative risk of a country. What we're being asked to do is to give -- that is to say, given a category of BSE possibility versus non-BSE possibility, to move on to whether or not we think that it's a risk or not.

So we're just going to make the assumption that the USDA and other organizations are doing the best they can in making a valid estimate of the risk. We are going to move beyond that and just accept that, and then talk about whether it's a good thing or not.

DR. KOHL: I think some clarification for me, in particular, and the audience, possibly in general, might be helpful.

It seems that the USDA has put out much more stringent kinds of regulations and actually bans on certain animal products, whereas the FDA has, it appears, made recommendations without apparently enforcing them.

I'm not sure how that happened, and I presume it's based on what would happen when you withdraw certain kinds of products. But if that could be clarified for us, it might help put this into some kind of context.

CHAIRMAN BROWN: Dave, do you want to clarify it now, if possible, or shall we wait until this afternoon in general discussion?

DR. ASHER: Yes, it sounds like it has a large element of compliance involved. All I can say is that you have to keep in mind that guidance -- failure to follow guidance is not per se a violation unless the underlying regulation or a statute is violated.

When one finds out that there has not been compliance with guidance, there are only a number of things that you can do, absent an immediate public health emergency. One of them is to assert that failure to follow the guidance is a failure of following GMP, good manufacturing processes. Another would be to convene a meeting, a meeting like this.

CHAIRMAN BROWN: I'm going to terminate this discussion now. It's eleven o'clock. We're running one hour behind schedule. We will reconvene at 11:15.

(Whereupon, the foregoing matter went off the record at 11:01 a.m. and went back on the record at 11:16 a.m.)

CHAIRMAN BROWN: We have three presentations between now and the lunch break, and the first will be given by Dr. Gerald Wells, who has been a consultant -- well, he is now a consultant veterinary pathologist, but he's worked for years and years and years at the Veterinary Laboratories Agency, New Haw, the United Kingdom. Dr. Wells.

I might also add, just by way of introduction, it was Dr. Wells who made the initial diagnosis of BSE in the United Kingdom. Gerry?

DR. WELLS: Thank you very much, Paul. In this presentation I'd like to provide a background on the studies which have provided some estimates of the presence of infectivity in tissues of cattle with BSE, either those cattle in the clinical phase of the disease or, more importantly, I'd like to consider those at various stages in the pathogenesis, during the pathogenesis.

This presentation is not, by any means, comprehensive of the transmissibility studies of BSE, but concentrates on the most recent observations. All the studies that I'm going to discuss are funded by

the U.K.'s Ministry of Agriculture, Fisheries and Food, and the standards of the new Food Standards Agency.

The pathogenesis of the TSEs in general gets its reputation initially from work that was carried out on scrapie of sheep, particularly by Hadlow and others, and the dogma regarding scrapie is that by parenteral routes or oral routes of infection, by non-neural routes, there is a lymphoreticular phase of infectivity prior to neuro-invasion.

That has led to, as we've seen already today, categorization of various levels of infectivity that occur in the different tissues in sheep, with Category I high infectivity in brain and spinal cord, medium maybe in lymphoreticular tissues, and then Category III in another series of tissues, and finally no detectable infectivity in Category IV tissues.

Bioassays were carried out in conventional RIII mice of the infectivity in tissues of naturally infected cattle, clinically affected with BSE. Infectivity has been found in those studies only in brain, cervical spinal cord, the terminal part of the spinal cord, and retina, all central nervous system tissues.

No infectivity was found in 51 tissues,

but this indicates here approximately a total number of assays of 100, that the number of animals sampled per tissue is variable, and in most cases extremely limited.

With the occurrence of BSE has been the accompanying geographically and contemporaneously associated occurrence of disease in several other species. So this in itself has given a clue to the fact that the BSE agent does not deal -- does not occur with the same sort of frequency in species as scrapie, in other words has a different species range to that of scrapie.

Here are species that have been shown by bioassay to contain the same --

CHAIRMAN BROWN: Can we get someone to focus this slide projector, please?

DR. WELLS: -- the same agent as BSE here, Greater Kudu, the domestic cat, and the association of these species in Britain with exposure to meat and bonemeal products and the exposure of exotic species of cats to products of the bovine carcass, probably as raw meat material or spinal cord material from half-necks.

So with the occurrence of BSE, various studies indicated the -- In the early course of BSE,

various studies indicated that there was a feasibility of carrying out a pathogenesis study of BSE actually in cattle. Certainly, the lesion profile in cattle, the lesion profile in mice and the biological characteristics of the disease in mice indicated that we were probably dealing with a single agent.

Furthermore, the apparent homogeneity of the PrP gene throughout the cattle population indicated that we could carry out a pathogenesis study with reasonable degree of predictability of results, of uniform results in the pest animals, providing a sufficient dose of agent was given.

So a pathogenesis experiment, which has been alluded to already, was set up, the objective being to determine the temporal and spatial development of infectivity and pathology following oral exposure of cows to a single 100 gram dose of affected cattle brain homogenate.

The protocol: Thirty cows in total, not a large experiment by some of the later standards, but all the number of cattle that could be housed in the facilities available at that time. Thirty cattle dosed orally at four months with the 100 gram brain stem material, and then groups killed sequentially at intervals through to 14 months.

The inoculum consisted of a pooled brain stems from 75 cases of BSE, and the material was sourced in 1991. The inoculum was assayed in RIII mice with an incubation period of 373 days, indicating that it was not the highest titer material, but probably equates to a titer of somewhere about 10^4 in RIII mice.

The tissue is inoculated into mice from each kill of the sequential kill study in cattle. I'll just very quickly go through the series. This was the tissues, the neural tissues, inoculated, and neuromuscular tissues, including triceps, masseter, longissimus dorsi, absternocapellicus muscles.

Lymphoreticular tissues were, obviously, included, and spleen, thymus, tonsil, and a range of regional lymph nodes and lymphonodes from the viscera. Alimentary tissues comprised tongue, salivary glands, pillar of the rumen, pyloric region of the stomach, portions of the wall of the duodenum, the distal ileum including pars patches, the spiral colon, not necessarily including lymphoid tissue, pancreas and liver.

A few other tissues were also selected for inoculation into mice, including kidney, lung, a portion of lung, respiratory epithelium from the nasal

chamber, the left ventricle of the heart muscle, blood and bone marrow.

The results of the early assays showed infectivity confined entirely to the distal ileum. Here, if you can see that, the infectivity denoted by the red dots against an incubation period in mice here, in RIII mice, showed first at six months post-inoculation, and showed a decreasing mean incubation period up to 14 months and sort of plateaued out at 18 months.

No infectivity was found during the other sequential kills of the study until infectivity was detected in the central nervous system at 32 months after exposure.

Clinical disease was first apparent in cattle at 35 months, and here also parts of the peripheral nervous system, the dorsal root ganglia, and the trigeminal ganglia were involved and, interestingly, bone marrow infectivity was detected at 38 months post-exposure.

Also in this clinical period of disease, infectivity was again detected in the distal ileum here in the three final kill sequences, and we'll come to that in the next slide.

Ignore the term interim here. These are,

in fact, now final results of bioassay here in C57 black mice from the distal ileum of cattle killed between 36 and 40 months PI.

Here we can see -- Again, ignore the coloring here, because these are now final results in all kills. Here the number of positive mice over the number of mice surviving wherein the first mice was confirmed positive, so any one of two here, at 942 days for the 12 and nine over 19 at 40 months.

A decreasing mean incubation period in the mice, but the incubation periods are close to the limit of detectability of infectivity, probably denoting limiting dilutions of infectivity in that tissue.

Just a quick look at the bioassay results of infectivity in the bone marrow of cattle 38 months post-inoculation, the only time point at which infectivity was detected in this tissue.

The clinical status of the mice: Only two out of 16 in the group at this incubation period of days -- two out of 16 were also histopathologically positive, but on application of PrP immunocytochemistry to the mouse brains, a further -- that should be six -- a further four animals became positive, again with incubation periods close to

indicating limiting dilutions of infectivity.

In summary then, the original part of the study of the pathogenesis of experimental BSE in cattle showed clinical signs occurring initially at 35 months post-exposure; abnormal PrP from 32 months post-exposure; vacuolar changes in the central nervous system of the cattle only from 36 months post-exposure; and infectivity in the CNS again from 32 months and in the peripheral nervous system also from 32 months, and infectivity in the distal ileum from six to 18 months; and this hiatus here where no infectivity was detected until it again appeared, but at a much lower concentration, from 36 to 40 months.

A further number of tissues were taken from the same pathogenesis study at two particular time periods, 18 months pi and 32 months pi. These were tissues which had potential significance to medical procedures, and those tissues were heart valve, pericardium, aorta, skin, collagen, and bone, and collagen taken from the Achilles tendon. Those were all negative, and that study is completed.

Just to go back now to some older studies that were carried by Marsh and Hadlow before I introduce the next experiment: These studies indicate the value of within-species assays.

Since many of the -- All the assays we've been talking about so far are from cattle to mice, using the most effective route of exposure, the i.c. or sometimes the i.c. plus i.p. route; but here with TME tissues -- tissues from TME experimentally infected TME mink, when assayed in mink, show relatively higher titers than if they were assayed across a species barrier.

Notably, skeletal muscle -- this is one of the very few observations of indicating any infectivity in skeletal muscle in TSEs.

So the next study was to compare the titration of infectivity within species, cattle to cattle, compared with a titration of infectivity in the most efficient conventional mouse model for primary inoculation, which was in RIII mice.

The injection in mice was by -- in cattle, rather, was by a semi-stereotactic method into the brain stem, and the needle was withdrawn during inoculation to deposit the 1 ml of 10^{-1} inoculant along the needle track.

The objectives of the study, as I've stated: to measure the underestimation of infectivity titer of BSE when titrated across a species barrier in mice, and to produce an approximate dosing incubation

curve of infectivity of brain from BSE-affected cattle.

The design of this study was six groups of four cows were inoculated i.c. at four months with a single dilution of BSE brain pool using a tenfold dilutions from 10^3 down to 10^8. Parallel titration was carried out in RIII mice i.p. with a range of 10^{-1} to 10^{-6} dilutions.

This gives results to November of '98, but interestingly, now the experiment has been terminated at 86 months post-inoculation, and the results in terms of numbers per group affected have not changed. So unlike some titrations, we have a rather messy result in that we have three groups here with an incomplete tape.

The mouse titration was completed, obviously, long before the cattle titration, and the titration -- the Karber titer in mice is $10^{3.3}$, relatively low.

The results of the comparative titration showed that the Karber titer of bovine brain stem pool, five cases of BSE went into the pool. In RIII mice, as we said, $10^{3.3}$; in the cattle, 10^6.

Side by side with this comparative titration there was a study carried out where a pool

of lymph nodes and a pool of spleen tissues from the same five cases was inoculated at a 10^{-1} dilution into mice and in cattle.

The good news is that the Fresian/Holstein cattle were negative at the endpoint of the study, 86 months p.i., and at the end of this presentation I'll show you a dose response curve calculation for this part of the study. In RIII mice, negative again at the endpoint of 700 days.

So the conclusion from the comparative titration study is that the underestimate of infectivity titer of BSE brain tissue titrated across a species barrier in mice is around $10^{2.7}$ -- in other words, 500-fold, somewhat less than the previous more pessimistic estimates of a thousandfold.

The spleen or lymph node pool from confirmed cases of BSE clearly must contain less than 10^{-1} log 10 i.c. LD_{50} gram.

So taking tissues from the pathogenesis study, we have now or sometime back now started a study in which we have titrated the tissues from the pathogenesis study or selected tissues in cattle to determine infectivity in a range of these tissues at different time points from the original pathogenesis study.

The only results of that study to date are three positive groups, the distal ileum taken at ten months post-inoculation with an incubation period of close to two years, distal ileum at 18 months here, definitely at two years, and caudal medulla and spinal cord pooled from the animals at 32 months, again as expected, an incubation period here, which is indicating a fairly low titer.

If we now look, finally, at the estimated dose response curve of bovine brain from cases of BSE after i.c. inoculation, here the data only goes up to 39 months, but this is the projected dose response curve at limiting dilutions, and here we can see that around the two-year those cattle in the previous slide will have an approximate titer in cattle of 10^2.

There I'd like to leave it and just to say that, clearly, from these experiments there is no evidence as yet of infectivity in any of the tissues that we are concerned with in this session today. Thank you.

CHAIRMAN BROWN: Thank you very much, Dr. Wells. I think we'll go on immediately to the next presentation, given by Dr. John Wilesmith, veterinarian and head of the Epidemiology Department at Weybridge.

Again, by way of introduction, Dr. Wilesmith was responsible for, I think it's fair to say, unraveling the mystery of the epidemiology of BSE in a very timely way, and I think the United Kingdom and all people concerned with these diseases should be very grateful both to Dr. Wells and to Dr. Wilesmith. John?

DR. WILESMITH: Thank you very much, Mr. Chairman. That's very kind.

What I've got to say to you is probably not very much new today. Most of the studies I've been involved in, the epidemiological research has, obviously, been more concerned with the animal side in this pool, sorting out that side. But there have been some, hopefully, important things which have been related to human health, both in BSE and also perhaps FSE, the feline spongiform encephalopathy epidemic.

I'm going to concentrate on BSE, and it's going to be sort of bits and pieces perhaps which, hopefully, are of some relevance. The title, you'll be pleased to hear, is longer than the talk.

Well, the first thing I wanted to say is something about the sort of update on past control measures and onsets of exposure, and then say a little bit about the current status of the epidemic.

I'll restrict my comments now about the European situation to a very few words, because that's really been covered, and then finally I was prompted, rally, to say something about the large cohort study which was completed in 1997 and started up in '89, because I gather that has had some sort of interpretations with respect to the risks of calf fetal serum. So we'll go through in that order.

Well, you've seen the epidemic already, and this takes you up to March 2000 for the confirmed cases, and this is by month and year of onset. The epidemic does appear, as you see, to be going away. But coming back to the, as it were, beginning, there have been a number of things that we were interested in, and that's when, you know, was BSE a new disease and could we identify when the first cases were, and could we determine when the onset of effective exposure was?

The rest of the interest, really, has been then throughout the epidemic of trying to determine what the effects of the interventions have been, and of trying to determine whether there is any other means of infection other than the food borne source or the feed borne source, I should say. So I'm going to say a little bit about those with some relevance to

the sort of human health aspects.

Well, there's been a lot of work going on right from the beginning in terms of trying to get some idea of when this thing started. I think we really have got some fix, and it does look as this whole thing started around April '85 in terms of clinical disease, and that comes, really, from my initial epidemiological studies and also Gerald's sort of review of archive material, and we keep getting back to April '85. I'm not saying there weren't cases before, but that seems to be the substantive start of the whole thing.

When it comes to the onset of exposure, then we did some fairly simple modeling way, way back in 1987. That suggested that we had this sort of sudden onset of effective exposure at least to cause the clinical epidemic in '81-82.

Now we've done all sorts of things in between, and myself and others have sort of modeled this, and they come up with a similar date. We've recently sort of taken the whole of the epidemic and done some rather large and grandiose sort of spatio-temporal analyses, and we seem to have substantiated that.

So to summarize what I've just said is

that we had this initial suggestion of the winter, if you like, of '81-82 as exposure starting. The modeling studies seem to have supported this time, and having done a great deal more at trying to get to grips with this, it does seem that this all fits together without being too tautological and going around the same houses in these studies.

So if one needs any confidence about sourcing and dates, then that might give the committee some assistance.

In terms of the intervention measures, these are probably really irrelevant maybe to the human side of things, but because we are looking at the ruminant derived protein ban in July '88 and the SBO ban, the specified bovine offal ban, in November 1990. Of course, the SBO ban for humans was the year before in September 1989.

To give you a flavor of what's perhaps been happening in the animals in terms of immediate effects -- by immediate, I mean in the first 12 months after their introduction -- again a number of efforts have been made to look at this, but this is the results of the really sort of survivorship analyses in some detail which we completed recently. Hopefully, the papers will be published shortly.

The ruminant protein ban had a 67 -- or produced a 67 percent reduction in the first 12 months after that ban. Not perfect, because as you all know, there were some imperfections in terms of the SBO ban itself and also we have this problem of continued cross-contamination, particularly in mills before the -- hopefully, before the August 1996 total ban on mammalian protein being fed to animals.

The other one which may be convertible to what the effects of the SBO ban in humans are is that we had a 46 percent reduction in risk in the first 12 months following that ban.

Personally, I think one care needs to be taken in that. People have got a little bit worried perhaps in terms of the human risks because of that figure, but my view is that I think the noncompliance with the SBO ban was probably more hazardous to the animal population than the human population. But that perhaps gives some sort of start to the whole thing.

In terms of exposure windows, this has been something of interest to those people who have been trying to model variant CJD, and this perhaps is a little bit crude. But we started off by thinking that the main exposure window was between 1985-89.

Obviously, there's scatter around both

ends of that because of the preclinical cases pre-'85, and if the SBO ban was not as perfect as perhaps it might have been, there might be something happening after '89. But that seems to be the high risk period.

The '85 start-up is quite interesting in terms of some of the exposures to other species in that it does seem that, although we have incomplete ascertainment for the cats, the domestic cats, the ones that we see at the beginning of their epidemic would have also been exposed in '85, and it does seem to indicate this quite -- indicates the build-up of infection in the circulating meat and bonemeal in animal products at that time.

The epidemic had really driven the propagation that occurred to get really high prevalences of infection in that circulating material.

The other is a minor point, and perhaps for consideration in terms of vaccines, but it's still interesting that we can't find out what the exposure of the human population was in terms of CNS, brain and spinal cord, and that contained in mechanically recovered meat. It really is quite difficult, and we probably know more about the feeding of animals than the feeding of humans.

Back to the epidemic curve, there are a

number of things going on in terms of monitoring this decline in the epidemic. We have a number of problems that the critics sort of have fun with in that currently in terms of reported cases we are getting around about 20 to 30 a week, of which on average 25 percent will be negative histopathologically.

If we look at the 1996-born suspects reported, then we have nearly 200 of those reported, and we only have two positives. This is an unprecedented negative range, and it leads people to say that this is -- you know, we are now seeing BSE II. In fact, it's just a fiction, really, of the surveillance system, and we will, hopefully, see these negatives coming in. However, there's also people wanting confirmation that this epidemic is going away.

Surveillance has been mentioned in the European context, and I'll come back to that. But just to put you in the picture of what's going on, in the first three months of 1999 we conducted an over-30 months scheme survey of the OTMS animals.

We actually pointed the survey to the animals greater than five, just to get a bit more power in the whole survey. You can see that we took a sample of just over 4,000 animals, which was me estimating what we might actually find, given the

current diagnostic tests.

Well, we did find .45 percent of animals histopath positive. The survey was designed to detect half a percent. So that wasn't too bad.

On the new tests which may be of interest, we did process these samples or colleagues in Switzerland did process these samples by the prionix check test, and that did not reveal any additional positive animals. It entirely matched using a blind technique. They were not told which were the histopathologically positive animals. They just matched the histopath animals, which was quite interesting.

In terms of further tests then, we are using a Delphia technology which was developed by Jim Hope and colleagues in the Institute of Animal Health in Britain, together with colleagues in the VLA, and we are still processing these samples.

It's now been sort of set up for survey use. It's not actually being alternated, but we are processing these. It is interesting to see what these tests are actually detecting.

The Delphia may actually be somewhat better than the others at detecting preclinical infection. It's a complicated business, and we seem

to be learning more and more.

CHAIRMAN BROWN: John, were the histopathologically positive animals clinically ill or were they clinically healthy?

DR. WILESMITH: Sorry. These were clinically normal animals.

CHAIRMAN BROWN: Normal?

DR. WILESMITH: Yes. There were 18 of them, if you want some expansion. There were 18 to make up that prevalence, and going back to the farms, 17 of the farms, 17 of the 18 farms had all had cases before. There was no indication that these animals were being shipped off, and there's no financial advantage for them to be done so.

As a follow-up, an additional survey to try and get this sort of independent assessment of the decline, we started in May 15. We don't have any results yet. As I say, we're trying to get this independent assessment of the decline and, hopefully, allow for evaluation of the Delphia.

I should say the Delphia is a post-mortem test of brain or spinal cord, and it will also allow me to see if we can actually work out the sample size for the next survey in 2001. It is likely that this is going to exceed the resources, because it could get

into the hundreds of thousands, and unless some automation of testing goes on, we might not achieve that.

Turning back to Brussels and what Brussels now are requiring from one of the more recent amendments to one of these Commission decisions -- The Commission decision number, if you collect them, is 98/272, and this is about surveillance for BSE, and it is enforcing all member states to do surveys on fallen stock, and they are designed to detect - I think it's a half-percent prevalence with 95 percent confidence.

This is not estimating prevalence. It's detecting the presence. I think that will be important. Some of the results of that surveillance will be important in making some further assessments of the geographical BSE risk assessments that I was involved in and have already been alluded to, to actually see precisely -- not precisely, but estimate somehow better when these countries became exposed, when things started happening and so on.

So it's not ideal for the British situation to take fallen stock. I would prefer to go on with the over-30 months abattoir survey, but that's the decision that's been made, and it will, hopefully, reveal some interesting results.

France, as you probably gathered from the press, have already started on this and are in the process of trying to collect 44,000 such animals over a period of 12 months.

Right. Back to the epidemic curve. All I wanted to say was, in terms of the future incidents which people still are quite interested in, the predictions are actually going quite well. You can see that we have some 95 percent confidence intervals for 2000 and 2001, and all I can advise is to look at the righthand end of those confidence intervals, because those seem to be the ones that are nearest.

So we've more or less got a 50 percent reduction in decline in the epidemic, which is much as expected from the intervention on the food-borne source.

Now I was going to say something about BSE in Europe and other countries. I'll try and keep it brief, especially as what the Chairman has advised on this issue of the geographical BSE risk assessment. But it is true that we did write a paper a few years ago on the risks of exporting British animals to member states.

This caused -- The paper caused a certain amount of commotion. It was unfortunate, because

everybody sort of thought that we were criticizing their animal surveillance.

I wrote the last three paragraphs of the discussion of that paper fairly carefully, and it was actually saying that you didn't really need to detect BSE. You could do a decent risk assessment and consider control measures, irrespective of whether you had found it or not. However, that was ignored, and it started into a battle on import figures and quality of surveillance.

Since that, as you've learned, the SSC stimulated this very, very large project to look at the geographical risk assessment, and just to put it in perspective, this project, if you like, was initiated because of the need to perhaps persuade other member states to put in SRM bounds, which they were reluctant to do because of the cost and so on, and the countries are saying why should we do this when we think our risks are low.

That is the background to it. I think, in terms of interpreting some of it, summaries, as far as I know, are on the SFC's Web site. The full risk assessments should be available. They might even be available on the Web site since I came away, but they will require -- If you need to look to see when

significant risks might have been present in any country, you may need to read those risk assessments in a little bit more detail.

All I will say is that the one thing that we have learned from that exercise is that, really, most, if not all, of the European member states were capable of propagating the BSE agent once seeded, and that is a change from what everybody was trying to claim, that it wouldn't happen with us.

That might sound critical, but it was a kind of feeling of denial that has been prevalent in the past, and I think the risk assessment has been useful. It may be a bit delayed, and I hope that it's useful to answer the question about categories of countries.

I think, when you get to the ones and twos, you shouldn't worry too much whether you're in I or II. It's quite subtle in terms of that sort of categorization. Again, I can only point you to read the details. So I'm not going to say anymore about that.

Just to finish off, Mr. Chairman, I'd just like to say something about this cohort study which has been criticized in all sorts of manners, and people have had expectations of it more than it really

deserved. This is the basic plan.

What we were trying to do here was to get in a simple epidemiological way a population estimate to determine whether there was a maternal risk, a maternally associated risk.

That is, where offspring of BSE confirmed cases more at risk than offspring of dams which did not have clinical BSE in their lifetime? Was there a difference between those two lots of animals? So nothing to do with how long were they with their mum and so on. It was much simpler than that.

So what we did, we used the BSE database, because we had been recording all these details about offspring and so on from the beginning, and we went out to the naturally affected herds, and we purchased classically the pairs of animals, born in the same herd, in the same season, an they had to be castrated or virgin heifers.

We started this in July '89, purchasing them. We actually ran out of animals in December 1989. We had exhausted the population, and this is another thing that people don't quite appreciate. We did not have an infinite population to go at. We were buying these animals, and they weren't that common.

So we have one -- One of the pairs is an

offspring of a confirmed case, and the other is the offspring of a normal dam. That is, she lived until six years of age without getting clinical BSE. We maintained these animals in their pairs on three of the old farms -- that's what the ADAS really means -- until seven years of age unless death or the need to slaughter intervened.

Anything suspected casualty or when they got to seven, they were all looked at histologically by Gerald and his team, all blind. What it says on the bottom lefthand corner -- you probably can't read -- is that the last animal reached seven in November 1996. So very expensive, but actually was quite a straightforward hypothesis or objective.

Now just to put this a little bit in words, the objective of the cohort study was to provide this estimate of the risk of offspring of confirmed cases of BSE of developing BSE themselves compared to the offspring of BSE unaffected animals. Ever so simple.

The study was not concerned specifically with maternal transmission. So the study could not really identify or even suggest perhaps the mechanisms involved in any positive maternal effect observed. So I don't want to get this out of context. I don't want

to labor the point, really, either. But it is important to realize what the limits of this big study were.

Well, the results have been published, and this is just really the summary table, giving you the -- The results have been published. As you have seen, there was a risk difference between the two groups of 9.7 percent.

In summary, if you want a summary statement of that, then it means that offspring of animals born to confirmed cases in the last six months of their incubation period probably have a ten percent risk of BSE. That has been used, actually, the results of that.

Although such effect is really true of maternal transmission, it couldn't maintain the epidemic. Nonetheless, an offspring CO was commenced in 1998 and is proceeding prospectively.

So we've got this apparent ten percent risk for offspring of clinically affected cows born during the last six months of the dam's incubation period. The results cannot confirm the occurrence of maternal transmission, only this apparent maternal effect. There's a great debate, as some of you will know, then about the whole business of maternal

transmission.

There was no evidence for a reduced age of onset of clinical signs produced in the offspring and, therefore, reduced incubation period, suggesting that they probably got it as calves, and further research is required to investigate the hypothesis of the maternal effect, notably its presence in the absence of a feed-borne source.

I'm afraid that's not going to be possible, because of the offspring CO, and we've not been able to do any further studies. I'm afraid it will remain as it stands in terms of BSE.

Thank you, Mr. Chairman.

CHAIRMAN BROWN: Thank you very much, Dr. Wilesmith. If there are a maximum of three questions that might be posed for either Dr. Wells or Dr. Wilesmith, we will ask for them now. Well, that's four. Seems the Vaccine Committee is the aggressive part of this joint meeting.

DR. HUANG: I'm Alice Huang. I think that for risk assessment as well as for surveillance, one of the most important questions we have here before us is an understanding of the assays that are being used.

I have here, from what I understand, that certainly between infectivity doses and species in