FOOD AND DRUG ADMINISTRATION

2495 5 NOV 28 P12:20

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

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE

October 31, 2005

Holiday Inn Bethesda
Bethesda, Maryland

OPEN

Proceedings by:

CASET Associates, Ltd.
10201 Lee Highway, Suite 180
Fairfax, Virginia 22030
caset@caset.net

PARTICIPANTS

Freas, William, PhD

Priola, Suzette A, PhD

Bias, Val D

Creekmore, Lynn H. DVM

Hogan, R. Nick, MD, PhD

Telling, Glenn C, PhD

Kranitz, Florence J.

Johnson, Richard T, MD

Salman, Mo D. DVM, PhD

Sejvar, James J., MD

James R. Allen, MD, MPH

Paul Brown, MD

David C. Bolton, PhD

David Gaylor, PhD

Michael Geschwind, MD, PhD

Bernardino Ghetti, MD

Susan F. Leitman, MD

James W. Lillard, Jr, PhD, MBA

Arthur W. Bracey, MD

CONTENTS

P R O C E E D I N G S 8:06 AM

Administrative Remarks - William Freas, Ph.D., CBER, Executive Secretary, TSEAC

DR. FREAS: Ms. Chairperson, members of the Committee, invited guests, consultants and members of the public, I would like to welcome all of you to this our 18th meeting of the Transmissible Spongiform Encephalopathies Advisory Committee.

I am Bill Freas. I will the Executive Secretary for today's session. The entire meeting today is open to the public.

At this time I would like to go around the head table and introduce to the public the members who are seated at the table.

Will the members please raise their hands as their name is called.

In the first chair on the right side of the room, that is the audience's right is Dr. David Bolton, head, Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

Next is Dr. Richard Johnson, professor of neurology, Johns Hopkins University.

Next is Dr. Glenn Telling, associate professor, Department of Microbiology, University of Kentucky.

Next is Dr. Lynn Creekmore, staff veterinarian, APHIS Veterinary Services, US Department of Agriculture.

Next is Dr. James Lillard, associate professor of microbiology, Morehouse School of Medicine.

Next is Dr. James Sejvar, medical epidemiologist, Division of Viral and Rickettsial Diseases, Center for Disease Control and Prevention.

Next is Dr. Nick Hogan, assistant professor of ophthalmology, University of Texas, Southwestern Medical School.

In front of the podium is Mr. Val Bias, Co-Chairman, Blood Safety Working Group, National Hemophilia Foundation, Oakland, California.

Next is Dr. James Allen. Dr. Allen is Chair of FDA's Blood Products Advisory Committee. He is, also, president and CEO of the American Social Health Association.

Next is the Chair of this Committee, Dr. Suzette Priola, investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories.

Next is Dr. Arthur Bracey. Dr. Bracey will be serving as a non-voting consultant today. He is Associate Chief of Pathology, St. luke's Hospital, Houston, Texas.

Next is our consumer representative, Mrs. Florence Kranitz. She is President of the CJD Foundation,

Akron, Ohio.

Next is Dr. Michael Geschwind, assistant professor of neurology, University of California, San Francisco Medical Center.

Next is Dr. Susan Leitman, Deputy Chief, Department of Transfusion Medicine, National Institutes of Health.

Next is Dr. David Gaylor, President, Gaylor and Associates, Eureka S[ring, Arkansas.

Next is Dr. Bernardino Ghetti, distinguished professor, Director, Indiana Alzheimer's Disease Center, Indiana University, School of Medicine.

Next is Dr. Mo Salman, professor and Director, Animal Population Health Institute, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.

The chair at the end of the end of the table will soon be filled by Dr. Paul Brown. He is a consultant from Bethesda, Maryland.

Our non-voting industry representative could not attend today's meeting due to a medical emergency. Our efforts to recruit a replacement in time for this meeting were not successful.

I would like to thank the members for attending this morning. I, also, have one announcement to make. Dr.

Alan Jenny passed away last Thursday night. Dr. Jenny served as a member of this Committee since September 2004 and was a consultant and speaker at many of our meetings prior to his service on the Committee. Dr. Jenny was a pathologist at the National Veterinary Services Laboratory for the US Department of Agriculture in Ames, Iowa. He was well known and respected for his research on investigative studies on numerous livestock diseases in the United States.

He was a kind and gentle man. He was a wonderful person. Alan Jenny will certainly be missed by his family, this Committee and many people the world over.

I would like to ask for a moment of silence in his honor.

Thank you.

I would now like to read into the record the conflict of interest statement for this meeting. Some of you might think you are in the wrong room. This has just recently been revised by our attorneys.

The Food and Drug Administration is convening today's meeting of the Transmissible Spongiform Encephalopathies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

All members of the Committee are special government employees or regular federal employees from

other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with the federal conflict of interest laws including but not limited to 18 US Code, Section 208 and 21 US Code, Section 355(n)(4) is being provided to the participants in today's meeting and to the public.

FDA has determined that members of this Committee are in compliance with federal ethics and conflict of interest laws including but not limited to 18 US Code, Section 208 and 21 US Code Section 355(n)(4). Under 18 US Code, Section 208 applicable to all government agencies and 21 US Code, Section 355(n)(4) applicable to certain FDA committees, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for the particular individual's service outweighs his or her potential financial conflict of interest, Section 208, and when participation is necessary to afford essential expertise, Section 355.

Members of the Committee are special government employees including consultants appointed as temporary voting members. Committee members have been screened for potential conflicts of interest of their own as well as

those imputed to them including those of their employer, spouse or minor child.

Related to the discussions of progress in the development of a risk assessment model for vCJD in human plasma-derived Factor 8 products and discussions of the reductions of TSE removal, TSE agent infectivity from blood components by filtration, these interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda topics are considered general matters discussions. In accordance with 18 US Code, Section 208(b)(3) general waivers have been granted to all Advisory Committee members including Val Bias, Lynn Creekmore, Nick Hogan and Richard Johnson, Florence Kranitz, Susan Priola, Mo Salman, James Sejvar and Glenn Telling.

In addition, a general matters waiver has been granted to Paul Brown. A copy of the written waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Foundation Office, Room 12A30 of the Parklawn Building.

With regard to FDA's guest speakers the agency has determined that information provided by these speakers is essential. The following information is made public to allow the audience to objectively evaluate any presentation

and/or comment made by these speakers.

Dr. Lisa Ferguson is employed by the USDA in Hyattsville, Maryland. Dr. Azra Ghani is Director, UK, CJD Foundation, London School of Hygiene and Tropical Medicine, England. Dr. Richard Knight is Director, UK CJD Surveillance Unit, Western General Hospital, Edinburgh, Scotland. Dr. Marc Turner is Clinical Director, Scottish National Blood Transfusion Service, Edinburgh, Scotland.

As guest speakers they will not participate in Committee deliberations nor will they have a vote. They are more than welcome to answer questions though of the Committee and we hope they stick around to answer questions of the Committee.

In addition there may be regulated industry and other outside organizations making presentations. These speakers have financial interests associated with their employer and with other regulated firms.

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

These individuals from industry were not screened by the FDA for conflicts of interest. The conflict of interest statement will be available for review at the registration table. We would like to remind members that if the discussions involve any products or firms not already

on the agenda for which an FDA participant has a personal or imputed financial interest the participants need to exclude themselves from such an involvement and their exclusion will be noted on the record.

FDA encourages all participants to advise the Committee of any financial relationship you may have with firms that could be affected by the Committee's discussions.

That ends the conflict of interest statement.

Before I turn the microphone over to our Chair, I would like to request that everybody check their cell phones and please place either in the silent mode or turn them off so that it won't be so disruptive to the meeting.

Thank you.

Dr. Priola, I turn the meeting over to you.

DR. PRIOLA: Okay, everybody. There are lots and lots of questions and the first topic is basically to assess the risk assessment model for variant CJD exposure. They want us to refine the input parameters and help them to define input parameters. They just want advice. I am going to hold questions after each speaker to just technical questions and only one or two of those. We can ask after each group of speakers all the questions that we couldn't get to in that first part and also ask some questions in the discussion period.

Dr. Goodman?

Agenda Item: Recognition of Committee Service - Jesse L. Goodman, MD, MPH, Director, CBER

DR. GOODMAN: Okay, I have the opportunity to recognize the services of three very distinguished individuals here and I would appreciate if they would each come up, Richard Johnson who is of course a distinguished neurologist. Should I do it one by one?

Okay, so, okay, it is the picture again. Dr. Johnson, thanks so much.

Then we have Dr. Arthur Bracey and I will try to do better with Arthur. Thank you, Dr. Bracey.

Okay, and Dr. Bracey, by the way is going on an HHS committee or has already done that. So, thank you for that, too, and then Sue Priola who obviously in addition to being a member has been the Chair of the Committee for the last 2 years.

Thanks, Dr. Priola.

Agenda Itedm: Opening Remarks - Suzette Priola, PhD, NIAID, NIH, Chairperson TSEAC

DR. PRIOLA: Okay, we are ready for the presentations. The first is Dr. Ferguson from USDA.

Agenda Item: Informational Presentations - Update on US and Worldwide BSE Status - Lisa Ferguson, DVM, APHIS, USDA

DR. FERGUSON: Good morning. I just have a few brief slides. You probably get tired of hearing me every time you get together. Anyway I thought I would go over a little bit an update both on what we are doing for BSE here in the US, also, a brief summary of data from Europe as that is where the vast majority of BSE cases have occurred worldwide.

Total BSE cases worldwide at this point greater than 189,000 cases worldwide with a couple of important points to remember about that. First of all more than 96 percent of those cases have been in the UK but more importantly more than 89 percent of those have really occurred in 1996 and before.

If you are really interested in specific information on individual countries and cases reported by year I have listed the OIE web site and OIE is the world organization for animal health and as countries report cases OIE has a specific table for BSE status and a calculated apparent incidence rate.

Let us talk a bit about what the Europeans have done. They have had very intensive surveillance since 2001. So, we have very good numbers for comparison within the EU. One point though, as of mid to late 2004 there used to be 15 member states in the European Union and now it is 25. So, that has changed the numbers somewhat with the addition

of 10 new member states to the EU, but in 2004 they did a total of more than 11 million tests.

Of those about 9.5 million were apparently healthy animals greater than 30 months of age at slaughter. One point five million are what they call risk animals. These would be the same as our targeted population in the US. These are animals with some type of clinical signs, falling stock, non-ambulatory animals.

Out of all of those tests in 2004 they had a total of 865 positive cases and this is a decrease in the number of cases by about 37 percent and overall apparent prevalence also was decreased by about 38 percent.

If you look at the numbers for the year before similarly in 2003 they had about a 35 percent decrease form 2002. So, you see things continuing to decline in Europe which is very encouraging. These reductions and also the increasing age of positive cases really indicates the success that they have had in Europe with their control measures. So, those measures that they have imposed increasingly stringently do seem to be working.

If you look at an analysis by year of birth the positive cases and we are assuming that most exposure occurs in that first year of an animal's life, at this point with the 2004 data and granted this can change; with long incubation periods you can still see increasing cases,

but there do appear to be exposure peaks pretty well defined in certain member states, obviously the UK but outside of that. The data in 2004 show that France and Ireland have an exposure peak about 1995, Germany, Belgium, Italy and Netherlands about 1996. So, it would be interesting to see is that stays the same as they get more data over the next couple of years.

There, also, is one note. They have increased their TSE monitoring in small ruminants and are doing extensive analysis with that data from sheep and goats and they did find one goat positive for BSE. It is an animal that was actually slaughtered in 2002 with extensive analysis of how to define that case.

So, let us jump a bit to the US and I think as everybody knows we have been doing an enhanced surveillance program since June 2004. I would note we have done active surveillance for BSE in the US since 1990 but in response to the cases in Canada we ramped up our surveillance a drastic amount beginning in June 2004, and our goal of our enhanced program was to get as many samples as possible from the targeted population in a 12-to-18-month period. So, we were trying to go out there and get all the samples we could from that population where you are most likely to find disease present.

Our targeted population is those animals that

have some type of a clinical sign that could be considered consistent with BSE. So, this is a pretty broad definition. It includes animals that have classic clinical signs of BSE, animals that have central nervous system signs, other types of clinical signs that could be considered consistent, animals that are non-ambulatory, animals that have died for unexplained reasons and then we are also sampling animals that are condemned on antemortem inspection at slaughter.

This talks a bit about our assumptions. We are looking in this targeted population as we have been since 1990 with the assumption that if we can't find disease there in that population where we are most likely to find it if it is present then we are even less likely to find it in a broader cattle population or in a non-targeted population, but we can use the data that we get from this targeted approach and extrapolate that as we try to estimate prevalence in the broader cattle population.

Then just a summary of the targeted populations where we are getting samples and we are working with diagnostic labs and public health labs around the country also as they get neuro cases or rabies cases. We ask them either to forward those samples on to us or to work with us to obtain those.

This actually is previous surveillance. I didn't

put in all since 1990. So, you can see where we have been. Beginning in about 2002 we were looking at between 19,000 and 20,000 samples a year and then in our enhanced program since June 3, 2004, we have looked at more than 510,000 samples. So, we have had very good success in obtaining access to the populations that we need and getting these samples.

Out of all of this we had one positive case in June 2005, a case found in Texas. This was a 12-year-old animal, a Brahma-cross, so a Bos indicus type breed. We did an extensive investigation. Our FDA colleagues did an extensive feed investigation. Clearly with a 12-year-old animal it is sometimes a challenge both on the feed history and trace backs and trace forwards. We were a bit constrained by records on the premise of origin but we attempted to trace birth cohorts which we defined very broadly from this animal due to the lack of records, traced those animals, and we actually euthanized 68 animals total and tested those as birth cohorts.

Our FDA colleagues in their food investigation really didn't find something specific that they could pinpoint and say, "Here is a likely source of exposure," but then that is not entirely unexpected again especially if you are working with 12-year-old records.

As we go through my program we are continuing to

evaluate where we are and to ensure that we are accessing appropriate representation around the country and we are getting pretty good geographic distribution.

The vast majority of our samples tend to be from dead stock and non-ambulatory animals. This is entirely what we expected and really what we wanted.

We are getting good representation from all the different collection sites but clearly the majority of these samples that we are getting are from animal disposal facilities, rendering facilities, what we call 3D, 4D plants or salvage slaughter plants, dead stock. This is where our targeted population shows up. So, that is where we are getting those samples.

We will be doing a very detailed analysis when we complete our program. We are now in the 18th month of this and we hope to do an analysis and have that out for public release very shortly thereafter after we are done completely with the program and I just realized I didn't actually put anything in about our Canadian colleagues and their situation. I know there is lots of interest in what the Canadians are doing and have done. They have a total of four cases and the last cases were those two in December 2004, January 2005.

They have ramped up their surveillance similar to what we have done, also, doing targeted surveillance and at

this point in 2005, they are up to close to 40,000 samples.

So,they are, also, having very good success with obtaining the samples that they need and with no further positives since those four in an apparent cluster out there in Alberta, and in line with Sue's push to keep us on time if you are looking for more detail, more info we do try to post everything that we can on our web site including updated numbers and you can always look there to see the latest release from us.

Thank you.

DR. PRIOLA: You will be around for the next few hours?

DR. FERGUSON; Actually I need to leave at the end of the morning.

DR. PRIOLA: Our second international presentation is by Dr. Sheila Murphy and she is going to update on a new FDA Device Panel that discusses scientific issues in evaluating decontamination products.

Agenda Item: Scientific Issues in Evaluating Products Intended to Decontaminate Surgical Instruments Exposed to TSE Agents: Discussion of a Recent FDA Device Panel - Sheila Murphey, mD, CDRH

DR. MURPHY: Good morning. Thank you for your interest in our committee. The Center for Devices and Radiologic Health has asked one of our advisory committees

to address the scientific issues related to TSE screening of products intended to decontaminate surgical instruments. This was our general hospital and personal uses devices panel. The advisory committee is asked to address the issues surrounding the evaluation of products or processes intended to reduce the viability of CJD transmissible agents on contaminated surgical instruments.

We believed that we needed more guidance on these issues. There are a number of scientific issues addressing the removal of TSE from instrument proxies is increasing in the literature.

Public interest about CJD and variant CJD and its potential for causing disease in the United States is in fact increasing and DAGID believes that it should prepare for the possibility that products or processes intended to reduce TSE infectivity on surgical instruments will be submitted to FDA for premarket evaluation.

There were a number of presentations at the scientific panel. I am going to give you just some quick background on the four from FDA. First, Dr. Elaine Mayhall presented a general overview of transmissible spongiform encephalopathy concentrating primarily on iatrogenic transmission.

There are only six reported cases in the literature and four of those are considered possible, not

probable. None have been reported since 1980. Small epidemiologic studies of the potential association between surgery and risk of CJD have not resulted in consistent associations, some of them positive, some negative. There are reports of patients exposed to instruments used in the care of patients with Jakob-Creutzfeldt disease where the recognition of that exposure did not occur until after the instruments had routinely processed and used on other patients.

There have been at the present time no reports of transmission of disease related to these exposures. TSEs of course in man are rare diseases. Iatrogenic transmission has been quite rare. We have a number of clinical procedures now in place to reduce this risk but the question is could we do better and how should we evaluate the possibility that products could in fact do this. I was asked to present the experimental design issues on this point. We looked at such things as the types of prions and animal models which could be used to possibly validate such studies, the problems with such validation which particularly relate to the small, simple instrument proxies on the one hand and the reality of complex used surgical instruments on the other hand with their hard-to-clean shapes and the realities that that poses.

This, of course, is a huge surface which is

obviously dirty after initial cleaning. There are other issues such as the proper design of large animal studies which would be appropriate not so much to the making of a scientific point but rather to the validation of a commercial product with a degree of statistical significance that would be appropriate for that which is a little bit different from scientific investigation.

So, we asked the committee to consider the risk/benefit ratio in possibly approving such products. the benefit of course of having a product that could in fact reduce TSE transmission by contaminated surgical instruments would be to further reduce risk to patients.

Are there risks involved? These would be primarily behavior risks, the creation of a false sense of security about the possibility of transmitting TSE by contaminated instruments perhaps leading to the failure to adequately follow the practices currently recommended to reduce that risk for surgical instruments.

Is the potential benefit of approving processes or products which could reduce risk significant? Does this benefit outweigh the potential risks?

Dr. Estelle Russell-Cohen from the Division of Biostatistics in the Office of Biometrics and Surveillance gave a presentation on the statistical considerations of study design for product evaluation. The studies of course

must support the intended use claim.

Again, this is a little different from scientific investigation. The labeling instructions for product use do need to be supported by the study design and there needs to be a reasonable degree of statistical confidence in those results.

Good study design of course would include removing systematic error and reducing bias, looking at the endpoint, the time to death or range of symptoms. Are there extraneous variables particularly in veterinary study design which could have an impact on study performance? What about calculation of uncertainty and/or statistical significance?

We paid particular attention to the most common endpoint in the prion literature which is the log reduction endpoint. In the device literature we pay particular attention to a 6 log reduction in infectivity in our evaluation of sterility processes. That is sterility not prion decontamination.

In conclusion Dr. Russek-Cohen pointed out that the actual study design will vary with the scientific model and exactly what is being examined. This will drive how the systematic sources of variation will be designed but it is very important that the study be sufficiently sized to produce an appropriate level of certainty in the results.

Again, we are looking at the product evaluation not just the scientific studies.

To put our risk in a little perspective Dr. Ron Brown from the Office of Science and Engineering Laboratories presented a risk analysis on the likelihood of transmitting sporadic CJD in the United States by contaminated surgical instruments at the present time. Dr. Brown did not address the risk assessments that were developed in the United Kingdom but he has done it with numbers that are appropriate to the United States. He did not consider in this analysis the risk of transmitting variant CJD.

This is the formula that was used for a deterministic model and the default values are listed. He also looked at a probabilistic as well as a deterministic model and again used our default values appropriate to the United States in terms of number of neurosurgical procedures, estimated prevalence of sporadic CJD in the United States and when you solve these equations this is the range for the probabilistic model.

On the average you get a figure of a risk of less than one transmission of CJD by contaminated surgical instruments in the United States per year. It may be as low as .1. With a worst case scenario for the range of parameters it possibly could be as high as 3-1/2 to 4 cases

over year, but we consider that rather unlikely.

So, we really feel that in the United States at the present time the risk of transmitting sporadic CJD by contaminated surgical instruments when the appropriate precautions are used is quite low. It is certainly not zero.

We were fortunate to have a guest speaker from the United Kingdom from our sister agency and that is the Medicines and Health Care Products Regulatory Agency. Mr. Hidderley is the representative at MRHA who is particularly in charge of products involving TSE contamination and I have shortened his speech to the high points which are his opinion that new decontamination products are being presented to the market but the models chosen may not be substantive enough to assure that the product or process is adequately validated.

I should point out that the product has been approved in the United Kingdom at the present time for reducing the risk of TSE transmission related to surgical instruments.

In the United Kingdom the processing of contaminated instruments has been centralized to a specialized center. They are not using this product at the present time. Mr. Hedderley also pointed out that there is a great deal yet to be understood about reducing prions on

materials other than simple surgical instruments and at the present time there is not uniform agreement in the scientific community on the appropriate animal prion strain model which is most representative for variant CJD and studies appropriate to that.

I am going to present to you the questions that we asked of our panel and the answers which they gave us. The first question was assuming that a product sponsor seeks a claim for reducing TSE infectivity on stainless steel instruments is it in fact reasonable for such an indication to be validated using animal studies of TSE transmission and the committee pointed out that while there are other ways of studying the general issue of TSE biology that at the present time looking at such a claim animal studies would be the reasonable way to go. In fact, they are probably the only way to go today.

The committee was then asked to discuss the relevance of various design features for such validation studies. This was a rather wide-ranging discussion but the advisory committee agreed that the following points were particularly relevant to validation studies for a claim of TSE reduction and those were maximum study validation. One should try to go beyond 1 year in particular in observing the animals. The study population should be large enough for sufficient statistical validity.

Now, that was not further defined, but the committee made very clear that we want large-scale very statistically significant studies. The log reduction in infectivity shown by such studies should be as large as possible. The committee declined to put an exact numerical figure on that log reduction. The committee decided that human prion sources would be the most appropriate to these studies for both variant and sporadic CJD models and the committee did point out that they really felt that variant CJD strains as well as sporadic strains should be studied.

Transgenic mouse models were felt to be most appropriate for these studies and should a sponsor need a new not previously studied human CJD source the committee pointed out that it would be appropriate to characterize such a strain against known animal TSE models and/or the WHO reference strains.

There was a question as to whether or not the WHO reference strains should be suggested for actually doing these studies. It was pointed out by Dr. Aher that they are intended to be reference strains not primary study strains.

Another question for the panel of the three study endpoints cited in the literature log reduction in infectivity, mean incubation time and survival, either median survival or percent survival, which if any might be adequate for the validation of a reducing TSE infectivity

indication. Should demonstration of a particular level of reduction of TSE infectivity in one or more endpoints be expected in order to support such a claim and how may clinical benefit be estimated from these endpoints?

The advisory panel agreed that the log reduction in infectivity is the appropriate study endpoint for the validation of a reducing TSE infectivity claim. The committee declined to specify a particular level of reduction and stated that linking the mean incubation time to a log reduction in infectivity could demonstrate clinical relevance.

They asked what additional issues should be considered by FDA when evaluating indications for use for devices other than simple stainless steel surgical instruments. How can devices constructed from or including materials other than stainless steel, devices with complex shapes or difficult-to-clean surfaces be in fact validated, and the panel suggested that we should look at modification of the test wire surface, consider testing different materials and test simulated or surrogate device shapes.

The committee was asked how closely should we consider the treatment conditions for a product or process that would be used for such a claim. Should we look at things like instrument cleaning, the risk of fixing proteins, interactions between various steps in the

cleaning procedure and the committee said, "Yes," they wished to see the study conditions simulate the clinical conditions of instrument processing as closely as possible and specifically mentioned attention to a large bioburden dried on the instrument before reprocessing.

Finally, we asked the committee considering the current state of the science could an indication for use of complete elimination of TSE infectivity in fact be validated, and the committee said, "No."

This was the substance of our discussion.

Thank you very much for your time.

DR. PRIOLA: I think we will move on to Dr. Scott who will introduce the questions to the committee,

Agenda Item: Topic 1: Progress Report on FDA's Risk Assessment for Potential Exposure to Variant Creutzfeldt-Jakob Disease in Human Plasma-Derived Antihemophilic Factor (FVIII) Products

Introduction and Questions to the Committee - Dorothy Scott, MD, OBRR, CBER

DR. SCOTT: I am going to start with satisfactory products. Now, as of the last meeting we presented to you a risk model looking at the potential risk of vCJD transmission by plasma-derived Factor 11 and at that time we also presented to you a model for US plasma-derived products. As we started down this way after that last

meeting in February we recognized the complexity of the input for the risk assessment model for US products and so the purpose of this topic today is to have a public discussion and to ask you for your advice prior to selecting these input ranges.

Why a risk assessment? I am just going to go over this very briefly. Blood plasma may have risk. There has been transfusion transmission of vCJD reported in the UK, two cases and plasma has also been shown to be infectious in animal models of spongiform encephalopathies.

However, I would point out that there have not been any variant CJD infections diagnosed in derivatives of plasma recipients. Risk estimates provide a basis for examining the adequacy of current measures to protect blood in plasma-derived products and these assessments may trigger a threshold for actions including risk management communications, surveillance and these risk assessments contribute to public health decisions and I would just point out that with regard to actions that the UK and France and some other countries have taken actions based on their risk assessments.

Back in February we presented to you a risk assessment model and you were asked to comment with regard to the model per se. You will be seeing this again today. Dr. Anderson will be reviewing it for you and we also ask

you what additional information is needed to improve risk estimates with the various plasma derivatives.

You approved in general of the risk assessment framework and you felt that additional refinements should be made as more input information is collected. Different products obviously may have different risk levels and the committee recognized this. The donor travel history is important to consider and you will find out today what some of the variables are in figuring this out. The committee was also concerned about the 1-month exposure in the UK by a Japanese traveler who later developed variant CJD because this suggested that there may be a residual variant CJD risk in donors even with very brief travel to the United Kingdom.

Very briefly these are the main elements of risk assessment, the prevalence of variant CJD in US plasma and of course this is linked to the exposure to BSE and basically to travel in the UK and other countries, the amount of variant CJD infectivity in plasma, TSE clearance by plasma derivative manufacturing processes and patient exposure, that is how much of a product the patient has used.

The main outcome of a risk assessment for the main parameter is exposure per patient per year to one infectious dose 50 or more and 1 ID50 is only defined in

animal models but it represents a 50 percent risk of infection in these animal models.

Another outcome of risk assessments is to identify sources of uncertainty. That is what we will be talking about a lot today. I just want to point out to you that the uncertainty in a risk assessment model increases with its complexity and when data is lacking from multiple input parameters. We also get a sensitivity analysis out of the risk assessment and the sensitivity analysis identifies input parameters that have the most impact on the outcome and among other things this can focus data collection efforts to the most important parameters.

Some aspects of risk assessment are important to acknowledge. The uncertainties and ranges that are provided, it is really a probabilistic model. It doesn't give you an exact number. It gives you a range of numbers at the end. Data gaps need to be communicated with a risk assessment to provide context to the people who are affected by the risk assessment. Input parameters should be adjusted over time to reflect scientific findings and the outcome should be compared to the actual observed risk over time.

These are the folks you will be hearing from in this session. First Dr. Steven Anderson will give a review of the FDA risk assessment model and then we will hear from

Dr. Ghani and Dr. Knight about an update on vCJD in the UK and other countries, estimates of prevalence.

Dr. Alan Williams will talk about the modeling risk of variant CJD or rather the modeling of variant CJD in US illness, the residual risk and the efficiency of donor deferrals, and we will hear from Dr. Asher about the variant CJD infectivity of plasma, the estimates that have been made from experimental models. Then we will be discussing a review of TSE clearance in factory product manufacturing and then Dr. Mark Weinstein will be talking about Factor 8 product usage in the clinical Setting. So, overall we are going to be covering all those main parameters of input variables that go into the risk assessment and we are going to ask you a lot of questions and don't worry about remembering these right now because you will be asked these before each individual talk and we will put these back up at the end but this is just to start you thinking.

What is the estimate that should be used to reflect the prevalence of variant CJD in the UK?

How effective are current donor deferrals for geographic risk of variant CJD. In other words what is the residual risk in US plasma after donor deferral?

What intravenous infectivity range in ID50 should be selected for plasma based on animal studies?

Is there sufficient evidence to estimate when during the incubation period human plasma is infectious?

Do you agree with our proposed approach for estimating clearance of variant CJD infectivity from Factor 8 by the manufacturing processes and what experiments might enable refinement of these clearance estimates and allow comparison of clearance offered by various steps and methods used to manufacture plasma-derived Factor 8?

What data should we use to estimate how much Factor 8 is used by typical patients?

What is the effect of plasma pool size, that is the number of donors that contribute to a final lot of product for Factor 8 recipients and can a cumulative effect from repeated exposures to low doses of the variant CJD agent be incorporated into the risk model? We are also providing you with proposals to help you discuss these questions, and finally at the end of all this we are also going to ask you given the present scientific uncertainties in the underlying assumptions of the Factor 8 risk assessment do you believe that the risk assessment model as applied to Factor 8 could provide a useful basis for communication to patients or families and health care providers?

Thank you.

DR. PRIOLA: Next is Dr. Steven Anderson.

Agenda Item: Variant CJD Risk Associated with Human Plasma Derivatives: Introduction and Overview of Risk Model - Steven Anderson, PhD, OBE, CBER

DR. ANDERSON: Good morning. As Dr. Scott alluded to I am going to give an update and a progress report on the variant CJD risk model for US manufactured Factor 8 products.

So, I think most of you have seen this slide before in many of my presentations. It is sort of the grounding framework that we use for all of these risk assessments that we do. This is the elements of risk assessment that were developed by the National Academy of Sciences in 1983, and I am just going to point to some of the highlights of this particular slide as it sort of relates to what I am going to be talking about today.

Most of what I am going to be talking about today will deal with the exposure assessment component and what we are interested in this exposure assessment component is what is the frequency and level of exposure to a particular hazard.

In this case the hazard we are interested in is variant CJD agent in these Factor 8 products potentially and also then what we do is we relate this exposure which gives us the dose, and we add that along with the dose response information and the relationship which is a linear

relationship based on the ID50s that are published in the literature for animal experiments to finally get the risk and then we characterize the risk in the risk characterization section of the risk assessment.

So, this just sort of provides some basic background of what risk assessment is. Risk assessment is basically conducted when information is limited and uncertainty is high. So, throughout my entire talk one underlying theme throughout the entire talk is going to be this issue about uncertainty because it is a considerable element in risk assessment.

I think one of the important things to do though is to highlight the value of risk assessments. What role do they play in our decision making? Well, they are a tool that provides an estimate of risk and that can be the magnitude of risk or more specific information about the level of risk.

It details the uncertainties around that risk. So, it gives us a confidence level or confidence bounds around our estimate of risk and also it allows us to determine the effectiveness of mitigations, compare mitigations, identify which of those mitigations are potentially most effective in reducing risk and then finally it helps us identify data gaps and then determine research priorities.

All right, so again just to talk a little bit more about uncertainty and how uncertainty arises in these models as Dr. Scott alluded to uncertainty arises in risk assessment when there is only limited information available or when data are lacking and if data are lacking where this information is very limited it forces us to use assumptions or expert opinion in the model which increases the uncertainty in the model. There are also errors in measurement or data collection that can be an issue.

So, if the experimental data that we are basing a particular parameter on are flawed then that potentially can add to our uncertainty in the model.

There is also incorrect specification of the model. So, there can be problems. The model actually is incorrect. It is not considering all the factors that it should and that is an important part of uncertainty as well. So, I think you will see in some of the models that are going to be presented on predictive modeling for the size of the epidemic in the UK that those models are, the earlier models at least sort of just focused on the homozygous individuals at position 129 so they were methionine homozygous at position 129 of the PRP protein.

Now, what we are finding out more about as time goes on of course is that there are other individuals that are becoming susceptible to this disease. Those haven't

been included in some of these more recent models and some of the recent models under development actually are going to focus on those.

So, let me just go on?

Factor 8 risk assessment that we are developing, again I have to say it is under development. So, we don't have any results from the model specifically. So, we don't have any output. We haven't done any runs of the model. So, don't ask which I know people are usually are very interested in the results right away.

I think it is important just to tell you that the model for variant CJD risk that we are develop really specifically models the risk for these Factor 8 products made in 2002.

Again, 2002 we have a fair amount of data for that year. It is a recent year and also was the first year that the FDA deferral policies for blood donors and plasma donors was fully in place.

We can do assessments for additional years and I think you will see that we have proposed to do 1999 as a potential year and that would be prior to the implementation of the deferral policies here at FDA and through the blood centers and the plasma centers as well.

I think it is important just to emphasize that this is the beginning of a very long process to assess risk

for plasma derivatives and in the future we may assess variant CJD risk not only for Factor 8 products but for additional product classes. So, for instance we can go down the line for Factor 9 to anti-thrombin or a variety of other products.

We can also change the type of risk assessments so that we can possibly assess risk by specific products and manufacturers that produce those products. We could do it per individual per specific patient population, per individual, etc.

So, there is a wide range of possible routes for populations and products that we can potentially go with and choose to conduct risk assessments for.

Again, what type of risk assessment are we talking about? We are talking about a process model that analyzes the probability and quantity that the variant CJD agent will be in plasma pools and then if it is potentially in these plasma pools manufactured in the United States what are the potential reduction levels during processing and manufacturing, in the amount and levels of variant CJD infectivity in these pools and then what is quantity of factor by used by patients and that gets really at the question of exposure to variant CJD ID50s.

So, moving on I am going to provide just a brief overview of this model in a sort of diagrammatic format.

So, let me just orient you. Going down the middle are the modules and the components of the model. We have a four-part model here and on the left hand side we have the input and this is very important to focus on because these are the actual input information and data that we are using in the model and then on the right hand side we have the actual outputs.

So, these are what is being predicted from the model; what is the model generating as output, and it is important to note that is what is generated here goes on and becomes input into the next stage of the model and so on.

So, what is generated here goes here, here, goes here and then what we are finally trying to do is to estimate the annual exposure of recipients of Factor 8 products for the variant CJD agent.

I can walk you through at least a few steps of this. Our first module we are predicting the variant CJD prevalence in the United Kingdom. I will talk more about that in a minute and I will talk more about each of these components in just a minute but also we go from this variant CJD prevalence in the United Kingdom and that is used as a basis to predict variant CJD prevalence in US donors.

I will talk and sort of detail that more. What we

are interested in with donors is donor travel history, specifically those individual that traveled to the UK, France or Europe since 1980 and then what we do is we adjust that donor travel information that we have for each donor population, we adjust for duration that they traveled, the specific year they traveled and then donor age and then finally I think one of the most sort of effective mitigations that we put in place is we analyzed in this risk assessment the effectiveness of the screening questionnaire that reflected policies for donor deferrals.

So, that is a large impact on the model because that is the step where risk is reduced considerably. So, what we do then is we get the total number of variant CJD donors, the number of variant CJD donors post-screening and then the total number of variant CJD donations. That goes in and once we have calculated this those donations end up in plasma pools.

So, we go down to our next step which is the processing of those plasma pools into Factor 8.

We are interested in plasma pools because these donations are going to be going into those plasma pools. So, what size pools do they go into? What is the quantity of agent in the pools and then what is the reduction level through the manufacturing and process that the variant CJD agent if it is present undergoes during this manufacturing

process?

So, just to sort of emphasize what we get after that, we get the percentage of plasma pools and vials that may contain variant CJD agent and that is if they are made from a pool that contains the variant CJD donation from an individual infected with variant CJD and then what is the quantity of variant CJD agent in those vials?

Then finally what we are interested in is if patients use these vials what level of exposure will they be exposed to of this variant CJD agent? So, what is the patient's annual dose of Factor 8 and then finally we use that not only to predict annual exposure to Factor 8, I am sorry to the variant CJD agent but then to calculate their risk to that potential agent and I will explain a little bit more about that toward the end of the talk.

What are our proposed modeling approaches for modeling prevalence of variant CJD in the United Kingdom? Our proposed modeling approach is we propose to use two sources of data to estimate UK variant CJD prevalence. First would be a predictive modeling approach based on variant CJD cases in the United Kingdom.

Our second approach would be to use surveillance data and that surveillance data specifically involves the examination of tonsil and appendix samples from UK patients I believe in the mid-1990s.

I should mention that there is a disparity right now of approximately 10 to 100 fold between these two approaches. This seems to give a higher level in prediction of prevalence than the models.

I think what we are going to find in the future is that these two sort of estimates and these data sources are coming closer together as far as their estimates and I think they are going to probably sort of meet perhaps somewhere in the middle of these two estimates but we propose to use actually data from both in our modeling. So, let me just go through what are the predictive mathematical models.

These are some of the data we may use again. There are probably hundreds of these types of models out there and hundreds of publications.

Dr. Azra Ghani is going to talk more about here work and I think I have got this right. Her publication in 1990, she estimated a median of 100 cases in confidence intervals of variant CJD in the United Kingdom. That worked out to a median of about 1 in 500,000.

There are some other recent estimates, too, by a French group and the author is Belleli et al. They estimated approximately 180 to 300 cases and then there is also Lewin who estimated a variant CJD infectious prevalence in the population perhaps of 1 in 15,000 to 1 in

30,000. That works out to about 1000 to 2000 infections. I think this one is probably quite different from these other two.

These other two basically just model the clinical cases that could potentially develop in individuals that are methionine homozygous at position 129 of the PRP gene while this considers the other backgrounds, not only those methionine homozygous individuals but also the methionine-valine heterozygous individuals and also the valine homozygous individuals and just to remind people that the methionine homozygous individuals represent about 40 percent of the population. The methionine-valine I believe represent about another 40 percent as well.

So, again, this sort of brings home the point about model specification maybe slightly incorrect for these earlier estimates but this is an evolving field as we get more information about the infection and the type of infections that can occur. These models are getting updated probably as we speak.

Let me go on to the surveillance data. I just wanted to remind people that the surveillance data is based on tissue samples in UK patients in the 1990s. It was a surveillance study, a very large study and what they found was 3 prion positive samples in appendices in 12,674 samples tested.

That works out to this mean positive of about 1 in 4200 individuals. That works out if you correct it to about 13,000 variant CJD infected individuals. This isn't an age corrected number at this point. It is just a rough estimate.

This comes out as a very high estimate you will notice and this is, if you will remember the estimate that w used in the Factor 11 model that we presented to the committee in February of this year.

At that time we thought that perhaps this type estimate was higher and we used it because we thought it might capture some of those other methionine, valine heterozygous individuals that are asymptomatic and then also the valine individuals that are homozygous at codon 129, that it might also catch those individuals and what you asked us to do with that data that we used in that model was to age adjust that.

So, if we used this data we would of course age adjust this because this was collected in individuals that were 20 to 30 years old. So, we would adjust it to reflect prevalence distribution across all age groups in the UK population.

I think it is important to talk about uncertainties in this data because basically all data and all the information that we used in these risk assessments

have some sort of limitations or uncertainties associated with them and the uncertainties of the proposed modeling approach is that predictive modeling really is based on the known variant CJD cases in the UK for the most part.

Most of the estimates although some of the models now are estimating in other populations but most of the models are valid for clinical cases of again this methionine homozygous codon in position 125 for those individuals. It doesn't capture the other genetic backgrounds.

Again, they use assumptions in these models for incubation period, time of infection and other factors. So, again that adds another level of uncertainty to these types of approaches.

All right, the surveillance data are no better. Using those again these are examinations on appendices samples. One sort of critical drawback here is that you can't go back and determine what the disposition of that patient was from which that sample was harvested and so we don't have any idea whether those patients actually became symptomatic or not or whether they actually came down with variant CJD or another TSE disease per se and another sort of drawback is variant CJD agent maybe in the appendices at the time but they may not really represent a threat for the blood supply if the agent isn't in the blood.

So, we may be overestimating the risk if we use this particular type of approach. Some people may say that we may underestimate the prevalence of the disease again. In one cases, one of the infected cases that were identified the agent actually wasn't in the appendices at the time the infection was identified.

So, again, both types of data have particular drawbacks and uncertainties associated with them. Again, probably neither case sort of adequately addresses the clinical or asymptomatic cases for the methionine valines or the valine homozygous individuals. That potentially could exist in the population and then they probably don't also sort of well represent the variant CJD infections in all of these groups that don't progress to symptomatic disease.

Okay, just going on through model 1, I think it is important at this point as I sort of end on this module that this is a critical parameter in the model and it is used to estimate not only variant CJD. We are not only using this for the UK population but we are going to be using a relative risk approach to estimate variant CJD prevalence for France and for Europe, and then ultimately what we do is we add up all those prevalences for the donors in the United States that have traveled to those regions. So, we are going to be using that for this variant

CJD estimate of prevalence to also estimate plasma donor risk in the United States.

So, this is a critical parameter really to get correct. So, we need the best information available and possible for this particular point in the model. Just going back to the next step which is modeling prevalence of variant CJD in plasma donors and there are several modeling approaches that were, not several modeling approach that we are using.

Our goal is to estimate the size of the US donor population with a history of travel to the United Kingdom, France or Europe since 1980. Again, if you will notice this model if we go to 2002 is going to span 23 years of information. So, it is a rather large model at this point.

If we model this portion correctly we plan to determine travel characteristics from a survey that we have and that data was from the American Red Cross and then what we would do is adjust the travel data for each individual that has traveled by their duration of stay, the year of travel and their age and then our plan is to estimate the probability of infection in those individual donors based on the amount of time that they stayed in these particular countries and then ultimately what we would do is we would hope that we will add up the potential number of variant CJD cases in US plasma donor groups and then get the number

of donations that they would donate and those would feed into the next portion of the model.

So, our model output, what we hope to predict would be the potential number of variant CJD infected US plasma donors, the variant CJD infected donors that are actually deferred from donation. The real risk that lies here I should say is in the donors that aren't deferred.

Those donors that are deferred from donation even if they have variant CJD don't really pose a threat to the blood supply or the plasma supply. What we are interested in is those individuals that actually evade the screening process by some way either incidentally or accidentally.

Then finally what are the potential number of donations that potentially contain variant CJD agent that enter these plasma pools that are used in manufacture of Factor 8?

All right, so moving on about prevalence of variant CJD in the US plasma donors our major assumption in the model is that variant CJD in US donors basically derives mostly from dietary exposure to BSE agent during travel. Again this is mostly travel in the United Kingdom but then secondarily travel in France and Europe.

Now, our current deferral policy is listed below. It defers donors with a travel history for instance, travel to the UK for individuals that traveled 3 months or more

from the years 1980 to 1996, 5 years or more from 1980 to present, either in France or Europe and I think the important thing for Europe is that it is travel for 5 years or more from 1980 to the present for blood donations only and not for plasma donors. Again, I think Alan Williams is going to talk a little bit more about this in the subsequent talks but we are estimating somewhere around a factor of 90 percent to 99 percent factor of effectiveness in eliminating these variant CJD donors and the risk they may pose in transmitting infection if indeed they have agent in their blood or plasma.

So, what is the actual residual risk then after this policy has been put into place and where may risk lie in the system for plasma and for blood products?

What we have identified are two specific groups of interest. Again, it is these with deferrable risk and it is those 1 to 10 percent that have the deferrable travel history but for some reason evade the screen and get through and are able to donate plasma or blood and then the second source potentially would also be those with short duration travel to these countries and that again would be just what is not covered by the policy. So, that would be UK less than 3 months, France less than 5 years and Europe less than 5 years again during these specific time periods.

So, again, we are not only planning to model the deferrable risk but we are also planning to model this short duration travel as well because we believe that may pose risk as well.

Again, a number of individuals, probably the bulk of individuals fall into this category and that is why we are modeling it whereas fewer individuals have traveled to France for 5 years or more or to Europe or the UK for these long periods of time.

So, then we move on to the concept of relative risk and how it is being used in the model. Again, we are doing this modeling for a period of about 23 years for all donors that potentially donate plasma in the United States and how we are doing that and what we are using for prevalence is we are using this concept of relative risk that was used when the policy initially was set up and it is used to estimate the variant CJD prevalence for France and Europe relative to the UK prevalence.

So, I will provide an example down below in a minute and this relative risk estimate is based on a number of factors such as the potential for BSE exposure in France or Europe, the number of variant CJD cases, imports of feed and those types of factors. So, for UK the relative risk assigned to the United Kingdom has been a value of one and that is equivalent to the UK variant CJD prevalence.

France is thought to have about 1/20th of the risk or .05 of the risk. In our calculations these factors just become multipliers against the UK variant CJD prevalence. Europe has a risk estimated at about 1.5 percent or 1/60. Again that becomes a model, a multiplier in our model against the variant CJD prevalence and then there are individuals that spent significant amount of time in the military. That is estimated at 3.5 percent. Again, that becomes a multiplier in our model as well and then a final group of interest to us that may have been exposed to the variant CJD agent is those that received Euroblood and Euroblood was blood that was collected in three regions in Europe and then was used in the New York City region in the United States and given to recipients from donors that lived in Europe.

So, that multiplier is .015 times the variant CJD prevalence and then we have again further adjusted for the age of the European donor in that case.

So, relative risk for UK plasma donors, for US plasma donors with travel history -- so just to remind people what we are actually doing is we are applying this relative risk concept to US plasma donors with this history of travel to UK France or Europe since 1980. Again, as I mentioned this is a 23-year period. I just wanted to reinforce that we are adjusting for the duration of travel

during this time period. It is a very critical factor because a lot of individuals spend only a few days in the United Kingdom. So, this is actually the biggest adjustment to that relative risk factor.

The specific year of travel we are also interested in spanning this time period and what we are doing is we are linking this to the variation in the BSE epidemic essentially linking it to the BSE epidemic curve.

So, somebody that traveled for instance at the height of the epidemic in 1993, would have a higher risk than somebody that traveled for instance at the start of the epidemic in 1980 or at the end which is probably around 2000 or even currently, so, those individuals or 2002. So, we account for the specific year of travel. We are also accounting for the donor again to apply the age specific rates for variant CJD in the United Kingdom. Again, the median age is 28 years and this is very important since most of our blood and plasma donors fall into this around this age category in the age 20 to 40. It is important to do this age adjustment for the specific rate of variant CJD.

All right, so we adjust by those three factors. I, also, wanted to say that we plan to model two types of plasma donors specifically the plasma donors and that represents greater than 80 percent of the donations. That

is the source plasma donors. Again, those are collected by processes such as plasmapheresis.

Again, the second population then would be recovered plasma donors. Those represent less than 20 percent of the donations and those are whole blood donations actually that are recovered. The plasma is recovered from those.

Again, we have age-specific donation rates for each of these groups and we are planning to include those in the model as well.

Then finally just to give you an idea of where this plasma donor travel information is coming from we estimated this from survey data that was conducted by the American Red Cross. The survey was conducted in December 1998 and January 1999, and was presented in front of this committee I believe in 2000 or 2001, and what that survey covers is it queried travel history and accumulated stay information for the UK and Europe and from that we can make a few assumptions and infer travel specifically for France during this period from 1980 to 1996.

So, that gives us the bulk of the risk that we are interested in and then we are having to extrapolate further to cover the additional years since 1996 for France as well.

So, we do have some survey data and just to

remind people that this is survey data in blood donors; it is not for plasma donors. So, that adds a level of uncertainty to this information.

Again, modeling the effectiveness of geographic deferral is an important aspect to this model. Again, we have this deferral policy for UK, France and Europe. Dr. Alan Williams is going to discuss more about that in his presentation.

I think I would just lay out some of the basic values that we are interested in that could be used in the model. We haven't particularly modeled either of these yet but we could use a factor that reduces 90 to 95 percent of the risk for first-time donations and then add a second layer to that which is a level of reduction of 99 percent of the risk for those that are repeat donors, and I should mention that probably greater than 90 percent of the donors of plasma are repeat donors.

So, we are eliminating essentially two logs of risk or 99 percent of the risk if we use this factor. So, that is something the committee may want to think about as well when they are discussing this particular issue.

So, let me move on? Another key factor is when is variant CJD agent present in blood during the incubation period. There is going to be a detailed discussion of the data by Dr. David Asher.

I think that I should just touch on the two potential approaches that could be modeled. What we could do is model if the agent is present in the bloodstream or plasma during the entire incubation period and I wanted to remind people that this is an assumption that we used in the Factor 11 risk assessment that we presented earlier.

We could model it as being present in the last half of the incubation period or later in the incubation period and this is based on experiments or one experiment by Dr. Paul Brown in which blood was found to be present later in the incubation period for a specific TSE model. I think one thing to point out is that the modeling in this case would be complex. It would increase uncertainty perhaps in the model and then also we would have to make a few assumptions about the duration of incubation periods.

So, we would have to think carefully about whether this approach is really something that we want to do, but we would like, I think, some feedback on that from the committee.

Uncertainties in the model, I will sort of speed through some of this since I am running short on time. The survey conducted on whole blood, so we have survey information on whole blood donations and the travel history for those individuals but what we don't have is survey information on the travel characteristics of source plasma

donations and anecdotally people believe, I think that source plasma donors may travel less. So, if that is true then our blood donor travel information that we are currently using may slightly overestimate the risk for the source plasma donations. So, that is a little bit of uncertainty in the model.

Estimation of the deferral effectiveness is a challenge because there is the issue of self-deferral. So, many people don't even come in to donate blood or plasma because they know about the policy that is in place and then they just don't show up to donate blood or plasma, and that is a significant problem.

So, we don't actually know the total number of individuals really being affected or deferred by this policy. We don't know the denominator information. So, that is a challenge and then estimation again of when variant CJD agent is present in the blood from the animal data whether this is accurate or not for humans we don't know. It may be present the entire time in humans and it may be present only toward the end of the incubation period. We just don't know.

Just going through quickly for getting onto module 3 for Factor 8 processing and manufacturing our proposed modeling approaches to estimate the probability that a plasma pool will contain a variant CJD donation

estimating the quantity of variant CJD per ml of plasma and then the amount of agent per pool we would estimate the efficiency of exposure and incorporate this into the model for the IV route versus the IC route and we would also include log 10 reductions and the log reductions in the quantity of the infectivity during the processing and manufacture of these products.

So, once we have that type of information input into the model then we would use t he model to output to predict the percentage of pools and vials that contain variant CJD agent and then the quantity of agent per vial.

So, we are getting further and further down the chain to the point where we are at the point of estimating the percentage of vials and the quantity of agent that may be contained in those vials.

A proposed modeling approach at least for the quantity of infectivity, Dr. David Asher is going to discuss this more in a minute in his presentation and this is intracerebral ID50s of the variant CJD agent per ml of blood. We propose to use a triangular distribution with the minimum of .1, a most likely of 10 and a maximum of 310.

Again, these are just sort of ranges that we found in the literature and we are interested in what the committee's perspective is on these particular data.

Again, this is just proposed approaches for the

estimation of the efficiency of the exposure route to variant CJD ID50s or infectivity. In the Factor 11 risk assessment we used a value with a range from 5-to-10-fold based on experiments by Kimberline and also by Paul Brown's lab.

Recent unpublished data suggest that this might be lower. It might be only 1-to-5-fold. So, that is a question for the committee. We would propose again to use the estimate of 1-to-5-fold now for the adjustment in efficiency from intracerebral to the intravenous route.

As far as the plasma pool size we would propose again, we have information that suggests the plasma pool size used in the manufacture of these products ranges from 20,000 up to 60,000 donations. I think it is clear that we need more accurate information on the size of these pools used in manufacturing. So, at this point what we would propose to do is we would propose to use a bimodal distribution that favors sort of this 20,000 and also favors the 60,000 as an estimate of pool size.

So, 20,000 to 60,000 is the estimate for pool size for these products at this point. Just getting towards the modeling of the reduction in the amount of infectivity during the processing Dr. Scott is going to talk about this, Dorothy Scott, some of the reduction levels again, we are expecting that at least some level of

reduction will occur during processing and manufacture of Factor 8.

I think it is important just to emphasize the designations for the degree of Factor 8 purity whether it is intermediate or high purity products may have little relationship to the level of variant CJD ID50 clearance.

So, I think that is an important thing to keep in mind. Just because these are high purity we are not sure exactly if they are going to be a high level of clearance or not.

We propose to use three values for the log reductions around these ranges of two logs of reduction, five logs of reduction or eight logs of reduction.

Again, uncertainties in the data, there is only a limited amount of data available on TSE reductions for a small number of processing steps and few products. The levels of reduction have been achieved in these experiments with spiked infectivity. The question is will that reflect actual levels of reduction using the endogenous material that is used during the manufacturing process.

Experimental data obtained for TSE agents that are other than the variant CJD agent that we are interested in; so the question is is there going to be an exact correlation between variant CJD reduction and for instance scrapie reduction or other types of agents that were used

in these experiments, and another bigger question is does addition of these orthogonal reduction steps reflect the actual reduction of ID50s during manufacturing, so a lot of uncertainties in this type of data.

Utilization of Factor 8 in module 4, again we are very near the end of the models. So, our proposed modeling approach is to estimate. Again we are getting this from the previous section, the percentage of vials with variant CJD agent, the quantity of agent per vial and then we want information on annual utilization and dose of factor 8 that each patient might use or patient groups may use and our goal would be to model the annual dose of variant CJD that a patient is exposed to either per patient, per year is a possibility and then a prediction of the risk ultimately of variant CJD infection based on animal dose response relationship.

Just for time I think I am going to skip over an important set of slides but moving on just to talk about utilization of Factor 8 some of the utilization factors we are considering in the model is the severity of hemophilia. So, we are going to be modeling risk for severe, moderate and mild individuals and under different treatment regimens, prophylaxis and sporadic types of treatment or episodic treatment.

The type of data we are interested in using for

the model would be the data for instance that comes from the Centers for Disease Control's hemophilia treatment centers. They followed 3000 patients from 1993 to 1998, and have utilization information based on review of medical charts. So, this is very good data and we may end up using it in the model if nothing sort of more recent comes along, but if available we may use additional data sources for instance from medical databases such as Center for Medicare-Medicaid Services, HMOs or Medicaid organizations for particular states.

Okay, so again just to highlight some of the uncertainties I will sort of rush through these. The utilization data isn't the most current and may not accurately reflect some of the current prescribing practices.

Patients may be on multiple products and the data don't really sort that out. So, that is one challenge that we will have. Patients may move among categories and that may not be captured in the data specifically from for instance prophylaxis to episodic treatment.

So, we are seeking additional data sources in order to get the best information possible on how patients utilize these particular products for treatment of their disorders.

Should FDA model the apparent cumulative, non-

linear effects of repeated dosing? So, one question that we have is if you get a dose one time of variant CJD agent how does that compare to somebody that is using this product multiple times; you know, how does that risk compare to one hit versus they take 10 injections of that product over a period of time? Is their risk higher?

So, we would like to at least try to incorporate that into the model in some way and we are sort of having a challenge as to figure out how to exactly do that. So, we are interested in the single dose episode but also repeated and cumulative doses.

Dr. Mark Weinstein is going to talk a little bit more about the details of this but again it is a big challenge for us to model this.

The limited data available suggest in some cases there may be an added non-linear increase in infection rates with repeated dosing. So, to account for this what we propose is to model the cumulative variant CJD exposure per annum or per year and we would assume a linear ID50 dose response with that.

So, that is our answer right now is to assume exposure for a year and then try to estimate risk based on the dose-response information that we have.

That is certainly something that we are seeking input on. Again, just to remind people this exposure

assessment is going to give us information on the dose of variant CJD ID50. So, we get this estimated dose from the model coupled with dose response information that we have to finally estimate risk.

Another issue that has come up is this sort of reflects our relationship for the linear dose-response. We assume that an individual exposed to one ID50 has a 50 percent probability of infection. Somebody exposed to .1 ID50 has a 5 percent probability and we don't really know if this is true or not. What is the meaning of a fractional dose? And that is an important question I think that we need to answer in the future and definitely need more experimental data to resolve that issue, but again right now we are assuming a linear dose response to estimate the risk. So, we are taking dose times the dose-response relationship to estimate the risk or the probability that a person will be infected with the agent.

Finally, again, a lot of uncertainties here; we are using an animal dose response to estimate human risk, a lot of uncertainty there. It is limited data to get that dose response. Human data are not available just to remind people of that and the development of the human dose-response model therefore is not possible at this time.

Some of the conclusions are the estimate risk of infection based on the level of exposure can be predicted

using the model. So, we can get a relative estimate of the risk and the level of exposure that a person using Factor 8 products may be exposed to this variant CJD agent.

The risk prediction is based on animal data and animal dose response. So, again, it is going to be highly uncertain but I think one of the important things is that it will highlight the data gaps and uncertainty and hopefully t hose will improve in subsequent iterations of the risk assessment.

It is important to just sort of emphasize that risk assessments provide information on relative magnitudes of risk and this is somewhat useful for risk management purposes depending on the types of predictions that are generated and that is the end.

DR. PRIOLA: Thank you.

Next is Dr. Richard Knight, Director of the CJD Surveillance Unit, Edinburgh.

Agenda Item: Update on vCJD in UK and Other Countries: Estimates of Prevalence - Richard Knight, MD UK Director, CJD Surveillance Unit Edinburgh

DR. KNIGHT: Thank you very much. This is a two-part presentation and I am going to begin talking from a clinician's point of view which is what I am and then Azra Ghani is going to follow on with a more statistical point of view and I am going to after a very brief introduction

talk about the illness and its diagnosis, deal with some important questions and then turn to human transmission before passing on to my colleague.

So, a brief introduction, I am not going to go into all this in detail because obviously everybody here is familiar with this, but I do want to stress that I am going to talk about CJD essentially and really variant CJD.

These are the underlying assumptions that I will take as given, that the key molecular event is the post-translational change of the PRP protein from the normal cellular form to the abnormal disease-related form, that t his is going to be deposited in tissue and that this is associated with disease and associated with infection but I am going to pass over the difficult and controversial issues as to the precise nature of that association and what is more and it is important of course, misconcepts that while the disease is limited to the central nervous system the deposition of the abnormal protein may not be, and as you have already heard about this I will pass over it quickly but the prion protein gene is of critical importance and in particular the common polymorphism at codon 120 and here you can see that people can codify the methionine or valine. Therefore all of those are either MM homozygotes, VV homozygotes or heterozygotes and the significance of this is that this to some extent may affect

susceptibility to these diseases. It may affect the incubation period in he quiet forms and it can also affect the clinical pathological features of the resulting illness.

This is the normal UK population. Just over one-third of those are methionine homozygotes, about one-half MV heterozygotes and the rest valine homozygotes. This does vary from country to country with roughly an east to west drift so that in Japan over 90 percent of the population are methionine homozygotes.

This is variant CJD, and you can see straightaway that all tested cases to date, 154 in total have been methionine homozygotes.

So, I will turn now to the illness and this diagnosis and we have identified 158 cases to date in the UK. You can see it is a disease of the relatively young. The youngest age of onset so far is 12. The oldest age of onset is 74, median duration 14 months although it can be very short and we have one individual who is still alive at well over 40 months. Apparently more men are affected but this is not a statistically significant difference and at any stage we tend to have a few people alive with the illness in the UK and at present we have seven.

This is just the background and I am not going to discuss it in detail but these are the three elements in

the theory of variant CJD and as you go down the line the color blue becomes lighter because the evidence becomes thinner.

Certainly the diseases do appear to be caused by identical agents although of course we haven't characterized the agent and therefore all the evidence is indirect. It does not appear to have passed from a third animal or somewhere else into cattle and man. It does appear to have gone from cattle to man and it does appear to have passed in diet. We don't have any other reasonable theories. Our observations in the UK do not suggest any other plausible route and indeed our case-controlled study has now started to produce evidence that modestly but does support the dietary theory.

This is a rough outline of what we think happens. Infectivity from cattle enters food. Food enters the human gastrointestinal tract and then enters obviously the human being in general. There appears to be an important lymphoreticular phase. These are the tonsils, the spleen and of course the appendix and they Peyer's patches in the intestine and after some period apparently by a neurological route the infection enters the brain.

It may be through nerves in the gut going into the spinal cord and descending northwards. It may be the vagal nerve going directly into the brain stem. It may be

through the trigeminal or glossopharyngeal nerve into the brain stem, then into the brain where disease results, and this is a probably pattern of tissue infectivity in humans, infection, a rise infectivity in the lymphoreticular system which then plateaus and later rising of infectivity in the central nervous system and at some point the beginning of clinical disease with central nervous system infectivity being significantly higher than that found in the lymphoreticular system.

This is just to illustrate the points about preclinical and subclinical infection as I am going to use them. You may become infected. There may be no evidence of an infectivity and then there may be lymphoreticular colonization. Then there may be neurological disease and the incubation period is the time to neurological disease followed by clinical illness and death from variant CJD.

In subclinical infection you may get nothing to start with and you may get lymphoreticular colonization but you get no variant CJD and die from another cause, and why would that happen?

One thing is the incubation period may be so long that it exceeds the life span of that individual either because the incubation period is longer than the normal human life span or because this individual dies for another reason before they have a chance to develop disease.

It may be there is a genuine subclinical state whereby no matter how long somebody lived they would actually never develop infection.

The difference between these two situations is of course rather theoretical at present. I don't know any way of distinguishing between them in human beings.

So, that of course brings us on to the incubation period of this disease and I think Azra Ghani is going to approach this in a rather more rigorous form but just to outline it in general we think the minimum incubation period is likely to be around about 5 years, the mean somewhere around 10, but the maximum may indeed be very long indeed.

Now, when you look at prion diseases there are certain factors which have been called determinants of the clinical pathological features but they may in fact be associations. I will pass over that point, and they are first of all cause, secondly route where these are acquired, thirdly, agent strain, a rather complex and controversial issue but nonetheless these agents do appear to exist in strains with different biological behavior, the type of protein found in the tissue and the 129 genotype, and if you look down at variant CJD there is apparently one cause at present, one route at present, one agent, one protein type and one prion genotype and therefore it is

hardly surprising perhaps that in the United Kingdom and elsewhere this disease has been very homogenous from a clinical and pathological point of view which is rather unlike what you see in some other forms of prion disease, but certainly from a surveillance system point of view the critical factors that you change any of these factors like have a route other than the oral or you have a different genotype, then it might be that the resulting picture would be different and we might have to look out for a new variant CJD.

The illness tends to present with psychiatric and behavioral symptoms rather than the typical neurological presentation of many of these diseases. You may get other symptoms but they are often non-specific and taken as part of the psychiatric picture, and neurological signs appear usually around about 6 months into the illness and this is an illness of median duration of 14 months.

So, these people present with multiples symptoms with a psychiatric flavor without neurological signs and early neurological diagnosis is really very difficult indeed. There is no simple clinical diagnostic test at present.

The diagnosis therefore requires neuropathology if you want to be certain and this is a critically important point if you really are wanting to know for sure

about variant CJD in the population. You need good neuropathology with effective autopsy rates and that does not happen in many countries.

A clinician approaches this by suspecting the disease in the first place which requires a suggestive clinical picture and for the clinician to understand of course what the picture looks like. They have to exclude alternative diagnoses and that I should stress includes other forms of CJD and so you need a knowledge of clinical neurology and of CJD in general and there are supportive tests which while not absolutely diagnostic are helpful if you understand their role and one particular very useful test is the MRI and what you see in variant CJD is this high signal in the posterior thalamic region, the pulvinar sign which is present in over 90 percent of our cases if you use flare sequencing and of course if you use certain standard techniques you do not find the abnormal form of the prion protein in lymphoreticular tissues in other forms of illness but you do find it in variant CJD and so tonsilar biopsy is sometimes potentially diagnostically helpful.

Now, I mentioned the differential diagnosis and it may seem perhaps a bit odd to anyone who has seen some cases of sporadic CJD but they could be confused with variant, but some genetic forms of prion disease may look

like variant CJD and there are atypical sporadic CJD cases that may be atypically young with unusual even psychiatric presenting features with an atypical clinical course and an unusually long duration and in the United kingdom the main differential diagnosis of variant CJD is sporadic CJD and throughout the world we get notified every now and again of cases that are thought to be variant CJD occurring for the first time in a new country which are in fact atypical sporadic CJD cases and I think that I would stress again the importance of autopsy and stress also that if you are really interested in surveillance of variant CJD you need to have an effective surveillance system for all forms of prion disease.

How would you tell variant from sporadic apart? The MRI appearances can be very useful but they are not completely reliable. Tonsilar biopsy is certainly a possibility but a negative tonsilar biopsy can't exclude the illness and it is a relatively invasive test.

The histological appearances of course are important and so is protein typing but they require of course brain material. In the end the final arbiter at present is experimental transmission characteristic, i.e., you take material put it into laboratory animals and you look at the incubation period and the neuropathological lesion profile. However, that is clearly difficult and

expensive and is only done in particularly important and difficult cases and just to finish on this topic this is the US CJD collaboration showing the standardized mortality ratios which of course should be around one and the countries in yellow are those countries that have mortality ratios that are not significantly different from one. The ones in blue, Slovakia and the United Kingdom are countries which have statistically lower mortality rates and I have no idea exactly why that is and two countries, France and Switzerland that have statistically higher mortality rates and again I am not sure why that is and certain countries like for example, Switzerland have shown a significant increase in identified sporadic CJD cases recently.

The explanation for this is not clear but there is a lot of collaborative research going on within these countries and all I can say at present is that there is no evidence that these differences or changes are due to unexpected infections with BSE.

So, that leads to questions, the relative youth, the numbers of cases, other genotypes, other countries and then going back to the preclinical, subclinical issue.

This is the graph showing the age at death or the present age if they are still alive of cases in the UK and you can see that they mostly fall in this 10 to 20 age

group and what is more striking is that over the whole period of the epidemic in the United Kingdom this age of onset has not changed which is a big curious for a disease which is supposed to have been due to a limited time exposure of infection and stands in need of some explanation, and the three explanations that I have heard put forward are one, different age-related exposures, two, age-related incubation period, and three, age-related susceptibility and all I can say is that from my UK data we do not think that age-related exposure is likely to be a major factor, and therefore it is likely to be one or both of these and indeed of course they may in some way be related.

These are the numbers of cases. These are onsets in the United Kingdom showing a rise and then a fall although the figures for 2003 and 2004 are incomplete and you can see that there almost appears to be a rise again in 2004.

Mick Andrews of the Health Protection Agency produces curves to fit these data and the best curve at present is a quadratic curve. These are deaths showing a peak in deaths in 2000 with a subsequent decline. However, these profiles relate to dietary and codon 129 MM cases and of course the numbers and predictions will be dealt with in more detail by my colleague afterwards.

So, will there be non-MM cases? The only thing that I can say is that it is virtually certain that there will be non-MM cases and why do I say that? Well, first of all if you look at other prion diseases, iatrogenic CJD or kuru, other genotypes are affected. Secondly, one of my colleagues in collaboration with other colleagues in Edinburgh is looking at the human transgenic mouse model and while I can't I am afraid disclose the results of this experiment in detail the experiment's preliminary data suggests very strongly that other genotypes will be affected by BSE infection and of course we do have a case report of lymphoreticular systemic involvement in an MV blood recipient. This of course was not variant CJD itself and presumed to be an infection related illness rather than a dietary one but nonetheless it does show that and MV individual can have BSE infection.

If all this is true what we expect is first of all that longer incubation periods will be apparent for these genotypes which is perhaps why we haven't seen them to date. There is also some reason for believing that you might get more subclinical infections in these non-MM types and certainly that is evidence that is coming again from these human transgenic mouse experiments and the clinical pathological phenotype might be different and again, the human transgenic mouse experiments are beginning to suggest

that the clinical pathological phenotype in non-MM cases might actually show some significant differences which is an important point for surveillance.

Well, now, aside from the UK these are the figures and you can see that France is next in the lead with 15, Republic of Ireland 4 and the rest of the countries single cases only.

The dark blue countries here are those countries in whom the cases are thought on good grounds to be intrinsic to those countries. They are cases in those countries who were infected in those countries. These colors here are those countries in whom they have had cases but it is thought that they were infected during stays in the UK and you can see here for example the USA case is considered really to be a UK case.

Saudi Arabia, the status is uncertain but I think it is likely to be an intrinsic case to Saudi Arabia. The Japanese case you have heard already is attributed at present to the UK. It is very difficult. The decision was a problematic one since they stayed for less than a month in the UK but it was thought that it was very unlikely that they would have gotten the infection in Japan intrinsically. It was also felt very unlikely that they would have gotten the infection during the 1-month stay in the UK but the probability that it was in the UK was

marginally higher than it was for due to Japanese intrinsic infection.

Now, I will move on to preclinical and subclinical and we do have definitive evidence that the lymphoreticular system can be involved preclinically. These are two cases, one with onset of disease in 1995, and one in 1998 both of whom had their appendix removed due to routine surgery 8 months and 2 years prior to onset of disease and in both of these cases the appendices were examined and found to be positive.

So, the appendix certainly can be positive at least 2 years prior to clinical onset of disease. We, also, of course, have two cases of probable transmission by blood donation from individuals who at the time they donated did not have variant CJD. They were preclinical cases and therefore infectivity implies infection. So, these individuals must have had some form of preclinical infectivity and there is also of course the case of the lymphoreticular positivity in a blood recipient who did not have variant CJD and therefore again was some kind of preclinical or subclinical case and we have the UK appendix study.

Now, this is something you have already heard referred to. This was undertaken by David Hilton and James Ironside and others and they looked at surgical specimens

from across the whole of the UK population. We don't know anything about the genotype of these individuals who had their appendix removed and presumably unless there is something peculiar about the prion protein and appendicitis they should represent a cross sample of the normal human population.

They were tested for PrPsc and nearly 13,000 appendices were examined and three of them were found to be positive. Now, if you extrapolate this data across the UK population then it would suggest that 247 per million of the UK population have appendix positivity. Of course, the 95 percent confidence intervals are wide. Most appendectomies are done in the 10 to 30 age group in the UK. So, if you adjust for that that would suggest that in the 10 to 30 age group in the UK nearly 4000 people have positive appendices for this abnormal protein, again with wide confidence intervals.

Now, you have heard there is a discrepancy here and indeed there is. If you say in this age group here there are nearly 4000 people with lymphoreticular positivity bearing in mind the wide confidence intervals yet within this age group we have only noted 92 cases of variant CJD and variant CJD in the UK appears to be in decline; so, what is the explanation for this?

Well, people have suggested that there could be

false positives in the appendix study. I am not a neuropathologist, but I am given to understand that this is extremely unlikely. Of course, we don't know if the codon 129 genotype of these three positive appendices. They are being studied but I cannot tell you the results at present.

Of course, all the cases so far have been MM and it may be that the appendix cases are non-MM and of course it also might imply as indeed most people are beginning to think that there may be substantial numbers of subclinical cases of BSE infection in the population which is very reassuring to a neurologist but not very reassuring to a public health doctor.

So, that is it really in the UK. BSE is controlled at least in the UK. Diet is controlled, at least in the UK. So, we are awaiting the outcome of this terrible accident to see what happens, but of course in the meantime there could be secondary iatrogenic spread particularly if there are preclinical or subclinical cases and that leads on to the concern of surgery and blood, and I am going to close by just talking a little bit about human-to-human transmission via blood.

So, first of all there are opportunities for this. It should be possible to avoid clinically ill people being donors. At least I hope so. Therefore the exposure will come either from the incubation period which of course

may be very long or even more worrying from subclinical infectivity which may extend through the whole lifetime of the individual especially in the absence of a simple diagnostic test.

If we are to consider this issue we have experimental evidence and we have epidemiological evidence and I am not going to review the experimental evidence at all except to comment on the sheep blood experiment which had most relevance, at least by Nora Hunter and her colleagues BSE was given to sheep. The sheep then act as blood donors and other sheep are intravenous recipients and just to summarize the present status of the study there is transmission of BSE by whole blood or by buffy coat, if transmission by intravenous route of a unit of blood it so parallels the human situation. Transmission has been successful with clinical phase donations and preclinical phase donations. So, there is evidence of preclinical infectivity again and the whole blood transmission rate at present is around about 25 percent but because of the methodology of this particular experiment this equates probably to a successful transmission of about 40 percent.

So, this is concerning but people always say can you really go from animals to humans. So, we don't experiment with humans but we observe them and the transfusion medicine epidemiological review was set up in

1997 between our unit and the National Blood Services and in outline for this particular topic what we do is we identify cases of variant CJD. We give their names to the national blood authorities. They look to see if they act as blood donors. If so they identify the recipients. They give the names of the recipients to us and we check to see whether they have appeared or in the future appear on our register and there is of course a reverse study whereby we traced the donors of blood when variant CJD cases report being recipients and there is a parallel sporadic study.

The data are present. When there were 157 cases in the United Kingdom we had 23 that had got donor records and the numbers from which the components were actually issued was 18 and the recipients were 66, so, essentially 66 recipients potentially at risk.

In addition 9 variant CJD individuals donated to 23 plasma pools which were identified as going on to make plasma products. What has happened to these 66 people? The first thing you note is that most of them have died. Forty out of 66 have died already and I suppose the reason for that is simply that if you have to have a blood transfusion you are ill and if you are ill you may die from that illness and you can see the majority of individuals actually died within 1 or 2 years, i.e., within the time period of the incubation period as we expected. In other

words they would never actually have had a chance to develop variant CJD.

The ones who are still alive, 26 of them, there are a number that are in a short period of time from transfusion and one would not have expected them yet to develop variant CJD if they were going to. There were a significant number in a kind of high-risk period. A few have lived beyond 10 years although of course we don't know what the maximum incubation period for this disease is.

This is just to illustrate that it is no longer a UK problem. These are variant CJD blood donors by year of disease onset and you can see that it was a UK problem until recently.

The Saudi Arabian case had been a blood donor. Some of the French cases have been blood donors. Spain and Ireland have had blood donors.

So, if variant CJD occurs in other countries clearly the risk exists there as well. We, also, identified two individual cases and I want to discuss them in a little detail.

The first instance occurred in 2004. An individual donated blood. Three point three years later they developed variant CJD which was neuropathologically proven. One unit of non-leuko-depleted red blood cells was given to a recipient who 6-1/2 years had variant CJD and

died after a fairly typical illness neuropathologically confirmed.

There were 68 slightly older than the usual case of variant CJD but they were still codon 129 MM. Now, of course, this individual had lived in the UK throughout the risk period and therefore had been exposed to diet and the question was couldn't this just be an accident. Well, the figure you heard earlier on of 1 in 15,000 to 1 in 30,000 my understanding was that it was not a prediction for the whole population but an analysis to see whether of the people that we knew who had been recipients of variant CJD blood what would be the chance that they had developed variant CJD by diet simply by accident, by coincidence and the answer in this particular analysis for this patient it would be about a 1 in 15,000 to 1 in 30,000 chance that they would have actually developed variant CJD through diet rather than through blood. In other words, this was very unlikely to be a coincidence and therefore a probable case of transmission.

In the second case a donor gave blood and 1-1/2 years later developed variant CJD, again, proven. An individual received non-leuko-depleted red blood cells and 5 years later died of a non-neurological illness. They didn't have any symptoms of variant CJD and neuropathologically there was no evidence of variant CJD.

However, at autopsy they were found to have the appropriate form of abnormal prion protein in the spleen and in the cervical lymph node. So, they had evidence of BSE infection and interestingly they were an MV genotype.

What is quite interesting about this case is that although the spleen and cervical lymph node were positive the tonsil and appendix were negative and of course I don't know why that is. It could be that because they were MV they have a different tissue distribution. We don't know. It could be because this is a blood transmission case rather than oral transmission case. There might be another reason. We don't know, and just to finish on the reverse study we have six variant CJD cases who have records of having received blood in the past.

Two of them the timing was just wrong. So, it couldn't have been that they got infection from the blood. In the remaining four one was the case I have described to you, the probably transmission of variant CJD with the time interval indicated here.

The other three cases we don't know. As far as we know the donors did not have variant CJD and have not developed variant CJD yet.

In one instance this individual here received a total of 106 components during her transfusion for a very serious illness. The intervals as you can see at present

are running about 5 to 6 years.

So, just to conclude the UK is showing a decline in variant CJD, but there are lots of concerns. First of all there may very well be MV and VV cases to come. Secondly, more countries are being affected and some of these countries are not entirely predictable countries. There is increasing experimental evidence of blood risk and there are now two instances of probable actual human blood transmission, one of them showing evidence of blood infectivity at at least 3.3 years preclinically.

The magnitude of the blood risk clearly must relate to the prevalence of infection and this is particularly important with increasing concern over the whole issue of preclinical and even subclinical cases and the UK TMR study continues to collect data and obviously various precautionary measures have been taken, but what I will do now is hand over to my colleague, Azra Ghani who will address the issue of prevalence in the population in a more rigorous and scientific manner than I am capable of.

Agenda Item: Azra C. Ghani, PhD, London School of Hygiene and Tropical Medicine

DR. GHANI: Okay, thanks very much. Hopefully I will follow on from Rich's talk and that has given you most of the background and I am going to very much focus on a more quantitative aspect which is the mathematical modeling

work that I have been involved with over the past 8 years and that other groups are also developing which really focuses on the first part of Steve Anderson's presentation in terms of trying to estimate the prevalence of variant CJD in the UK, and all of the work I am going to present today is work that I have been involved in but which over a period of time would have come from Oxford University and the Imperial College and now the London School of Hygiene and Tropical Medicine.

There are other papers published by other different groups. The predictions that we are all getting now are very, very similar and the basis of the models is also very much alike.

Okay, all the models to date have really been sort of risk assessment based on primary infection and by primary infection I mean ingestion through consumption of BSE-infected material and this schematic just shows the general process one might want to go through in trying to understand the potential for variant CJD cases arising through consumption of BSE-infected material.

So, at bottom here you have some sort of profile of the BSE epidemic in cattle and this is very well estimated. Certainly in the UK we have very good records of the clinical cases of BSE and mathematical models have been used to translate those clinical cases into estimates of

infected animals slaughtered for human consumption over time.

It is important to note that current estimates suggest that 3 to 4 million animals were infected and slaughtered for consumption in the UK over the course of the epidemic.

So, there was widespread exposure to the BSE infective agent. There are a number of steps then that BSE infected cattle will go through prior to being consumed by a human.

Very little is known about the production in particular types of tissue used for the food or indeed the effectiveness of certain precautionary measures that were put in place notably a specified bovine offal ban which removed the riskiest material from the human food chain in the middle of 1989.

Consumption patterns are also thought to vary and there have been studies looking at dietary data. Dietary data obviously is fairly difficult to analyze. Typically there will be some sort of recall bias, particularly when you are trying to ask individuals about what they consumed over a long period of time, but it is likely that there was some heterogeneity. These to date and these have been included in some other mathematical models have really focused on age and certainly for the UK the dietary data do

not support an age-dependent exposure as being the main reason why we are seeing the majority of cases in young individuals.

There is then the infection process. Infectivity obviously varies by different tissues that were consumed and some being riskier than others, also, by the incubation stage of the cattle and it is thought that the riskiest cattle would be those up to 1 year prior to clinical onset or onset of clinical signs.

There has been some discussion earlier about the dose response. In all of the models so far we have assumed a linear dose response and this is very much the simplest type of response to include in these types of models but obviously it is possible that there are some other forms of the dose response curve.

Heterogeneity and susceptibility are very much focused to date on two factors, variation in age-dependent susceptibility and I will go on to show how estimates about age-dependent susceptibility arise from these models and also genetic susceptibility and all of the models to date as has been stressed earlier have really focused on trying to predict what is happening in the MM homozygous population. So, that is approximately 40 percent of the UK population.

The reason for making that assumption is not so

much that it is an assumption but all clinical cases have arisen in MM homozygotes and so it is very difficult to predict anything in the other genetic subgroups because we haven't seen any clinical cases.

There is then of course the species barrier very much an unknown quantity and then we have an incubation period in humans. Once an individual has become infected there will be a long and variable incubation period. This again could be dose dependent. No models to date have actually included a dose-dependent incubation period really because it is mathematically quite difficult to do. It may be age dependent and genotype dependent and earlier models t hat we looked at with age-dependent incubation periods showed a shift in age profile over time. So, it would suggest that the average age of those coming down with disease would increase over time and that is inconsistent with the data that Richard has shown in his previous talk and so most models now only consider age dependent susceptibility and exposure.

It is also of course important to include survivorship for diseases with long incubation periods. People will die of other competing causes of mortality and so this is a schematic that was used to relate estimates of BSE-infected animals to what is happening in variant CJD cases.

So, the process that the models go through is to try to incorporate all the various uncertainties through this process to generate potential epidemics and then we look at those generated epidemics and say how well do they match what we have seen so far and we can exclude statistically those that are way out and those that match very well are our best estimates.

So, this is really the only equation which is the fundamental equation of the process that is being used for mathematical modeling in this area and it is an equation that arises from a technique known as back calculation which is used very much for HIV and was developed for HIV in the mid-1980s.

What you are basically trying to do is relate the number of people who are becoming infected at certain times to those cases that you will observe at a later date. So, you are trying to relate numbers infected to the cases through multiplying this by the potential for the incubation period. So, it is really a method very much developed for long incubation period diseases.

So, mathematics is a little bit more difficult to interpret for most people. So, this is the same method simply expressed in words. Suppose we have a case of disease that we have observed in 2005. Then under this very simple model we would say that the probability that we

would observe this case is equal to the number infected in 2004 times the probability that their incubation period was 1 year because if they had been infected in 2004 and the onset of disease was in 2005 they would have an incubation period of a year.

We then sum that with the number infected in 2003 times probability that the incubation period is 2 years and so on and we would go all the way back and in these models infection risk starts in 1980, and so that would be the probability for having an incubation period of 25 years.

So, that is the basic process these models are going through.

All of the models to date have a number of parameters and these parameters are uncertain and the approach to this uncertainty is to try to generate lots and lots of different scenarios to different sets of parameters and see which sets of these parameters are consistent with the variant CJD cases we have seen so far.

The first important one is some sort of measure of the exposure which is always estimates of numbers of infected animals entering the food supply by time and by disease stage at slaughter. So, in all of our models we assumed that those animals that are close to onset of clinical signs are more infectious than those early in their incubation period.

They all have an incubation period for humans which is either the time from infection to onset of disease or death. The term "incubation period" is used a little bit more loosely in the models dependent on whether the model is being fitted to the onset or the deaths.

They have some sort of age dependent susceptibility or exposure function which allows younger individuals to be at higher risk and that is a function that can be varied and we can try to see what function best explains the current data.

They all include the effect of control measures and most notably the specified bovine offal ban in mid-1989 which would have removed the highest risk materials from the food supply but we very much suspect it wasn't 100 percent effective.

Finally they have a transmission probability. That is the probability that someone who consumes infected material develops infection and so that is really dependent on the species barrier and finally competing courses of survival and birth cohort size are taken from census data. So, they are fixed quantities.

So, predictions of future clinical cases or deaths, this is what most of the models really have been set up to produce and models are able to produce fairly statistically robust estimates of future cases once the

epidemic has peaked and that is a feature really of the methods, that these methods are helpful once you have seen a peak in an epidemic. Prior to the peak as you will see from the sort of predictions that were made prior to 2000 you get very wide uncertainty in any predictions.

So, there was variation in the different predictions that were made prior to 2000 by the different groups and these were just really dependent on slightly different assumptions about the parameters or slightly different model structures but they now all give very much similar estimates.

One important thing to note is that the predictions really are only valid within the populations that are being studied. So, to date all the UK models include the UK cases but do not include any of those cases that were assigned to other countries but were probable UK acquired infections, for example, the US and Canadian cases.

They consider all the cases but one to be acquired from consumption of BSE-infected beef. So, we are assuming that all these cases that we have seen so far have been through consumption of BSE-infected materials and for example cases arising through blood transmission.

For reasons I have already explained we only considered the MM homozygous population to be at risk and

related to that they all assume what we call a unimodal incubation period so that the probability of coming down with disease after a certain time period increases and then decreases. So, we couldn't potentially see two peaks and situations in which we might see more than a multimodal incubation period really would be if we were trying to model wider genetic susceptibilities and we could see peaks coming in other genotypes.

The majority as I said, assume no age dependency in the incubation period. So, the cases I am going to present in the next slide are based on the models that are fit both to the time and age specified variant CJD deaths and the most recent predictions are based on cases up to the end of 2004, and importantly they also fit to the results in this appendix survey, so, the prevalence estimate that you will have seen in the previous talk.

To do that we need to include some sort of carrier state, subclinical infection. The terminology effectively mean the same thing so that we have a portion of individuals who become infected and are detectable having detected PRPSC in their appendix but do not go on to develop clinical disease and I will show estimates of how that is obtained in the model later.

They exclude the one patient thought to have acquired infection via blood and again they were only in

the MM homozygous population.

So, this shows you the long-term estimates and bounds or prediction intervals for variant CJD mortality that my group have published over time and we started fitting these actually back in 1998 and this shows just how the uncertainty has decreased and really critically. There was a big jump after 2000 from 2000 to 2001 when the epidemic started, the clinical cases started to decrease.

So, current projections are for fairly low numbers. So, the best estimate at the moment would be that there would be 37 future cases with confidence bounds that have of course decreased as well so showing decreased uncertainty.

So, these are just saying that the projections of future clinical cases in the MM homozygous population in the UK are fairly low. We are seeing a declining epidemic.

By doing those and producing those projections you can also get some estimates of how age-dependent susceptibility and exposure relates to the age distribution of the clinical cases and the best distribution looks something like this so that those aged really between about 5 and 25 appear to be at highest risk for acquiring infection. We can't distinguish in these types of models whether that would be due to exposure or due to some sort of biological susceptibility and very similar patterns are

reported from other models.

We can also obtain our best estimates for the mean incubation period and this is the incubation period defined as the time from infection to death rather than to clinical onset and that gives the best estimate currently around 11 years and you can see a tail here. The tail actually cuts off quite quickly but of course this aspect of it is less well fit by the model. There is more uncertainty in the tail simply because we won't have seen those cases arising with long incubation periods. So, there is uncertainty in that tail.

Okay, moving on then to estimates of prevalence of infection I think the most important point to note is that these models cannot estimate the prevalence of infection. You are taking models looking at the risk from BSE and trying to relate them to variant CJD cases.

All your information in this model is coming from those clinical cases. So they are quite powerful in predicting, making short-term projections onwards for those clinical cases but they can't say anything about prevalence because we could simply scale up and down the prevalence and increase the tail on the incubation period and we would get very similar projections in terms of what is happening with clinical cases.

So, if they are fit to the clinical cases alone

we are unable to make any estimate of prevalence of infection. One way we can try to understand the prevalence of infection is to also fit the models to this data, the appendix survey data because that then constrains the prevalence at a specific point in time. So, those appendix tissues were removed between 1995 and 2000 in a specific age group and we could therefore constrain our model to match that prevalence as well as the clinical cases.

The useful thing from the models is that we can then say that given the age distribution of the clinical cases and given that we have found this prevalence in our highest risk group, the 10 to 30 age group what would we expect the wide equivalence to be elsewhere in the population; so it is quite powerful in terms of extrapolating those survey results.

For the clinical case and survey to be consistent in any model that we fit we need to include the possibility of a carrier state or subclinical infection and just a technical point. The survey results only apply to the MM population when we enter them into the model because our model is only looking at the MM population.

So, including this carrier state this is our sort of estimates that we get. So, we get estimates that only 10 to 15 percent of infections would go on to develop clinical disease. So, we are saying that 85 to 90 percent of those

that appear infected or have detectable infection in their appendix will actually be subclinical infections that would never go on to develop clinical disease.

Just to stress that this is just an estimate from a model, it is not saying that subclinical infection does exist. This is one plausible hypothesis for why we get this discrepancy between the appendix survey results and the clinical data. It doesn't say that this is the only reason. This is just the reason that we have come up with that best fits the data at the current time.

The model then can also be used to then extrapolate and give estimates of prevalence by age group and these sort of data that are now being used to try to focus testing of tonsil tissues that have been collected in the UK.

So, there is a storage of tonsil tissues that started 2 years ago in the UK and we are now looking at ways to best test those tissues to try to detect infection and age is one aspect of that.

So, you can see also how we might see past, current and future prevalence coming out of these models by age. We would see a cohort effect so that infection in those that were young in 1997 will gradually move through the cohort.

So, this is just saying that a specific cohort

was at highest risk. Going on finally then to genotypes we have gone through a lot of this information already on the genotypes. So, one aspect that we wanted to look at was if we were to see cases in non-MM individual although we can't constrain epidemics in this group what can we say about the potential scale of an epidemic in the non-MM individuals based on what we have seen in the MM individuals and we know that they have either to have not seen any cases to date they would have either had to be less susceptible to infection and/or have longer incubation periods. So, we can do a sensitivity analysis say if we have an incubation period that is up to 5 years longer and if we have a reduced susceptibility what would this do to our projections?

So, I will just skip that. So, these are the sort of results that we would get in terms of cases in non-MM genotype. So, what this figure is showing is the scaling of the incubation period distribution in the non-MM genotypes.

Because we don't have very much data we haven't distinguished between the VVs and the MVs here. For example, here we would be saying that the incubation period in the non-MMs is twice as long as that in the MMs and here we have the relative susceptibility. So up here we would be saying that they are as susceptible but they may potentially have much longer incubation periods and as we

go down we are saying that the non-MMs are less susceptible.

So a value of .5 would mean they are only as half as susceptible to infection and the colors here are denoting the potential sizes of the epidemic. So, of course, our worst case scenario would be if they were almost as susceptible as the MM genotypes but have much longer incubation periods because that would suggest we have an epidemic that is going to occur later in time that we are waiting to see, but this sensitivity analysis did also suggest that future case estimates could really only be up to about five-fold higher because this depends on the relative frequency of the MM and non-MM genotypes in the population, also, that it is unlikely that we would have greater susceptibility. The biology doesn't really suggest that the non-MMs would be more susceptible but have much, much longer incubation periods.

Okay, finally I wanted to talk a little bit about blood transfusion. I will skip these couple of slides because they have been covered by Richard in his previous talk.

One question of interest at the moment is what the potential for an epidemic arising through blood transfusion and this is really the main concern because we have obviously seen cases arising through this route.

So, just to go through what actually determines the potential scale of a transfusion associated transmission mathematical models typically deal with this quantity called the reproductive number of R naught and this is basically saying how many on average, how many new infections are on average generated by one initial infection in an almost entirely susceptible population.

So, diagrammatically here we have the first person infected through the dietary route and that person donated blood and that went on to infect this second person and that second person could then possibly donate blood that was given to two more individuals but only infection occurred in one of those instances and so we could see this expanding tree of infections and the critical quantity is this factor R naught, the average number of new infections generated by each individual in this chain and if that is more than one so each individual is on average transmitting on to more than one other individual we will see that this chain is expanding and we will get an expanding epidemic. If it is less than one, so on average each new first infection generates less than one new infection then the epidemic will die out. It won't persist.

So, this is a quantity that we have been particularly interested in. This quantity R naught is really telling you whether you can get a self-sustaining

epidemic and a self-sustaining epidemic is obviously something we want to avoid.

So, this just shows you diagrammatically some very simple models, the types of picture you could get. Here if you have an R naught on two so on average each initial infection gives rise to two new infections, then you will see an epidemic appearing in this sort of form. It will become endemic and you will reach a steady equilibrium state of prevalence and over this time you will be accumulating new cases and you could see that cases could rise very, very rapidly for a R naught of this value.

For an R naught of less than one we see that the prevalence will die down and decrease and eventually we won't have infection in the population and so there is a lot of focus on keeping R naught less than one for all epidemics but I think it is very important to note that this does not mean that there aren't substantial numbers of cases arising. You can still get a substantial number of cases arising even if on average the epidemic is not going to be self-sustaining.

So, these principles really hold not just for the blood transfusion associated epidemics but also for transmission occurring via surgical instruments. So, what are the factors determining R naught? Most important obviously is the infectious dose. So, what is the