Center for Biologics Evaluation and Research, FDA
Immune Deficiency Foundation
Plasma Proteins Therapeutic Association
HHS Office of the Secretary/Office of Public Health and Science

Immune Globulins for Primary Immune Deficiency Diseases
Antibody Specificity, Potency, and Testing

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P R O C E E D I N G S 8:10 AM

Agenda Item: Welcoming remarks

DR. GOODMAN: It is definitely a pleasure to welcome folks here for this discussion on immunoglobulins and there are a few people who are going to make introductory remarks but certainly we thank NIH and IDF and PPTA for their involvement in this and if I have left anybody out we thank them, too, and I know that Dot Scott has put a tremendous amount of energy into this, and this is, you know, I was just thinking about this. This is a very unusual situation where really because of the complexity of the product and our successes in many ways in prevention of infectious disease and vaccine, etc., the product has been changing.

There aren't large numbers of products that change with time and obviously this meeting is intended to assess some of those issues that are relevant to the product. Dot put together a couple of things here but just to point out this is very relevant to our core vision of what we are doing. Obviously we need to be sure that these products which so many patients both depend on either chronically for immune deficiency disease or acutely for other problems are continuing to meet our needs. So, I think it is good that we are recognizing these issues at the laboratory and process and production end rather than at the clinical end at this

point, hopefully to prevent that and then I think also we have all recognized that supply and availability while waxing and waning remain consistent issues; so, if we can both assure the product is meeting our needs but also find ways to make the testing and release of product consistent with the medical and public health goal that would be good.

So, these are very consistent with our overall goals and the workshop is organized to look at issues of antibody in immunoglobulin as you know and I think it is timely to do that, both in essence the microbial world that our patients are exposed to and their immune status has changed and the donor status therefore in the immune globulins has changed, look at the issue of potency tests and specifically you know one issue which has attracted attention because of the declining levels is the measles antibody issue but I think this is sort of a probably what we have to think about here is not just what is on the table, the measles, the current released test but also think about that it is likely this product will continue to evolve.

You know the changes from natural to vaccine immunity I think for encapsulated organisms or from natural to a combination of vaccine in natural immunity for encapsulated organisms is something else to think about.

I know there are some data on that. So, that is

really the purpose here and to be ahead of the curve to get input and our agenda reveals that those of you who are here and the speakers are a great group. This is a good partnership involving the treatment community, patients, the industry that supplies this and the government scientific and regulatory community.

So, it is also an area where we are very happy for people like Dot to sort of be providing what I would say is science based regulation really thinking about what we are doing here.

So, with that I guess I don't have the order in front of me but I guess Jan Bult might make a few comments from the industry point of view or Marcia Boyle from immune deficiency. I will leave it to you guys.

Okay, Marcia?

Anyhow, thanks, all for being here and I will try to come back and hear some of this meeting at least.

Thank you very much.

MS. BOYLE: Thank you. Can you hear me? I am Marcia Boyl, President of the Immune Deficiency Foundation. I am not Jan Bult. So, I am delighted to be here and we are delighted to be co-sponsoring this very important workshop with CBER, PPTA, the Office of the Secretary of Health and Human Services.

As you know this product, these products are

absolutely essential to patients with primary immune deficiency diseases. They provide life, health and there are no alternatives.

It is actually refreshing today to be talking about efficacy and science rather than reimbursement which has been the topic that frankly I have spent the last 2 years worrying about and advocating about and Medicare and private insurance reimbursement continue to be threats to access to these products.

So, it is something we all have to keep in the back of our minds. For the well-being of our patients it is essential that we have this kind of partnership, that we have the FDA, the industry, the medical community and the patient community all sharing information and as Dr. Goodman indicated working in a partnership for the good of the patients.

A recent example of the success of this partnership was that the World Health Organization this week officially recommended that immunoglobulins be placed on the essential medicines list. They had been removed a couple of years ago.

So, that is a critical step and would not have happened if all stakeholders in the community hadn't worked hard on this issue.

I think during these meetings it is going to be

valuable to discuss how the community can gather better data going forward and perhaps conduct better research perhaps using the tools, unique tools of the USIDNET and ESID registries for surveillance and better research and at IDF we have actually established a permanent survey research center so we can have more timely data on the experiences of really what is happening with our patients.

So, I want to thank Dr. Goodman, Dr. Scott, Dr. Holmberg, Jan Bult for their involvement in helping to organize this meeting.

So, I hope we will have some wonderful results.

Thank you very much.

MR. BULT: Thank you, Marcia. I understand it is now my turn and I would like to have the first slide. I am sure that somebody is going to put it up. I am going to start.

First of all thank you, Jesse and Marcia and Dot for all the work so far. I would like to join Dr. Goodman and Marcia Boyle in the welcoming remarks to today's workshop, and we are very pleased to co-sponsor this event together with the two already mentioned organizations.

We are the International training association and standard-setting organization for the major producers of plasma derived recombinant analog therapies and I think it is no surprise but our members are committed to assuring the

safety and availability of these fairly important therapies.

The members of our organization provide about 60 percent of the world's needs for source plasma and protein therapies and that of course includes immunoglobulins that are needed to treat so many different diseases, one of them of course, the primary immune deficiency diseases.

The global companies that we represent you see five companies that actually provide their therapies into the American market Baxter Bioscience, Grifols, Optipharma(?), Telequist(?) and CSFDA(?).

We are responsive to the needs of the community that depends on these very important immunoglobulins both in terms of composition and delivery mechanisms. While we recognize and Marcia mentioned access issues and we are working with the community to remedy the reimbursement practices that threaten the availability of products we can demonstrate that our industry is doing all it can to ensure that the products are safe and of sufficient quantity for the community.

Manufacturers have included various steps both by chemical means and partitioning to address viral safety and have conducted numerous studies to demonstrate experimentally the efficiency of the manufacturing steps in reducing a prion risk.

In terms of supply the industry has increased the

distribution of IVIG by 85 percent between 2000 and 2006 and in the year 2000, 17.5 million grams of IVIG were distributed in the US market and in 2005 we had a record of 28 million grams and we all believed that was a number that was really remarkable but that number was shattered in the year 2006 with the distribution of 32.4 million grams into the United States market.

Factors in this growth certainly are the increase in the amount of IVIG produced by the manufacturers with yield improvement technologies which of course allows more retrieval of IVIG from each liter of plasma, the increase of plant capacity and the development of new therapy formulations in order to achieve the success.

PPTA really welcomes this opportunity today in this workshop to explore additional areas for continuous improvement of therapies.

The FDA regulatory requirements for lot release of immune globulins by testing the potency of antibodies against diphtheria, polio, measles are decades old. We believe it is good to periodically look at the lot release requirements and the composition of immune globulin preparations with respect to the needs of the patients and the antibody distribution and levels in a donor population. The agenda of this workshop was designed to delve into these issues and the organization committee and speakers are to be

commended for this work and we look forward to participating fully in the discussions during the next day and one-half.

Again, from PPTA we wish to welcome all participants to this very important workshop.

DR. HOLMBERG: Good morning and welcome. I am Jerry Holmberg. I am with the Department of Health and Human Services and he senior adviser for blood policy to the Assistant Secretary for Health.

I want to welcome you all and thank you for the opportunity to have this workshop first of all and I would like to thank FDA and especially Dr. Scott for putting this together and the planning committee that worked hard on this and also for the organizing groups such as IDF and PPTA for this workshop.

You know when we look back over the last decade there has been a lot of changes. We have covered a lot of ground in the whole field of plasma proteins and their therapeutic use.

I think in the last 2 years we have really addressed another issue and that was availability and access and as Marcia commented earlier it is refreshing to be able to talk about some scientific issues today.

I have really been dealing with a lot of the access and availability issues. Although the reimbursement is a center for Medicare or Medicaid services issue we are

very much involved within the department since that is one of our operating divisions but they do call the shots on the reimbursement and so it is refreshing to be able to look the progress that has been made.

We do know that worldwide there has been an increase in the utilization of the product and I look forward to this workshop to focus on the, not only to focus but to hear comments on the quality and characteristics of this product and also to ensure the purity, potency and efficacy of IGIV.

So, thank you for coming to join us and I am looking forward to the comments from the speaker. Thank you.

Agenda Item: Introduction to the workshop

Dorothy Scott, MD, FDA

DR. SCOTT: Welcome, everybody and I just want to mention I have recently been informed on a historical note that today is the 62nd anniversary of the first meeting of the UN. I think that is highly auspicious for a meeting like the one we are having today where we are bringing a lot of folks together to discuss our immune globulins in order to benefit the patients and to move the process forward, the scientific process where we look at our potency testing.

What I am going to do right now is just introduce an overview of the goals and issues that we have for discussion today, but first I would like to thank our

sponsors not only for their financial assistance in putting this workshop together but even more so for the intellectual contributions hat we have from the presenters and from the sponsors in organizing the presenters and helping us to get some excellent speakers. I, also, want to thank Jennifer Sharp and Rhonda Dawson for taking care of a lot of the technical aspects of the workshop in making sure that everything got done and my office and my center for all of their support and help.

This is a very brief overview of our workshop goals. In particular we want to assess the current potency testing of immune globulins and underneath this is really what we want to do in the first couple of sessions today.

One is to list the antibody specificities needed to protect primary immune deficiency disease patients from infections; what is relevant; what is important now? We would like to identify candidate antibody specificities for potency testing of immune globulins for treatment of primary immune deficiency. These two things are somewhat different. One is saying, "What do the patients need?" and the other is to say,"What is feasible to test for?"

We would also like to tomorrow address approaches to provide protection from measles with immune globulins, despite the diminishing measles antibody levels in the plasma donor population and therefore in our products.

I am going back to basics with some regulatory definitions. I am glad it is the morning so people can stay awake. The word "potency" is interpreted to mean the specific ability or capacity of the product as indicated by appropriate laboratory tests to affect a given result and I only put this up, well, it is obviously very important. It is our fundamental definition of potency but it links the laboratory testing to the effect in the patient.

We, also, have requirements for laboratory controls and this really provides us a regulatory underpinning for considering the science behind potency testing and also in the CFR it states that lab controls should include establishment of scientifically sound and appropriate specifications and test procedures to assure that drug products conform to appropriate standards of identity, strength, quality and purity. Okay, so, what does this mean for us?

The rationale behind all of this testing for potency is assurance of strength and quality but what do our specifications provide exactly and there are several different things that we would like to have out of a specification. One is it should be a measure for immune globulins of lot-to-lot consistency in production. This is one of the original reasons for looking at potency testing. It provides or it can provide an assurance of product

integrity, that is if you are looking at tests that measure not only the presence of antibody and its ability to bind but its function and it should be a measure of activity that is relevant to the indication and in this case we are talking about patients with primary immune deficiency.

So, immune globulins are a bit unlike any other product I could think of that we regulate. Unlike other biologics that are comprised of multiple specificities there are millions of unique antigen specificities and that reflects the diversity of the antibodies in each individual donor as well as across the donor population. So, we are not talking about just one potency really.

The potency for specific pathogens within the immune globulins might vary due to differences in the donor population due to age, vaccination status, epidemiology, that is have they been exposed to infectious diseases; what are those, and in fact, there are of course seasonal variations in exposures which might be reflected in the immune globulins depending on the time that donor plasma was collected, and finally if that weren't enough the patient population is exposed to diverse pathogens.

Dr. Goodman mentioned this as well. The appropriate antibodies I have seen defined. I believe it was by Charles Janeway as antibodies against those pathogens to which patients are exposed. So, it is a rather broad

definition.

So, how did we start out with this and it is a little difficult to get the history. There is no one place to find out what happened but in 1943; that is a salient date, the first immune globulin was licensed and that was manufactured by Massachusetts Biologic Laboratories and it has actually been produced nearly up to the current day and after that in 1952, Bruton described treatment of a patient with immune deficiency with immune globulin. So, this was licensed before people were really using it to treat primary immune deficiency.

I will go back and tell you what it was licensed for. In 1953, we were able to excavate the Department of Health, Education and Welfare minimum requirements for immune serum globulin which was the name of the current intramuscular immune globulin and here they state, this is the earliest information we can find something about potency testing and that is the ability of the manufacturing method to recover specific antibody shall be demonstrated by titrations for several antibodies for which there are recognized methods of titration.

Several lots of material shall be shown by clinical trials to be effective in the prophylaxis of measles and in fact the first immune globulin was licensed among other things for prophylaxis of measles.

In 1961, we distributed the first measles antibody standard called lot one for measuring anti-measles antibodies in immune serum globulin and somewhere between 1965 and 1968, the CFR requirement for measles, diphtheria and polio neutralization assays to demonstrate potency was published. Unfortunately, we just have CFRs before that time and CFRs after that time and I think it will take a reference librarian to find out when exactly that appeared, but in those days we didn't have the extensive Federal Register explanations of proposed rules and actual rules and a rationale behind those. That is something we have yet to find.

However, it makes a lot of sense that measles, diphtheria and polio were selected at that time because these were endemic and epidemic diseases in the US. So, the current US product potency tests that are used for immune globulins intravenous, all the immune globulins used for primary immune deficiency are antibodies to measles, diphtheria and polio and we also request testing for hepatitis B surface antigen.

Now, all of these tests except for anti-HBS are neutralization assays and this is specified in the Code of Federal Regulations. I will just mention that the anti-HBS provides an additional assurance of viral safety because it helps to clear virus and to neutralize hepatitis B virus

that might exist in immune globulins.

Now, of course, we have a lot of testing but this test has stayed. We are not going to consider it further today because the immune globulins are not indicated for prophylaxis of hepatitis B.

So, rather this was put in as a safety measure rather than as a potency measure per se.

So,what is going on now? Well, we know our products are changing, because the epidemiology of antibody specificities in the donors are changing and this was made most evident to us by the decline I measles antibody titers to a point where it is conceivable that lots of immune globulin intravenous could fail their lot release testing. This presents a regulatory and a practical problem because it is very important from the regulatory standpoint for products to pass their lot release testing and in fact the compliance regulations tell us that if a lot doesn't pass its lot release testing that it needs to be reworked or discarded.

So, that doesn't mean we should necessarily change what we ask for as a measles antibody titer but it does mean we have to think about how to address this problem.

That is actually what triggered this workshop. We began by considering the measles antibody and then we thought it would be a very good idea to reconsider what we

are already doing for all of these specificities that are potency tested in the immune globulins.

In addition to the products changing the patient epidemiology of what we know about it might have changed and we would like to know what are the current most important needs for infection prophylaxis in primary immune deficient patients.

Dr. Finlayson who is here today said in 1979, at an immune globulin workshop as the spectrum of products has progressed so have the techniques of potency measurement and protein chemistry. I am glad he said that in 1979 because since then not a lot has changed. We are still using the tests and the potency specifications that were decided upon in the mid-1960s.

There are challenges though to changing any potency tests because the current tests are well validated and they are routine within industry. So, changing tests like this would require a lot of expense and effort and there are some technically desirable attributes of any new test.

First of all it must be validated. It must be validatable(?). Standards have to be available. Ideally potency test would demonstrate functional antibody activity such as neutralization or opsonization and these tests are more difficult and have more variability than for example

binding assays like ELISA, and ideally such tests would not require the use of animals.

So, briefly here is the structure of the workshop and this is what we are going to be asking of you, the audience, the panel and the speakers is to identify the most relevant antibody specificities needed by primary immune deficiency patients and to review the data that we have now on antibody levels in the current products and to combine this information in order to think about which antibody specificities would be useful and relevant to measure with respect to clinical importance and to assure lot-to-lot manufacturing consistency.

So, we have really two sessions today. One is the clinical session and one is I would say the product session and then we want to put those together at the end of the day.

Dr. Blaese from the Immune Deficiency Foundation will be moderating the first session and in particular the questions there, what are the major infections in primary immune deficiency patients now, whether or not they are treated with IGIV that need to be prevented and also we have an opportunity here to ask what more do we need to know about infection epidemiology in the patient population today.

We have some reports of surveillance that are

ongoing in the EU and also that are beginning in the US through USIDNET and our opportunity is to look at the USIDNET new database and to offer ideas for additional questions that would respond to the needs up here

The goals are to list the relevant antibody specificities and to identify the information gaps in epidemiology to assist in the USIDNET efforts and Dr. Blaese is going to talk about that in a lot more detail.

The second part is to look at the levels of antibodies against pathogens in our products. Obviously if we have a concordance between what we need in patients and we have tests that we can do and where we know that there is some degree of consistency from lot to lot those might be good tests to consider as potency tests.

As I have mentioned measles, polio and diphtheria our current potency tests for immune globulins, Dr. Seward has come from CDC to tell us about the current epidemiology of those infections in the US population.

So, we are going to look at our current tests and what they are actually telling us now. The goals of the second part are to identify specificities that are useful and relevant to measure in immune globulins for their clinical importance and for lot-to-lot consistency, to identify gaps in information about specific antibody levels in products and to identify approaches to new test

characterization and development.

Okay, so we are having a workshop. What happens next? I think that we do have some goals and some outcomes that we would like to achieve.

One is to help USIDNET with their surveillance project and I say, "Improvements," but actually the fortunate thing is that this workshop coincides with the roll out of the new USIDNET efforts for surveillance. We would like to address knowledge gaps so that we can identify studies on current products that would fill these gaps and we would like to consider the possible development of new potency tests.

Now, there is a regulatory pathway for these changes. We don't make regulatory decisions at a workshop and these would include consideration by the Blood Products Advisory Committee and potentially guidance. I, also, think that this workshop could result in some very good industry, FDA and academic collaborations on tests and standards development and of course tomorrow we are going to address the decline in measles antibodies in products and for that we can also, we have the option of seeking regulatory advice from the Blood Products Advisory Committee.

So, with that I hope people have a sense of where we are and where we are going today. I would like to introduce Dr. Stiehm. He has been a long time researcher and

clinician for primary immune deficiency and immune globulins in general.

He has over 500 publications. He is currently a professor of pediatrics at UCLA, but I remember him from previous workshops as being a real advocate of looking at different markers of potency in immune globulins and the antibody specificities in immune globulins. I would say his interest has gone back quite far. I looked in his earliest paper on immune globulins which was in 1961 when he was looking at the effects of papain digestion on immune globulins.

I would like to welcome you, Dr. Stiehm and thank you for coming and for giving us the benefit of your thinking on the potency test and the antibody specificities and the impact on patients that need to receive immune globulins.

Agenda Item: Keynote Address: Use of antibody in infectious diseases, E. Richard Stiehm, MD, Mattel Children's Hospital at UCLA

DR. STIEHM: That is my disclosure. Thank you very much for inviting me here and Dr. Scott for all her good work in putting this very interesting symposium together. I look over at 100 different people, all experts in the field with about 500 different fixed opinions on what we should do and with that in mind I just want to relate a little story I

heard that was kind of interesting about a woman who arrived at Ronald Reagan Airport and she found out her plane was 2 hours delayed. So, she bought a cheap novel and a bag of cookies and sat down to wait and she took a cookie and then the man next to her took a cookie from the same bag, and she thought well, that poor guy is kind of hungry. I will overlook that cookie thief and she took another cookie, and he took another cookie, and it went on until all the cookies were gone. Every other one she took, he took, and finally at the end there was only one cookie left. He broke it in two and gave her half and ate the other half.

Well, by this time she was really steaming, but she decided to keep her cool and she got on the plane and got herself all settled and then opened up her bag and there was her bag of cookies.

(Laughter.)

DR. STIEHM: So, that reminds me of this little poem. If mine are here, she moaned with despair then the others were his. He tried to share. Too late to apologize she realized with grief, I was the rude one, the ingrate, the thief.

So, being sure is not the same as being right. So, let us take a look back at where we have come in terms of the use of antibody in infectious disease and then the last 5 or 10 minutes where we should be going and of course, it

all started out in Germany in 1890, and diphtheria horse antitoxin was developed in the 1890s shortly after the toxin was identified.

It had been used in both prevention and treatment and still used as equine antitoxin in the treatment of diphtheria antitoxin.

Emil von Behring was awarded the first Nobel prize in medicine in 1901 for the development of diphtheria and tetanus antitoxins and his citation reads, "For his work on serum therapy especially the application against diphtheria by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physicians a victorious weapon against illness and death."

So, what are the different agents that we have as passive immunization areas? Well, we still use animal sera or globulin and a few of these are fragmented so that they disappear more rapidly.

The best example is Digibind for digitalis overdose. We can use whole blood, sera or plasma and then we have a number of human immunoglobulins which are the subject of today's conference.

We have regular, intramuscular IG polyvalent and we have a number of very high titered IGs, hepatitis B immune globulin, tetanus immune globulin. We have a number of different IVIGs and then we have several high-titered

intravenous immune globulins, cytomegalovirus immune globulin, up to recently RSV immune globulin. We have anti-D immune globulin and of course the biggest area is the release and licensing of monoclonal antibodies. The first one was OKT3, a murine monoclonal antibody against T cells still used today but nowadays we have 19 different licensed monoclonal antibodies and one or two are being licensed about every year.

So, how are these immunoglobulins used in the treatment of infectious disease? The first use as I mentioned was in toxin-mediated diseases such as this little baby who has tetanus. These toxin-mediated diseases notably diphtheria and tetanus but a few others are readily prevented by immunization and we still use these today as tetanus immune globulin for the prevention and treatment of tetanus and diphtheria antitoxin for the prevention of exposed susceptibles and these are necessary in treatment because not only do you have to get rid of the bacteria, you also have to neutralize the toxins which are causing the damage and that is why these are used in toxin.

We occasionally use these intrathecally. In fact a large meta analysis has recently shown that tetanus immune globulin given intrathecally is better than just giving it intramuscularly alone.

Another increasingly use in diseases that we

seeing is botulism and there are three forms of botulism. We have inhaled botulism which a bioterrorist threat. We have wound botulism which is shown here and then of course we have food poisoning and then a boutique use of botulism antibody is in the treatment of botulism in the newborn and this shows a baby that has hypotonia and failure to suck because he has newborn botulism.

So, botulism is food borne, wound botulism and this seems to be an epidemic because of increasing use of injection for illegal drugs.

There is an equine antiserum distributed by the Centers for Disease Control. Human botulism is indicated for the treatment of infant botulism. It is called BABY BIG botulism immune globulin and the cost for one treatment is $45,000 and it is distributed by the California Public Health Department.

Clostridium difficile a severe pseudomembranous colitis refractory to vancomycin is sometimes treated with IVIG with efficacy and there are a number of studies particularly not in this country of oral bovine anti-clostridial antibodies used for treatment of botulism.

The subject of today which initiated this was this illness. This is scarlet fever. You can see the strawberry tongue and the red rash and after the use of antibodies for the treatment of tetanus and diphtheria and prior to the

development of antibiotics immunoglobulin or passive antibody was the only treatment for bacterial respiratory infections and in the twenties and thirties streptococcus, staphylococcus, pneumococci, Neisseria, H. flu were all treated with antibody and of course these are the same organisms that patients with primary immunodeficiency had and specific antisera were developed for each of these and they were used sometimes in conjunction alone or with use of sulfa drugs.

In fact there was a product that was never licensed called bacterial polysaccharide immune globulin which was tested and shown to dramatically increase the incidence of not only meningitis but otitis and respiratory viral infection.

So, gamma globulin works dramatically in bacterial respiratory infection. It also works in certain toxins associated with staphylococcus and this is a woman that has the staph toxic shock syndrome. Staph toxic shock syndrome is associated with a cytokine storm associated with TSST release of toxin with a tremendous amount of cytokines released.

Staph epidermidis is a major pathogen particularly in newborns and premature infants particularly with the use of increasing amounts of lines and hyperimmune IGIVs are under study, have a high titer of Staph epidermidis.

Refractory staphylococcal infections are sometimes benefitted by IGIV and they are synergistic with antibiotics as shown in laboratory tests and there is about eight or nine different monoclonal antibodies against staphylococcal antigens which are under study and some of these look extremely promising. So, the role of antibodies in staphylococcal infection is an area of keen research interest.

Streptococcus is also a problem and this shows a child with severe streptococcal toxic shock syndrome. These patients with severe strep get necrotizing fascitis, necrotizing myositis and these again can be treated with IVIG because immune globulin has antibodies to pyrogenic exotoxins A, B, and C.

Then there are a number of diseases where gamma globulin has been suggested without benefit, the use in Sydenham's chorea and this pediatric autoimmune neuropsychiatric disorder associated with streptococcus. People have used IVIG but without firm evidence that it is of any benefit.

In viral diseases immune globulin has a long role in the prevention and treatment. This patient has hepatitis and hepatitis A was the original reason why immune globulin was licensed back in 1943, as Dr. Scott showed and it was used particularly to prevent hepatitis A among travelers. It

is very effective if given before prevention and even after exposure it is somewhat beneficial but it doesn't prevent the illness. It prevents icteric hepatitis and in the old days before hepatitis A vaccine and we were going abroad that was the biggest use of immune globulin.

It is also occasionally used in infants if the mother has hepatitis A at the time of delivery.

Hepatitis B immune globulin was the first, I think the first high-titered intramuscular gamma globulin and the biggest use for hepatitis B immune globulin is not to prevent hepatitis B in newborns but in liver transplantation.

Hepatitis B is of course indicated for exposed susceptibles such as newborns, needle sticks, lab ingestions, sexual exposure and in newborns we now give all newborns that are exposed because the mother has hepatitis B antigen positivity, they get both the vaccine and hepatitis B immune globulin.

Hepatitis B immune globulin following liver transplantation is necessary because even if the liver, the donor liver is hepatitis B negative there is enough hepatitis B in the body that the new liver will become infected and so it is used immediately after liver transplantation for a prolonged period of time. It is interesting it is given intravenously very often because the

hepatitis B immune globulin from one company is a 5 percent product and even though it is not licensed for intravenous use the liver transplant people use it all the time intravenously and nowadays the hepatitis B immune globulin is used in conjunction with antiviral agents and the hope is that some of these patients can get off hepatitis B immune globulin eventually but it is an enormous use and as it perhaps doubles the cost of liver transplantation in a hepatitis B positive individual.

There is also a product out there called hepatitis C immune globulin that they hope will work in the same fashion. In preliminary studies it does not seem to prevent hepatitis C in the new liver.

This is the subject for today. This is for us old timers. We remember how a patient thought we were wonderful diagnosticians because we used to say, "This child is going to come down with measles in a day or two because of the spots and this is the baby with the rash."

Patients who are exposed to measles and should not get it perhaps for malignancy do get measles immune globulin and the dosage is based on the previous titers of antibody.

VZIG is indicated in all exposed susceptible immunocompromised patients in all prematures or term infants or seronegative mothers who have chickenpox already. So, this product used to be made by the Massachusetts Department

of Public Health. There is a new vaccine manufacturer and I think it comes from Cangene(?) in Canada but for a while varicella zoster immune globulin was not available but now again it is.

This is a dreaded illness, rabies and here is a little baby that had rabies and is going to die because all but one patient with rabies eventually succumb.

Rabies immune globulin is based on the following clinical observations. In 1954, a big bad wolf came into Teheran and they knew that wolves came into the villages and bit a number of people. So, the treatment up to that time was rabies vaccine determined by Pasteur, but in 1954, the World Health Organization thought that perhaps immune globulin in addition to rabies vaccine would be effective so that this wolf cooperated and bit 17 villagers. Three out of five just were given the vaccine alone. One of seven was given vaccine and one dose of rabies antiserum, and zero out of five given vaccine and two doses of antiserum developed rabies.

So, since that time their use of rabies either antibody or rabies immune globulin is the treatment of choice in exposed individuals.

Nowadays you use half of this vaccine intramuscularly and half locally.

This is vaccinia. It used to be a problem in individuals who had severe combined immunodeficiency that were given smallpox vaccine and of course now, the main use for vaccinia immune globulin is exposure of our patients to a patient who has recently been vaccinated and since the military and certain laboratory workers still continue to get vaccinations for smallpox the threat of this disease has not diminished and furthermore there is a concern that this is a potent bioterrorism illness.

So, we know that vaccinia immune globulin can prevent both vaccinia and can prevent smallpox and Jenner of course showed that if you are immune to cowpox it will also prevent smallpox and vaccinia immune globulin will prevent the serious complications such as vaccinia encephalitis.

Vaccinia immune globulin is indicated for accidental vaccination, autoinoculation, eczema vaccinatum, progressive vaccinia and vaccinia necrosum.

So, in summary for this portion prevention with immunoglobulin or antitoxin can prevent a lot of diseases such as tetanus, diphtheria, hepatitis, measles, RSV, varicella and it is used in the treatment plus antimicrobials in toxin-mediated diseases such as diphtheria, tetanus, botulism and toxic shock due to staff and strep.

Antibodies may also be adjunctive to

antimicrobials and CMV infections and RSV infections in newborns and ICU patients with sepsis, and a few illnesses, notably infant botulism, parvovirus B19, progressive vaccinia and Ebola can only be treated with antibodies.

Now, let me just spend the last few minutes talking about the meeting we had about 2 years ago where we were looking for surrogate markers for IVIG licensure as a way to accelerate and simplify the process of allowing more immunoglobulin to be brought into the market and these were some of the surrogate markers that were proposed at that time which include antibody and immunoglobulin levels, x-rays of the chest or sinuses or inflammatory markers and then the one that we tended to focus on was antibody titers and that is what our subject is for today.

So, which antibodies should be measured? How should they be measured? What is the protective level? How often should they be measured? Are serologic titers equivalent to functional activities?

What antibodies are in the donor pool? What are the most important illnesses to prevent? What are the most important pathogens? What less common antibodies should also be measured?

So, that requires knowing what illnesses are common in immunodeficiency and these include pneumococci, H. influenzae. We, also, have to protect these patients that

don't make any antibody to measles, tetanus, diphtheria, polio, hepatitis A and B and chickenpox and then there are certain unavoidable illnesses out there, CMV, Epstein-Barr virus and parvovirus which it is useful to protect against.

So,we are going to hear more later on today about what are the important bacteria and viruses that affect our patients and here is a list of the common pathogens that we see including ones that aren't typically bacterial or viral including Mycoplasma, ureaplasma(?) Cryptosporidium pneumocystis and Giardia infections and we know, however, that there are variable amounts of antibodies particularly for less common pathogens in IVIG and so several years ago I made this list of pathogens that might be useful to measure as surrogate markers for patients that are treated with intravenous gamma globulin and these were the semifinalists, Staph aureus, Staph epidermidis, E. coli, Pseudomonas, herpes simple I and II, Coxsackie, echovirus and parvovirus but they didn't make the cut. The ones that made the cut included H. influenzae, several strains of pneumococci, diphtheria and tetanus, hepatitis B, measles, varicella zoster and CMV and many of these are in the FDA requirements. Poliovirus seems like it is part of the antibody panel but it seems less important to have protective levels in this product,

So, for today should the FDA require additional

antibody tests on IG products? Should FDA require labeling of antibody content? If so, what assay should be used and what would be the effect of the cost if we had to do all of these antibodies on the product?

Finally I want to tell you some new events from the FDA. If immunoglobulin doesn't work the FDA has the answer for you. They have just approved the sale of prescription placebo and it is called Sucrosa(?). It is the evaporated juice of Saccharum officenarium. It is a white crystalline substance with a sandy consistency, molecular weight of 676, rapidly and completely absorbed, non-toxic doses of 1 to 40,000. Astra Zeneca will market it as a triangular green pill 50 and 100 milligrams or a good-tasting liquid at 10 milligrams per ml, wide application, minimal side effects. The indications are run(?) PDD, random occasional non-specific pain and discomfort disorder, pediatric board exam anxiety disorder, bipolar disorder, chronic fatigue syndrome, erectile dysfunction and seasonal affective disorder.

The side effects are slight elevation of blood glucose level, tooth decay if used continuously, sweet taste in the mouth if not swallowed, expensive, 50 cents per pill. Manufacturer says, "We have to recover our research costs which coves years of testing, most extensive drug ever

tested and there are many of these placebos in the pipeline. There is Inertia from GlaxoSmithKline, Appeasor from Merck, Pacifiex from Eli Lilly and the FDA says, "All placebos are not the same," and medical watchdog spokesman, Pim Naysayer says, "These placebos shouldn't be introduced to the public until we know more about their mechanism of action."

Thank you.

(Applause.)

DR. BLAESE: Questions for Dr. Stiehm?

Agenda Item: Epidemiology of infections in primary immune deficiency

DR. BLAESE: The first general session of this workshop is entitled Epidemiology of Serious Infections in Primary Immune Deficiency Disease and as we have already heard there are a lot of questions. What organisms are particularly a threat to our patients with primary immune deficiency disease? These diseases represent a broad range of different disorders in the immune system and host defense and as my old teacher made such a good point, these diseases are experiments of nature and have taught us a tremendous amount about what parts of the immune system are responsible for what kinds of protection against what kinds of organisms, and they really were the first insight into the fact that the immune system was compartmentalized as to what it was going to be able to help us with.

You know we are going to be discussion the impact of immunoglobulin replacement, you know which infections are controlled and which ones are not. There was certainly the observation when intramuscular gamma globulin was introduced for our patient population that there was a decrease in the incidence of acute infection, less unanimity of opinion as to whether it was effective in controlling sort of the smoldering persistent infections of the sinopulmonary tree. Then as higher-dose immunoglobulin became available in the intravenous form there was evidence presented that in fact you could control not only acute disease but some of the smoldering infections but there still is an issue I think about do we have enough specificity and what is the effect on all sorts of chronic infections and as another part if the workshop is going to be discussing some of the new tools that are just becoming available that we hope can be exploited to help answer some of the questions that have been very difficult for single institutions or single investigators to acquire enough experience with enough patients to be able to answer and so we are going to be hearing from Bodo Grimbacher who represents the European Society for Immune Deficiency, and he will tell us some things about their experience in setting up a patient registry which now has something in excess of 3000 patients enrolled and I will tell you a little bit about the USIDNET

patient registry which has some previous collections about 1500 primary immune deficiency patients in the registry and the online registry should be inaugurated within a few days that will then allow us to try to address some of the questions that are relevant to this particular topic and we would like input from the audience. Both Boda and I would like very much to hear how you think we could us these registries that we will be following in a longitudinal way patients with primary immune deficiency.

What kinds of questions should we be addressing in that registry realizing that we have to balance the accurate collection of data that really gives an answer with imposing a lot of requirements on our submitting physicians and whether they will actually comply with the request to collect this data.

So, we have this balancing issue that we want to discuss.

So, the first speaker this morning in this session is Dr. Charlotte Cunningham-Rundles from Mt. Sinai, New York and she is going to be discussing some of these issues of the epidemiology of serious infections.

Agenda Item: Epidemiology of serious infections in PIDD

DR. CUNNINGHAM-RUNDLES: This is a really daunting title and it is daunting because I think we don't actually

know very much about the epidemiology.

So, that is the word that sort of gets me down because we don't have that data, but I will tell you a few things that we do know.

Don't look for a handout. It took me forever to come up with the type of slides and information that I thought would be not off the point. So, going forward if we tried to say, "What do we know?" we are talking today really about antibody deficiency. At least that is the point that I am going to stick onto.

I am not going to be talking about some of the other immune deficiency diseases that you don't treat with immunoglobulin because that is just a little bit of a separate issue right now.

So, if you think which ones do we treat with antibody deficiency and what do we know about the infections that occur in this group of people these are the ailments, of course that we want to kind of contemplate more than any other.

For me you can see this is heavily skewed. Antibody deficiency for me is the biggest population that I see but I know from Dick Stiehm's textbook that of course is going to be about 70 percent of all the people with immunodeficiencies are going to be on gamma globulin and antibody deficiencies are actually the most prominent. So,

that is not just how I view the world. I think that really the world of antibody deficiency is a little bit larger than all of the others taken together.

So, there is a little bit of data that we can gather together and this one comes from the prior registry that the Immunodeficiency Foundation put together by Jerry Winkelstein in this case and we say, "What were the infections that were observed in the pure antibody-deficiency diseases?" taking that as the most obvious and worst case scenario for having absolutely no antibody to begin with and so Jerry had collected data on 210 patients and this is the kind of data that you can find and these ar treated and untreated but in the main these are people who were referred and the infections that appeared.

This article appeared last year but as you can see in the main you have the upper respiratory tract infections up here in the top and then the lower respiratory tract infections and other entities as you move on further down.

You have plenty of infections in these patients. Of course it turns out to be at least something like 90 percent of all the people with XLA really are having serious infections even before the time that they are officially given that name and most especially those who were diagnosed in infancy may or may not really have such serious infections due to treatment that is instituted early.

Of course, it is a problem because although you have an infection you don't always know what the bug is. So, out of the 210 there were 125 cases in which the actual organism was really identified and as you can see the numbers here are going to be really totally swayed by the fact that 105 of these cases it wasn't possible to actually know and either that is not reported and in most cases that is the case because paperwork is a problem or in fact it simply wasn't able to culture it.

So, pneumococcus comes out again on top. As Dick Stiehm was saying a moment ago that is one of the organisms that we have to take the most seriously along with Hemophilus and Pseudomonas as a big customer also in patients with XLA and so we know something about that but as you can see with about half of these cases not fully diagnosed we don't exactly know. We just know what was found.

If you talk about encephalitis, meningitis again a good number of those were not known. In this case there were 25 cases. Nine of them were not known but in the other cases it was a more clear-cut answer and Strep pneumoniae again ruled the day followed by echovirus, Coxsackie, polio, adeno and then Hemophilus type B.

So, the viruses actually came out on top as one knows so well from the XLA patients. Mike said moment ago

that we are really obviously very much trying to amplify what is known about patients with immune deficiency. We have kind of the beginnings of this taking all the patients from the registry existing and merging those with those for Mt. Sinai, about 400 patients or 350, whatever the number was in the registry now we have close to 700 patients in the USIDNET registry at least those who are perched on the brink to be entered, and this was data that one of our fellows, K. Knight put together and she subsequently moved to Alabama but what can you say about it is that we actually had the beginnings of some information on these patients and as you can see US physicians pretty much agree that these are very, very hypogammaglobulinemic individuals and I think that we would say, "Oh, these people definitely belong in this registry. It is not a case of mildly deficient. These are clearly deficient. The complications, about 90 percent of patients in that particular cohort have infections.

As you can see it is not 100 percent which is something that always makes me give pause because that is why infections are not part of the diagnostic criteria of CVID. If you don't have infections, the chances are that you have either autoimmune disease or you have come in the door with an inflammatory bowel disease. That doesn't change the fact that you actually have the capacity for having some serious infection and as you can see about 90 percent of

course do.

What infections are they? Sinusitis is a big one. Everyone would realize that. I have no idea what the organisms always are. In most cases the organisms were not entirely registered or we don't know. It is not possible to culture.

Pneumonia is about 70 percent, bronchitis, otitis, various abscesses, recurring herpes zoster came in at an interesting position here. About 8 percent of patients reported that and sepsis was something like 5 percent, meningitis, cellulitis and osteomyelitis.

So, I think this kind of forms a platform. I can't tell you it is wonderful data as of yet but I think it performs a kind of a beginning stage of what we might get to know about these individuals especially if we could do better in terms of culturing and when it comes down to empyema I think the bug you could go to the racetrack with this one and probably earn some money is nearly always Strep pneumoniae, and you can just make a bet about it. It will create this large empyema that has to be drained. It is a pretty nasty infection usually associated with bacteria as well.

Interestingly enough this is I would say one of the more common ways these patients get to be recognized. This is their first most serious and most major illness.

We don't expect to ever see that again when the patient is on gamma globulin.

The second largest one or another very large one; I am not going to tell you it is the second largest but it probably comes in third place and that is Mycoplasma. Again, there is kind of a secret handshake deal between people who are immune deficient with antibody lack and then having a Mycoplasma infection. We don't understand this very well because Mycoplasma is not really supposed to be an extracellular organism exactly.

On the other hand, antibody seems to be pretty crucial. Hemophilus, I probably should have put this slide first, hemophilus is our biggest consideration probably.

So, if you look at this particular paper by Samuelson I think it is a large amount of very nice data because they have really gone after this bug in a very concerted way. It is 117 patients followed with antibody deficiency for 5 years. They were either IgA subclass or CVID and the non-typable hemophilus was the sole respiratory pathogen for more than half of those people and it was mostly the CVIDs that were really concentrating this particular bug and many of the patients that have had many positive cultures and they are colonized really with the same strain for many, many months on end. So, it is something that we actually have an incredibly difficult time

actually eliminating from our patients. Whether they are on gamma globulin or they are not to me this is our single worst organism currently.

I think this is responsible for the little redness of the eye that you often seen in patients with CVID who haven't had their antibody for a while.

You know Bob Good used to say that you could always tell when they needed their gamma globulin because they get this little pink eye and I think that is true.

If you culture it is always going to be hemophilus and it would be non-typable and between you and me I don't know how we can get rid of it because of course non-typable means no capsule, and no capsule means antibody doesn't help a whole lot and of course many of the are on many courses of antibiotics and as you can see the isolates don't seem to be any different that were isolated from other normal immunocompetent people. So, there is something not so special about the bug as far as I know. It is just this is the open door for these patients as far as I can tell.

In the Finnish population a large amount of data has been done just to try to figure out what is responsible for the chronic lung disease that we see in these patients and in this particular case 14 patients were given a bronchoscopy at a time when they were not knowingly ill but they had some bronchial findings and in this case 11 had

CVID and 3 had XLA and as you can see they really isolated quite a bit of the same bugs we have been talking about, hemophilus here but then a few viruses also are creeping in.

I think this is what we don't know very much about though, the viral part of this because it is hard for me actually to culture this.

I am sure it is hard for everyone here to actually know when that particular bug is present. Returning to Mycoplasma that is the secret organism again commonly found in the chronic arthritis and this was a study by Franz in the British Journal of Rheumatology who concluded that they really had a really bad problem with the chronic arthritis. As you know that has been described for some time. So, it is again an organism that isn't necessarily in the lung. It may be elsewhere and some have CVID. Some have XLA but it is obviously a very big or bad problem potentially with the chronic arthritis seen in these patients.

Now, how much do we know about viruses? Actually not very much to be honest with you and I don't actually think about viruses very much when it comes down to antibody deficiency aside from those that I have touched on and the echovirus and XLA, but there is an interesting paper that the Webster group published last year in Clinical Experimental Immunology that sort of opens that thought again saying, "You haven;t resolved it," and what is the

point of the slide is that 50 percent of the CVID patients in their peripheral blood had circulating CDA T cells that were positive for CMV and/or EBV and then specific gamma interferon cytokine producing cells were also found in good number in the CVID patients as well.

So, it seems too say that perhaps they are a little bit more challenged with these viruses than I have ever thought about very much. So, although we don't talk about viruses very much with antibody deficiency, at least I know I don't give it a lot of thought, I have to say that that door is not closed in my mind.

There may be more to say about that that we haven't been really looking for and the other one which I know that most of the people here would be aware is that Jack Rudis is also very interested in the role of HHV8. Does it have one? Does it not have one and what might it do to the lymphoid overgrowth and the granulomatous formations which occur and this is from his paper in JEM last year, or 2 years ago and it shows a lot of lana(?) positive cells in the lungs of CVID patients with granulomatous lymphoid interstitial infiltrates. I don't know how I feel about this. I have sent him two samples of blood of patients of mine with this sort of ailment. They have not been positive. I think we need to find that out. Is it true or not true and of course Jack is continuing to work on that, but it says

that there are still things we don't know, that we put on the shelf and said, "We will think about that another day," but it could be that viruses are more of an issue than we know.

Okay, what do we know? Well, this was a study from Iran. It is a follow-up of 221 patient years and in this case it says that when you are diagnosed and then treated then the number and incidence of infections clearly diminishes. This is the number of patient years of follow-up down here in this lower part of the slide and what is the point of the slide is that pneumonia and diarrhea, sinusitis, otitis and everything else that is really the high rollers here of these infections here are definitely going to diminish after treatment is started. The number of follow-up years is in this case not very long but it gives you kind of a picture that what we see in the United States is actually very similar to what is seen elsewhere in an entirely different culture and an entirely different environment. It is the same organisms really and the same issues.

Taking 50 of our most recently referred patients, Paula Busse then did a study to say, "Well, does the gamma globulin really cut down the incidence of pneumonia?" and obviously it does. It is P .01 but as you can see we still have pneumonias left over. It has not completely gone away.

I mean we have to conclude that a good number of those people have lung damage and so having pneumonia is one of those things that is an anatomic fact of life almost because the airway clearance is no longer entirely normal and these patients of course had been in the hospital at least once in many cases and some of them had so many episodes of pneumonia that they actually lost count and that could be more in this group.

Pneumonia is not eliminated by IVIG. It is one of the things that we might like to just contemplate for a moment.

So, I am just going to touch on one other thing which is the relevant antibody titers in patients receiving IVIG and so I took four patients who don't have any antibody of their own. I guess it is five and with a commercial laboratory simply sent their serum out at a trough level to say, "Okay, fine, how much antibody do you have to these organisms?"

To be honest with you I don't care that much what is in the bottle. I care what is in the patient. So, to me I think trough levels of the patients although I have never given them much thought before, it actually rounds out the discussion here according to me because if you have a patient who is colonized then it could be that you actually have higher titer than you think you do. So, I am rather

interested in knowing what the patient ends up with who is on a steady dose, who is not ill, who has got no particular problems and these individuals don't, and I simply chose them because they had nothing to start with. So, everything you see was a result of the gamma globulin.

Now, I very arbitrarily drew this red line over here, 1 microgram per ml because that is what has been stipulated by many to be the so-called "protective level."

It is actually I think as far as I know either a microgram or 1.3 micrograms per ml that is often used as the cut off there for protection and for no colonization.

So, how does this stack up? Well, our RC down here didn't do very well, this particular one and some of the others actually have more as you can see.

Now, they are on different products and this is not very much data. I acknowledge it. Personally I think a study of this sort would be very useful to just gather a lot of data about what the patients end up actually having as their protective level. Some levels are higher than others and some are lower as you can see. I think that was the point.

The other thing, what about hemophilus because that is another organism that I am very interested in. This little red box is what has been stipulated by laboratories as being protective and the patients as you can see, these

four patients here are much better than the so-called "protective levels."

This is again a microgram per ml. So, I have often been worried that they didn't have enough hemophilus antibody available in their blood but if you look at this data you would say, "Well, going by anything that we know however bad that is and however insecure we feel about assigning protective, on the other hand they fall above that level of what we have assigned as protective."

This is to viruses because we are going to talk a little bit about measles, mumps and rubella. So, called "protective is the pink box here. So, these are three patients that again have no antibody of their own whatsoever and as you can see it looks to me as if everybody is falling above that level with rubella being somewhat higher.

So, this is something that we want to fold into the discussion somewhere. I am not sure where we need to fold it in but I think that would be another way to look at what our patients have going for them.

So, infections with bacteria and certain viruses are really quite characteristic and they are not completely reduced, these infections by IVIG replacement. We still have infections. I won't say it is common but we certainly have them .

Levels of the antibody in blood are variable but

so-called "protective levels" were found in the serum of patients with no antibody of their own but not in every case and that is my last slide.

(Applause.)

DR. BERGER: Mel Berger, Cleveland. Charlotte, I totally agree with you that the trough titers are really important in the patients receiving gamma globulin and there are some physicians, for example, Ralph Shapiro in Minnesota actually follows a lot of his patients that have lung disease with trough levels of antipneumococcal antibodies, not just the total IgG level and of course your patients may be on different doses also, right?

DR. CUNNINGHAM-RUNDLES: Is that a question?

DR. BERGER: Yes.

DR. CUNNINGHAM-RUNDLES: Oh, okay. They are pretty much all on 450 milligrams per kilogram. They are not on different doses but the products may be different but that is the kind of data that would be useful to gather and these were two on one product and two on another as I recall.

DR. BERGER: But this may be one reason why the studies, every study that has been done in patients with chronic lung disease where they compared 800 milligrams per kilogram or a quote, unquote high dose with a quote, unquote low dose, every study including the original British studies showed that the higher dose is more effective and

particularly in those patients and so maybe instead of just taking an arbitrary trough level like our practice parameters specify 500, I don't really know what data that is based on other than the opinion of the panel who wrote that article but maybe we should be calibrating our doses and our dosing intervals by trough levels of pertinent pathogens for that patient.

DR. CUNNINGHAM-RUNDLES: I never thought it was much worth repeating those titers so often as I have seen some physicians who send me their massive charts because it is incredibly expensive but I think we need more data like that and we certainly need it for those who are not getting any better or not doing all that well.

DR. GOLDING: You mentioned that Mycoplasma which I think is very interesting and maybe we need to pay more attention to that, the patients who are on IGIV do you see an improvement or a decrease in Mycoplasma infection?

DR. CUNNINGHAM-RUNDLES: I have almost not seen Mycoplasma at all in the treated patients, I think with one exception over a very long period of time but A, my culture is not good. I am not going to tell you we are very good at it and I don't know if it is indolently progressing in the lung where I can't find it and can't culture it very well, but as far as objectively obviously present, no, not in those who were given good standard amounts of treatment with

nice trough levels.

DR. GOLDING: May I just make one quick comment which is a little bit outside the scope of this meeting and that is it is interesting to me that you look at CD8 positive T cells and obviously in common variables some of these people have reasonable T cell function and I wonder if we shouldn't think about that in another context in terms of stimulating that type of immunity to protect those people against viral infections, Mycoplasma and other agents that are --

DR. CUNNINGHAM-RUNDLES: I think viral infections are still kind of the thing we haven't paid a lot of attention to because the bacterial has been so important but it could be the virus is really kind of the underbelly that we don't think about a lot. So, I can't close the door on it.

DR. BALLOW: Mark Ballow, Buffalo. Charlotte, you were talking about total IgG levels with regard to pneumococcal antibody titers. Do you have a feel for whether we should even be looking further than that perhaps at you know the different subclasses of the antibody against a particular pathogen? Might they function differently as far as protecting the host?

DR. CUNNINGHAM-RUNDLES: You know if we talk about pneumococcal titers at any national meeting of any sort or

function or subclasses it is a way to have a nice civil war because we don't actually know very much what is protective, what is not.

I mean yes, I think it would be great to know more about that but I know that people don't even really quite agree on the ground rules on that. Different individuals measure it differently. I like to measure 23 serotypes when I can. Some physicians get away with four. I know in Europe they do it entirely differently. They don't do it our way at all. I think it is something that somehow we need to settle but most importantly I think we need to sort of stick to what we are going to look for in the patients and in the bottle and then compare.

It could be that if you are colonized, too, that you are actually just absorbing out. So, RC up there on that slide, we had a couple of admissions to the hospital in the past year which I don't expect for the CVID patient who is well treated. I suspect that she has actually got a very high utilization rate and actually we haven't talked about that part of things yet.

You know, is she using up the antibodies that I am so merrily infusing?

DR. STIEHM: I would like to reiterate that last point. I wonder if the patient is colonized with say, type 4, will that titer to that particular pneumococcus be

diminished and that is really very relevant to recurrent infection.

DR. CUNNINGHAM-RUNDLES: Especially since according to me and I think Dorothy Scott's paper which she is going to talk about later type 4 actually was in the minority as far as the number of serotypes that were actually in the mix and for me, too, there is not that much type 4 present.

So, it could be if you are colonized with that that sinks you below the relative level.

DR. OCHS: One of the issues that we have to face is not only how much gamma globulin a patient gets per month but how often this is being given and if you ask patients who do self-infusion IVIG, they come and say, "I feel best if I do it every 2 weeks." They probably would feel better if they did it every week, and that gives you a much better base and trough level in antibodies that are not so highly present in IVIG and if you give it subcutaneous these patients seem to do much better because I give it once a week and some of them actually inject it once a day and so if we want to think about the best optimal treatment for these patients apart from what the differences in antibody titers are from one brand to the next or from one batch to the next it is how often they give it and so that is very important to consider when we do these studies, how much do they get; how often do they get it infused and what is

actually the titer in the preparation and that makes it very, very difficult to follow these patients with specific markers and so we have to come up with some surrogate markers which Dick has set and which ones are we selecting and what patients do we select for these studies and how often do they get the gamma globulin infused.

DR. CUNNINGHAM-RUNDLES: I mean it could be that we need to get data on patients who were given subcutaneous treatment. I have actually, maybe it exists; maybe I just didn't see it. I would like to see antibody titers in the patients who get subcutaneous treatment because actually I am not terribly interested in what is going in. I mean yes, we have to know that it has got good stuff but you actually want to know what you end up with at your trough point.

PARTICIPANT: During that clinical trial from CLB Berring(?) they collected the data but I don't think they actually measured but they have the serum available. So, they could measure anything in these patients.

DR. CUNNINGHAM-RUNDLES: I think the data is out there. It is just that we as a group have not collected that and visualized that ourselves perhaps.

PARTICIPANT: It is expensive to do but it is also very important data to figure it out.

DR. CUNNINGHAM-RUNDLES: No doubt about it and I think something like measles or mumps which is not a

ubiquitous antigen or hepatitis B or something like that you know would have to be compared to something which is quite ubiquitous with the patients such as the pneumococcal or perhaps hemophilus.

DR. BLAESE: Thanks very much, Charlotte. Our next speaker is Dr. Rebecca Buckley from Duke University. Charlotte gave us the perspective from the department of internal medicine and now we are going to get a perspective from the department of pediatrics.

DR. BUCKLEY: Thank you very much. The subject that Charlotte and I were given to speak is not an easy one to address and I think that I will just start off with my part of the presentation here talking about sort of the spectrum of what we are dealing with.

As you heard earlier from Dr. Scott until Ogden Bruden described gammaglobulinemia in 1951, we didn't know about any of these diseases and now there are at least 150 different immunodeficiency syndromes that have been described and we know the molecular basis of about three-quarters of these defects but the sad part about it is that these are usually recognized only when the person develops an infection or in the case of the common variables when they develop autoimmune disease but even when they develop an infection they still don't get recognized and the consequence of this is that you can end up with

bronchiectasis which probably accounts for why people who have common variables who are on IVIG still get pneumonia because they have bronchiectasis or they have pansinusitis and so the cost of late diagnosis is really very high, and this is a slide I always show to the residents when I am rounding with them. I don't know why there are dollar signs here but I think it was a different PowerPoint program,but I think the most convenient thing about this slide is to think about these defects as to whether they are B cell defects, T cell defects, phagocytic cell defects or complement deficiencies and for the purpose of our discussion here today and tomorrow the patients who had B cell and T cell defects are the ones who are going to need the intravenous immunoglobulin.

Now, the other point to bring out is that while these patients all have increased susceptibility to infection the other thing to remember is that we live in an antibiotic era and so because the data that Charlotte presented from Jerry Wickelstein's survey showed that many of the infectious agents were not identified this is because rarely are cultures done and many patients just automatically get an antibiotic. Many of these infections re probably viral infections but nevertheless the textbook picture presentation of primary immune deficiency is usually masked by the frequent use of antibiotics and the other

point from this slide is that these patients appear outwardly normal. They don't look any different from anybody else and so if they have an ordinary infection and I will show you a slide later that they usually do have ordinary infections then somebody has got to have a high index of suspicion in order to make these diagnoses and so again the characteristic infection that you see in the different types here for B cell defects, the ones you have already heard about, pneumococcus, staph, H. flu, strep and Mycoplasma, enteroviral encephalitic, Giardia is another problem but dominantly the infections are respiratory in these patients.

Now, patients who have T cell defects who by definition also have B cell defects because we know T cell function you can't have normal B cell function, but they also in addition to having these will have problems with herpes family viruses and they will also have problems with candida, pneumocystis and then the infections will be severe and persistent.

There are many other serious infections that occur in patients with immunodeficiency, granulocytic defects, monocytic defects or complement and there are characteristic organisms that you see in each of these types of infection, but discussing the problem of enteroviral meningoencephalitis I agree with Dick Stiehm that we rarely see this anymore but just last fall we had a new patient who

presented with what was called aseptic meningitis, underwent an extensive infectious disease work up with many antibody titers to many different agents and then finally someone a month later thought of agammaglobulinemia and this child had almost no immunoglobulin. He persistently had elevated cells in his central nervous system and fevers every day and despite PCRs for every know virus he still has a persistent meningoencephalitis. So, I am sure there are other viruses out there that can cause this syndrome.

Echovirus 11 is the one that has most commonly done this. We found polio in some of the CNS samples from our patients who had this and if there is a delay in diagnosis then these people are much more likely to get this and it can occur also in CVID patients and the series that Ross McKenney developed from Duke there were four or five patients with common variables who also had echovirus meningoencephalitis.

The other organisms to consider in pneumococcal infections are most B and T cell defects but now we know you can have that in many different of these genetic types of immune deficiency.

You can certainly see it in most B and T cell defects. You can see it in T2 deficiency. You can see it in congenital asplenia. You can see it in a condition called NEMO, ectodermal dysplasia with immunodeficiency and then in

IRAK4 deficiency. So, pneumococcal infection is something that occurs frequently in many different types of primary immune deficiency diseases and conceivably could all be helped by intravenous immunoglobulin.

Mycobacteria and salmonella would be suggestive more of a defect and monocyte macrophage immunity and this was a suggested defect in one of the either interferon gamma receptors or IL-12 or IL-12 receptor defect or STAT-1 deficiency and then Cryptosporidium is a real problem in X-linked hyper IgM and Pneumocystis jeroveci and also in many other types of T cell defects.

So, there are a lot of changing concepts. It was thought that a patient with chronic granulomatous disease which is a neutrophil defect would have problems primarily with staph and Serratia, but we now know that the leading cause of death in this condition really is fungal infection with aspergillus leading the list but there are now other types of fungal infections that have caused demise in these patients including Trichosporon pullulans and Penicillium.

So, what are the new threats for primary immune deficiency? West Nile virus, I think this is something that we need to talk about but as far as we know the patients who have died from West Nile infection have not really been investigated fully to find out whether or not they may have had some underlying host defect.

Also, we don't know much about titers of antibodies to West Nile virus and the various preparations of intravenous immunoglobulin.

A new threat would be as someone mentioned earlier bioterrorism with smallpox or with anthrax and then in my view a new threat to primary immune deficiency is this new live Rotavirus vaccine, Rototeq which is now being mandated as part of the routine immunizations of all babies at 2 months, 4 months and 6 months and contains five different strains of live Rotovirus agent in the vaccine.

Then another threat to our patient population is community-acquired infections such as MRSA, VRE and legionnaires' disease.

So, how many patients are there out there with these diseases? We really don't know because there is no screening for these defects and if you use live vaccines early in life such as BCG in third world countries or during infancy in the United States such as Rototeq or Varivax then this will make death almost certain for those who have genetic defects in T cell function.

I have already mentioned the problem with widespread overuse of antibiotics masking the presentation of these patients.

There was a survey done by the Immune Deficiency Foundation that showed that the average time from the first

infection to diagnosis was 9.2 years and just to bring home the point again the most common infections that these patients have really are the ones that are most common for everybody, in other words sinusitis, pneumonia, ear infections, diarrhea and bronchitis.

This was a survey of patients who belong to the Immune Deficiency Foundation and they were asked, "What types of infections do you have?"

So, they don't always have strange infections. They often had very common infections. It is just that they have more of them.

So, since there is no screening for any of these defects this is a major problem in third world countries where all infants are immunized with live BCG vaccine on day 1 of life and these infants will die if they don't have normal T cell function.

So, there are screening methods that are available and could easily be implemented if screening for these defects were accepted as a standard of care but the main obstacle to this is to overcome the general impression that these defects are so rare that the screening would not be cost effective.

Recently the Immune Deficiency Foundation conducted another survey. This was a random telephone call to 10,000 households in the United States and it was learned

from that that within those households there were approximately 250,000 persons. The percentage gleaned from that survey would suggest that there are at least 250,000 persons or 1 in 1200 people in the US who are afflicted by these defects and that these are much more common than diseases that people currently screen for.

However, we really won't ever know what the incidence or prevalence will be until there is population screening. So, the cost is a big question and to address this issue half of all persons with primary immune deficiency are not diagnosed until they are adolescents or older.

So, the cost of a late diagnosis is a heavy burden of disease on the patient and causes early demise. The majority of patients report two or more hospitalizations before diagnosis. So, the cost of hospitalization of these patients far exceeds what it would cost to screen for the defect and to implement the therapeutic for preventive measures and this is a pie chart showing from one of the I immune Deficiency Foundation surveys which shows that a majority of patients who are later diagnosed with primary immune deficiency had been hospitalized at least two times and 21 percent of them had been hospitalized five or more times before someone thought of this diagnosis.

So, getting back to the types of infections that

you think of in patients with primary immune deficiency I wanted to talk just a little bit about the patients I care for most of the time, and these are patients with severe combined immune deficiency.

At our institution we have transplanted now 158 babies with SCID over the last 25 years and we have been able to fortunately transplant 45 of these patients in the first 3-1/2 months of life, and you can see from this Kaplan Meier plot we have only lost two babies and one of these was from EBV and the other from CMV.

The other 113 patients that we transplanted which the transplants occurred after the first 3-1/2 months of life you can see the mortality is much higher.

Most of these deaths occurred in the first 5 years after transplant. We have had one late death which was in an ADA deficient SCID but the cause of these deaths you can see on this slide right here and so the big offenders for infants who have T cell defect really are viruses, CMV, adenovirus, EBV, enterovirus, rotavirus, parainfluenza 3, varicella. We have had three patients present to us who had chickenpox from the Varivax vaccine and then herpes simplex and RSV are other offenders.

So, one of the things that we have been very much interested in and lobbying for screening for these defects is would it be cost effective and so we went back and looked

at data on 74 of our transplants that could be provided to us by the administrators at Duke and we found that if you could do a transplant in the first 3-1/2 months of life that the mean cost overall is around $100,000 including the clinic visit, the rental apartment, the car to come to the hospital and so on whereas if you look at the babies who were transplanted after 3-1/2 months the mean cost was around $450,000 but we had several that were million dollar or 2 million dollar babies and the main cause for this really is infection.

So, despite treating these patients with high doses of intravenous immunoglobin all the antibiotics that were available we still had a very high mortality from viruses in this patient population and the cost of just containment of infection really is the major cost.

So, one other point I wanted to make in closing is that we have developed some guidelines. The Medical Advisory Committee for the Immune Deficiency Foundation has developed some guidelines which are posted on the IDF web site and these guidelines are written so that patients themselves as well as their physicians can refer to these guidelines about how to suspect these conditions and how to test for them and the reason we did this is that there is really no stronger advocate for the patient than the patient and his or her family and often the patient can call the attention of these

testers to their primary care physician and that way an earlier diagnosis can be made.

I will stop there.

Thank you.

(Applause.)

DR.GOODMAN: You mentioned rotavirus which I found interesting. I was wondering whether you have seen or others in your experience with either PIDD or SCID problems with natural rotavirus infections?

DR. BUCKLEY: Oh, yes.

DR. GOODMAN: And then I was also just going to mention that of course the vaccine viruses are much attenuated and children are going to be naturally exposed to more virulent viruses.

DR. BUCKLEY: We have seen many, many problems with rotavirus among the patients we have cared for who were in the group the past 3-1/2 months where they came in and they had to be inpatients and then we had epidemics of rotavirus infection on the floor and so it was transmitted from room to room. They usually don't get rid of it until they develop T cell function.

So, even though as you say these are attenuated strains they may still have problems and for them they may be just as pathogenic as the other non-attenuated strains are for normal people.

DR. GOODMAN: So for the SCID question what about in antibody deficiency?

DR. BUCKLEY: In antibody deficiency we have not really seen that much of a problem. It has been more Giardia causing diarrhea there.

Agenda Item: PIDD registries and wurveillance for infections in patients treated with Immune Globulins

DR. BLAESE: We are going to go out of order. I thought I would make a presentation, the next one and tell you something about this United States Immunodeficiency Research Consortium or USIDNET.

This was a 5-year contract that was awarded by NIAID to develop consortium investigators working to promote the field of primary immune deficiency and there are four programs within this USIDNET operation.

One is to provide research support to help the development of young investigators and so far we are 3-1/2 years into this program. We have given $7.1 million in grant support to 28 different investigators and more than half of those investigators this was the first NIH funding that they had received.

So, part of our mandate is to try to bring in new people into this field because as you can see a number of us are getting fairly old and will be leaving the field fairly shortly and we want to have a sufficient number of people

that are expert in the field to carry on.

There is another major part of this which is an education and mentoring component and there are a number of different areas for instance an immunodeficiency summer school for senior fellows, junior faculty from around primarily the Western Hemisphere. There is a visiting scholar program where we can give travel awards to medical students or fellows to go visit another institution if they don't happen to have a program in primary immunodeficiency at their own or if they want to learn a particular technique that is not available at their institution.

There is a cell and DNA repository of primary immune deficiency patient samples that is available on our web site and through Coriel(?).

There are now about 50 samples in that repository of different primary immune deficiency diseases. Sometimes there are many, many samples like ataxia telangiectasia or ADA deficiency and in some cases there are IgG subclass deficiencies and hyper-IgM and Wiskott-Aldrich and XLA. So, if people are interested in studying these disorders because they are rare and if you don't happen to take care of patients you may not have access to these materials and so the USIDNET set up this repository and finally one of the charges of USIDNET was to modernize and expand the existing immunodeficiency patient registry.

Now, the original registry was a chronic granulomatous disease registry that was established again under an NIAID contract with the Immune Deficiency Foundation and that has been going now for about 12 or 14 years. There are 396 patients with CGD in the registry and there have been a number of publications that have come out of that original patient registry.

About 10 years ago NIAID decided to expand the number of registries, the number of patients to eight different groups, a common variable. It now has 362 in the original registry patients and as Dr. Cunningham-Rundles explained we have collected at least another 100 to the new registry and all of these old patients will be converted to the electronic format along with the incorporation of newer patients.

You see we have patients with DiGeorge, with hyper-IgM, with SCID, Wiskott-Aldrich, X-linked agammaglobulinemia. There was also a registry for leukocyte adhesion defect but we have been not able to accumulate andy patients so far with that particular disorder.

In expanding the registry the steering committee decided to work with the European Society for Immune Deficiency. It has already developed an Internet based data entry and review process so that we could have a more standardized way of data entry and a more efficient

collection of patient follow-up data.

Most of that initial IDF registry was a static one-time enrollment and there wasn't a mechanism for getting continuous follow-up and updates on the patient's status whereas this new one that is electronic that is web based we will be sending out e-mails to the enrolling physicians on a periodic basis perhaps every 6 months asking them to update the data on a particular patient and at that time ne of the areas that we have asked this audience to consider is what kinds of questions should we be using the power of these registries to help answer as it relates to for instance the use of immunoglobulin and I think we have heard a number of situations where we simply don't know what the appropriate answer is and if we can design a good survey document to help answer those specific questions.

If you visit our web site at www.usidnet.org you can get instructions about how to become a registered user, how to obtain a password and a user name.

We have already sent the protocol off to the Western IRB and gotten approvals along with approvals of informed consent documents.

Some of you will be able to use those Western IRB documents but others at least can use these documents to help establish your own IRB documents.

There is informed consent in both English and

Spanish and a tutorial on how to use the registry and we have just recently hired a full-time manager for the registry. It is Beth Garrett who can be contacted at the IDF and you have got her e-mail address there and Beth has been brought on for a number of things, not only to manage the registry but actually to go out to various centers and actually help enroll patients.

One of the things that we learned with the initial registration process in that first registry was that more than half of the patients were submitted by docs who took care of less than five patients with primary immune deficiency which is telling us that the major centers were not participating in proportion to the number of patients that they saw and partly we have learned it is that it was just a burden. There was no one available to do it, and some of the institutions felt that they had enough patients for their own studies. They didn't really to participate in a larger registry.

So, we have been encouraged to develop a way for having an individual go out to the different centers and actually help and Beth will help give the materials to work on getting an institutional review process for everybody that needs to get IRB approval to have registration and as I have said will be willing to come out to institutions.

So, I would encourage people to take advantage of

this. Now, our registry has a demo version that will show you exactly what it looks like and it is available at this Internet address with a fairly simple user name and password and I would encourage people to take a look at that. We would like feedback from anybody who might be interested in looking at this to help design it to make it the most effective data collection system available.

What could we use the registry for, and there are a number of issues that we are trying to design it somewhat differently from the previous registries and one is as a surveillance tool and this is just one example. For instance, what is the actual experience in different primary immune deficiency diseases with live agent vaccine?

As you know almost every new live agent that comes out it is recommended that you don't use these in patients with primary immune deficiency and yet from what Dr. Buckley showed you the mean time from onset of infections until diagnosis is 9.1 years for many of these disorders and by that time a huge number of these patients actually have acquired and received live agent vaccine.

So, what we need to discover is what is the appropriate denominator and this is one way of developing that data. So, we can actually figure out for which diseases are these agents a potential threat and for which ones might they be beneficial.

So, this is just a listing of them. This is a very simple one. Was the vaccine given, yes or no? Where there complications from it and if there were complications please describe.

Another way is to try to answer other kinds of questions across a broad range of disorders. This is another question that is being looked at. A number of patients get treated with immunosuppressive agents. They get autoimmune phenomenon. Wiskott-Aldrich is an example that I use all the time. The major problem with Wiskott-Aldrich besides their infections is that they have a severe auto-aggressive disease that ultimately forces us to use immunosuppressive drugs which then gets you into the terrible cycle of immunosuppressive drugs, getting more infections and how do you get them off things like steroids and so we are trying to just get a feeling for which diseases whether it is CVID or Wiskott or others are getting immunosuppressive drug treatment,what do they get and did it cause problems or not, data that we know from just the experience of a number of investigators that they see these problems. We don't have a quantitative number to really nail it down, and finally you can collect very specific data. One of the features of this USIDNET registry is that we are going to be using pull-down menus that give you a whole bunch of choices. For instance if you click on the infections button you will a lot of

different abscesses whether it a brain abscess, a colon abscess, a liver abscess that you can check off and we have asked people to grade them. Is it something that was present at the diagnosis? That is one of the things that helped you decide whether the patient had a problem. Was it just observed occasionally in these patients or was it a prominent feature of that particular patient and also addressing in this case the organisms that are involved and we hope we can develop the kinds of data that might be useful for the questions that are being raised by this workshop.

Will the registry be successful? You know, after 10 or 12 years we had about 1400 patients enrolled in the initial registry and we had a lot of push back as I mentioned from the major institutions that didn't get involved. So, we have a balancing act to do between making the registry easy enough to use and yet comprehensive enough to collect useful data and we are just going to have to see how this works out but a number of the questions how do you actually incentivize a physician to participate? Dr. Grimbacher will tell you about the European experience where they have provided a bounty for each patient that was enrolled of I think 10 euros to encourage individuals to enroll their patients.

As I mentioned there is a balance between the

quality and the quantity of the data requested and what level of tolerance the submitting physician may have to answering lots of questions.

One of the ways we are going to be doing it in this country is to have the patients be able to initiate the registration process. If the patients get access to the database, can enroll, put in their own information and then e-mail it to their doc and say, "Finish this," that may be enough of an incentive to get more patients enrolled so we can increase the number of patients in the registry and as I mentioned USIDNET will provide assistance and this database has a capacity for periodically requesting follow ups.

So, with that I would like to introduce Dr. Grimbacher from London. Bodo was involved with the European Society for Immune Deficiency in the establishment of their original database and they have been online now for 2-1/2 years, nearly 3 years collecting data on more than 3000 patients.

DR. GRIMBACHER: Thank you very much for inviting me to this hearing and I am pleased that I am allowed to report on the European efforts to collect data on patients with primary immunodeficiency diseases and this is a project sponsored by PPTA and the European Commission and it started in 2002 when I took over the registry from Leonard Thomas in Stockholm and he had collected more than 10,000 patients sa

you did with a one-time registration.

However, the data was not followed up. So, after 10 years we wouldn't know how many of those 10,000 patients would be still alive and how many have deceased and how they are doing on therapy. So, we decided in 2002 that we want to have a new registry, an online-based registry where follow-up data to the patients can be added and so we started out to develop this new online registry for primary immunodeficiency diseases and as you can see as of today we have 66 documenting centers who are agreeing to enter their data and however, only 42 have already started documentation and this is because we require three things to happen prior to documentation.

One is there has to be an agreement signed between the documenting center and ESID and this is basically that everybody knows to what rules we are playing or according to what rules we are playing and that is that the documenting centers know that they have to keep their password secure and things like that.

The second requirement is that all the documenting centers need ethical approval. So, they need to go to their local IRB committee and ask for approval to documenting into that European registry and this is because unfortunately also the European Union does not have a central ethics committee in place.

The third requirement is that every patient who is registered has to sign a written consent form or the parents. A legal representative has to sign such a form and before that we cannot register patients into this registry and so 66 centers want to do that. However, only two-thirds of them have already achieved those three requirements and are documenting patients into the registry and these red dots represent where those 66 centers are located and you can see that some of them are even outside of Europe and this is because those countries also want to participate in the clinical research we are doing, and I also have to explain that some of the countries have national registries. For instance, in France there is one big national registry located in Paris and since France is very centrally organized this national registry has obtained data from more than 1000 primary immunodeficiency patients from all centers across the country.

So, although you see here only one dot it is a representative dot for all the other documenting centers within that country.

There is a national registry in Spain for instance in Majorca. You can see that Maria Matamoras in Majorca collects all the patients in Spain meaning that you have only one dot doesn't necessarily mean that thee is only one documenting center per country.

We started the online registry in 2004, and it was kind of a slow start because of those regulatory issues and because all these documenting centers had to go through ethical approval and collect consent forms.

However, in the more recent month we have seen a huge increase in patients documented. So, this number of 3000 is from a couple of months ago and because just in recent months you know we added additional patients now amounting to 4142 patients in the registry.

I would like to use that slide, also, to mention some of the incentives. For instance at that time point here we decided to give the 10 documenting centers who get the first 50 patients in an additional incentive of 2000 euros. So, this steep increase here is because those centers then decided to enter the first 50 patients and have a student or a documenter sitting there and enter the patients just to get those 2000 euros.

So, yes, there is a financial incentive you can put to the documenting center because some of the centers can actually use actually extra money and for any documenting data set per year the documenting center obtains 10 euros per patient.

So, then it is also interesting to know out of those 4100 patients how frequently are they entered again and again and again. So, of course most of them and I

apologize, I should have plotted that in absolute numbers. So, most of the patients have already entered once because most of the entries have only been in the last year. However, you see that a fair amount, one-fifth of the patients have already been entered twice some of them three times. So, three times over the last 3 years and you also see that some of the centers actually chose to document the patients more frequently than only once a year, and what is very interesting here that we have 3 percent. That amounts to approximately 120 patients who have been entered already more than 10 times in the last 4 years and this means that those centers are documenting these patients probably every single time they are coming to their clinic and that generates very important data because this is very close maybe every 3 months documentation of the patients enabling you to look at very dense data and very deep data.

These are the current statistics. Of course, most of the patients suffer of predominantly antibody deficiency disorders, 60 percent of the patients do so and others have well-defined immunodeficiencies like Wiskott-Aldrich syndrome belongs to those 17 percent of the patients. Fourteen percent suffer a phagocytic disorder, neutropenia for instance being one PIDD diagnosis and 6 percent suffer severe T cell disorders, for instance PIDD. Two percent have unclassified immunodeficiencies. There is only 1 percent of

complement deficiency so far into the registry.

I think this is mainly because the centers documenting the complement deficiency have not yet embarked to enter the patients and there are some patients with autoinflammatory syndrome and immunedysregulation syndromes in there as well.

These are the different diagnoses. As expected CVID with more than 1000 patients in the registry is the most prevalent. The second most prevalent is XLA due to mutations in BTK, more than 300 patients, IgG subclass deficiency more than 300 patients, selective IgA deficiency more than 250 patients and I have plotted in red the diagnosis where we do use IgE replacement to treat the patients and I have plotted in blue where some of the centers would use the IgE replacement and some of them would not.

So, you see here that a huge amount of patients in the register do receive immunoglobulin treatment. So, this is a clinical online database system accessible by standard Internet browser and the database is hosted in Freiburg in Germany where I worked for the last 6 years before going to London. It is online since August 2004. You can at the documenting center opt to have the pseudonormalized version so work with a number as an alias for the patient but since last year the personalized version that the documenting

physician can work with the patient's name on the screen has also been accepted by regulational ethical authorities. So, you can opt whether you want to work with patient names or whether you want to work with patient identifiers.

It covers all 206 primary immunodeficiency diseases as set forth in the IUS table of primary immunodeficiency diseases and in all of those conditions we document a common core data set of 22 data fields.

In addition to this common core data set we offer a disease specific extended one for 29 of the diseases and I am going to show you which those are in the next slide.

We have a continued documentation of patients to obtain follow-up data and we can document the mutation and this mutation documented in the patient is then linked to public mutation databases which then can be accessible by researchers from all over the world and we also have some goodies for the documenting centers like percentile curves. So, the pediatricians actually can see how their patients do and get something out of the registry. So, it is not only feeding into the registry. The documents centers can actually also use this registry and print out reports, send those reports to the referring physicians and monitor the quality of their treatment in the registry.

We have implemented questionnaires for quality of life monitoring. The first one going in there was the SF36

for adults and there will be also questionnaires for the quality of life for children and we have predefined queries. So, as a documenting center you can always compare the patients you have entered to the other patients which are in the registry and as I mentioned this is sponsored by five PPTA member companies and the European Commission.

This is a screen shot of how the database actually looked like. As I indicated we have a core data set which are the red fields. So, the red fields the core data set represents the characteristic data we feel are necessary to capture primary immunodeficiency disease.

However, this also contains some preliminary data on quality of life and for instance how many days have you been sick or have you been in hospital in the last year and this would be entered into the core data set field and then we have in addition as you can see here for the CVID subregistry a big subregistry to capture additional data sets.

So, this is more than 350 additional data fields, more similar to an electronic patient chart. So, you can enter all types of information into that subregistry.

So, disease specific data sets where you can do a very in-depth study on the patient are available for CVID, for agammaglobulinemia, for selective IgA deficiency, for IgG subclass deficiency, for ataxia telangiectasia and for

several other immunodeficiencies which are less prevalent and those types of subregistries are needed to address specific clinical and research questions. Those you would not be able to answer with the common data set of 22 data fields.

This is only to describe the epidemiology of primary immunodeficiency diseases in general but if you want to do disease-specific study you need to develop a subregistry for those diseases as USIDNET has done for eight of the conditions.

This is another screen shot of the registry, what we capture for therapy and adverse events. You can see here the data fields we are capturing and the question mark here always defines what the registry wants to have documented in the field. So, there is always definition of the data field. We have drop-down menus as the USIDNET registry and some of the drop-down menus can be edited because we cannot a priori think of all the systems being involved in primary immunodeficiency diseases.

So, if you are on that system you want to enter here. It is not in the drop-down list. You can add that to the drop-down list and by that expand the drop-down list which then can be selected from all the other documents.

We also have free text and we also have different colors of fields. For instance you see a red color for the

core data set, a black color and you also see the blue color and the blue color would indicate that there is a current study going on in that specific disease.

So, the red fields are mandatory anyhow for all of the patients and the blue fields are in that case mandatory for the CVID substudy going on right now.

So, we looked prior to coming here, we looked a little bit into the immunoglobulin therapy which has been entered into the database and the total number of patients immunoglobulin replacement therapy out of those 4100 patients is 1741. All of them receive immunoglobulin replacement, most of them through the intravenous route. However, almost 20 percent already by subcutaneous measures. In 50 percent we don't know what the route of administration is because it has not been documented.

I was surprised to learn that we still have four patients in Europe which have at least in Germany and the UK considered obsolete intramuscular applications and there are six brave patients in Sweden actually which drink your product and I have contacted them and this is because the treating physicians think that by drinking the immunoglobulin product they can get rid of the diarrhea and I would be surprised to learn then what the outcome of this is in future documentation to the registry.

We looked into the infections. We have infections

with immunoglobulin replacement and on patients with the same diagnosis without immunoglobulin replacement. So, you se that the immunoglobulin replacement, excuse me, just the other way around. This is without immunoglobulin replacement, the numbers of infections and with immunoglobulin replacement.

So, you see that the immunoglobulin replacement leads to a reduction of the overall numbers of infections in patients with antibody deficiency syndromes.

You also can see and this is similar data which has been already presented here that it leads to a drastic decrease in the numbers of pneumonias. However, the decrease in sinusitis is not that steep and the decrease in bronchitis is quite considerable and this is actually also supported by a paper coming out now from the Rome group. Isabella Quinti, et al will publish in a clinical immunology journal. I don't quite remember which one it is, but the paper is in press and I want to point out that you look out for that publication because she looked in more than 250 CVID patients from Italy and what are the effects of immunoglobulin treatment and she in addition to what has already been presented by Charlotte found that immunoglobulin replacement on the IV route decreases the severeness of the infection. So, it is very potent in treating otitis, in treating pneumonia, in treating sepsis.

However, the incidence of the chronic infections, chronic sinusitis and the chronic deterioration of the mucosal membranes is not very well affected by the treatment and I have to add to what has been said already this morning that that is probably because we are giving IgG and not IgA. So, if we treat all those bacteria which have been mentioned this morning we still need to consider that there is still the IgA component. The body will need to defend itself from those bacteria.

Another analysis and we did, and I have to apologize, we didn't redo it; so this is from 2006 data and so less patients. We looked at patients without hemoglobin replacement, with CVID and patients on immunoglobulin replacement with CVID how frequently they missed days at school or work and you can see here that this is pretty much a well-defined effect of immunoglobulin replacement leading to better performance and quality of life and this has socioeconomic impact as well.

The database and the results of the database have already been published and this is also in your printout so that you don't have to scribble it down. It has been published in Clinical and Experimental Immunology this year and this is the first clinical result of the database and the bioinformatics publication which is the publication on the platform and the IT behind that.

So, in summary in Europe we have an online database suitable to answer clinical and research questions. It has run stably since August 2004. It contains data of more than 4100 patients. It covers all the PID which are known with a common core data set. It has 29 disease-specific extended registries for studies and it offers a continued follow-up of the documentation on single patients. It is ready to address clinical studies including post-licensing surveillance.

So, anybody who comes forward with the data set, they want to capture we can put this data set as a green data set or as a pink or purple data set into the relevant subregistry to capture that data and it can be easily adapted to other diseases because it is meant in XML programming and so this is why it was possible to adapt the ESID registry into the USIDNET registry and accommodating those uses but it can also be used for, this platform can also be used for other diseases. In Freiburg we have a registry for rheumatic diseases and for nephrology diseases and for HIV.

So, this is the contact and I want to finish with thanking the sponsors of this project listed on the bottom of the slide.

Thank you very much.

(Applause.)

DR. GRIMBACHER: Are there any questions?

PARTICIPANT: Yes, thank you, Dr. Grimbacher. Could you clarify your last point? Were you saying that the ESID registry can now integrate data directly from the USIDNET or is there a system in place to merge the two data sources?

DR. GRIMBACHER: From the old USIDNET registry into the new one or between the ESID registry and the USIDNET registry?

PARTICIPANT: Between the two including the new USID electronically?

DR. GRIMBACHER: Yes, so, since the two of us developed the USIDNET registry together we paid a lot of attention to make this the new USIDNET registry as close to the ESID registry as possible.

However, there were many requests by, specific requests by US researchers and documenting centers to add additional fields.

So, yes, the core will be analyzed together but in addition what we analyze in Europe you will have additional data fields specific for the US.

DR. HOLMBERG: Jerry Holmberg. As far as adding the data sets that a researcher may want to incorporate is there a charge for that? Is there a governing board to determine whether these data sets are appropriate? How does that function?

DR. GRIMBACHER: For the ESID registry when an ESID researcher comes and wants to add additional fields that is all covered in the project. Since it is XML programming you can add and delete and change fields really quickly and it doesn't cost a lot and you can just update the registry. So, that is very quick and fast to do and it doesn't cost anything for the ESID researcher. How it will be for the USIDNET registry I am not so sure but --

DR. BLAESE: There is a steering committee for the USIDNET registry and all applications for that kind of a modification or additions to the registry would go through the steering committee and if they believe that it is a scientifically valid thing to do I am sure that they would approve it.

It, also, will depend a little bit on our experience about compliance with actually doing it and we have to keep in consideration it may be just a subgroup of for instance individuals that might be participating and a specific research project could be built in with a certain number of investigators.

DR. HOLMBERG: And how will this affect the IRB approval process if you are adding new data sets?

DR. BLAESE: Every participating physician basically must go to their local IRB and if you are going to add additional questions that is a good point about if it

goes to everybody I suspect that everyone would have to potentially modify but we haven't addressed that with instance the western.

DR. GRIMBACHER: How it works in Europe is that the IRBs request an update of what has been changed and then they will come forth and tell us if they are happy or not happy with it.

So, every time we change the data set we will have to submit it to the respective IRBs and by mailing and then they would tell us whether they think that was a major change or not.

DR. HOLMBERG: You mentioned the Western IRB. I am not familiar with that. Is that a standardized IRB?

DR. BLAESE: It is one of the commercial review organizations that happens to be located in Spokane, Washington, and it is used for multicenter trials frequently in the country, that is the Western IRB reviews and approves it. Then often many local IRBs will just sort of give it a stamp because it has been reviewed by another IRB and has been accepted.

It is certainly not universally accepted across the country but is something that is used frequently for multicenter trials which is basically what this is.

PARTICIPANT: I was surprised that hospitals and private practices go through Western IRB. Universities tend

to want their own but lots of other facilities will accept the Western IRB.

DR. HOLMBERG: I was, also curious, do you track the trough levels?

DR. BLAESE: We don't. I think you do.

DR. GRIMBACHER: Yes, in Europe we do.

DR. BLAESE: At least in the version that is going to be put online hopefully next week before the USID network we don't track trough levels.

DR. HOLMBERG: Do you have the capability or currently is there a capability to track any adverse outcomes with the administration of IGIV?

DR. BLAESE: It is one of the questions that is part of that section, you know, notation of adverse events associated with any of the therapies that are being used and a description of what it is.

So, that is currently built in.

DR. HOLMBERG: One final question. We know how the US is funded but how is the European funded?

DR. GRIMBACHER: The European registry is funded one-half by the European Commission. So, it is an EU grant and where we applied under the Sixth Framework and now we applied again under the Seventh Framework and that is the other half of the funding.

DR. PIERCE: Ross Pierce, FDA. Is the question on

adverse events of immunoglobulin infusions purely open ended or are there any specific choices offered such as aseptic meningitis in either the European or the US registry?

DR. GRIMBACHER: For the adverse events you have a drop-down list and you can choose what has been already entered but if your adverse event is not within that drop-down list you can add the plus function and add your specific adverse side effect and then that will be reviewed every month by the registry committee whether this was a valid adding to the drop down and then it will be permanently there or they can also decide that was not a good entry and then they merge maybe two of those entries to that purpose.

DR. PIERCE: Are there any routine follow-up submissions to any regulatory authorities based on those data?

DR. GRIMBACHER: Not yet but that would definitely be probable.

DR. OCHS: Ochs, from Seattle. I just wanted to clarify the national registries in Europe, are they independent or are they transferring their data into the ESID registry?

DR. GRIMBACHER: They use the same platform, first of all. They use the same platform. It is just that the organization is that the ESID just has one agreement with

the national documenting center and from there the national documenting center is basically an organizational part.

Then the national documenting center then goes too their documenting center and has an agreement between the documenting center and the national registry. Basically ESID just talks to the national registry and they then talk to the other centers. They use the same system. They use the same rules. They use the same criteria. They,also, have to follow the same procedures. and so it is just an organizational part.

DR. OCH: And where are the data? The data are in the national registry and in the ESID?

DR. GRIMBACHER: They can choose. The national registry can choose whether they only want to export for instance the red field into the ESID registry and keep everything else, you know on their own and analyze it on their own and publish it on their own and that is on the discretion of the national registry. That is actually at the discretion of all the document centers. So, all the documenting centers can decide whether they want to release the data they have entered because the data still belongs, although entered into the registry, belongs to or is possessed by the documenting center. So, ESID doesn't have the rights on the data. They just put it onto the platform and whether they want to grant access in addition to the red

field, they want to grant access to additional data sets and they have to agree and then the password the other users will get will be available for those other fields or they can also say,"No, we want to keep that data set separate.

DR. OHS: And how does this pan out in practice? For instance, the Italian registry I see them publishing their data, are those data in the ESID? Are they kept out?

DR. GRIMBACHER: The Italian registry is a little different because they started before the ESID registry started and so the Italian registry only transfers these 22 red fields into the ESID registry once a year and all the other data is kept separate and also published and managed separately and that is an exemption in the national registry and they also have their own Italian data input form and so yes they are separate and they do separately.

DR.SIEGEL: Fred Siegel. I assume that the funding companies don't have access to protected information.

DR. GRIMBACHER: They have access to aggregated data. So, they will for instance know aggregated data for 3 million people how many patients for instance are immune globulin replacement and how many use subcu, how many us IV and how many of those have CVID as a diagnosis. They do have that.

DR. SIEGEL: But they don't have personal information?

DR. GRIMBACHER: No.

DR. SIEGEL: They are not going to contact the patients?

DR. GRIMBACHER: They don't have access to data from the centers. They don't have access to data from the centers. They have just access to the aggregated data and not personalized.

PARTICIPANT: Some of the data that you collect could be very helpful in terms of the way we even regulate IGIVs. Regarding the infection rate what we did a few years ago to help facilitate trials is to say that if you have a certain number of acute bacterial infections per year without immune globulin and that was based on all data then with the immune globulin you should have much fewer. It is like four versus one. Do you have that data and will you be able to publish that data in terms of acute bacterial infections that are proven hopefully by culture per year without treatment and with treatment?

DR. GRIMBACHER: Numbers of infections are right now not part of the red data set. However, the evaluation of the first 2 years of the registry have shown that we should make the numbers of infection mandatory.

So, now the question is are we going to use what we have in the separate histories meaning that every infection has to be registered or shall we have something

like you said you know the numbers of infections were greater than four or less than four, so some categorized interproject data. Right now what we have in the subregistry is the primary data we have asked to put in. So, this is an ongoing issue. We have not decided yet but right now if you want to know the numbers of infections you need to fill out the subregistry and the blue field in the subregistry and document all the infections one by one, but this is done in the subregistry studies. That is not done for all the patients on immunoglobulin replacement. This is why I had to restrict some of the analysis to the CID patients because this is where the substudy is going on.

DR. BLAESE: I think it is time to break for coffee if you want to have some and we should reassemble at 10 minutes to the hour.

(Brief recess.)

Agenda Item: Panel Discussion

DR. BLAESE: The first half of this part of the program is a panel discussion and with input from the audience. So, we would like everybody to be involved to discuss some things that we did go over this morning with two questions that were listed. Which pathogens are of greatest concern in immune globulin treated and untreated PIDD patients and what additional registry data would be useful to characterize infection types, rates and severity

in PIDD patients?

So, with those questions and our esteemed panelists we did address I think the kinds of infections that we see in our patients and I think the interesting problems were for instance the really significant problem with viruses that occur in patients with severe T cell deficiencies that don't seem to be responsive to immunoglobulin.

Dr. Buckley?

DR. BUCKLEY: Yes, I would say that if you had to say a broad category of pathogens that you need to worry about it is those that we don't have an effective antibiotic for because in contrast to Dr. Janeway back in the fifties when he first started using IVIG we have now many more antibiotics that can save our patients' lives but I think that the major problem we have is with the bacteria that are becoming resistant as well as with the viruses for which we don't have a very good antibiotic.

DR. BLAESE: Certainly the question of resistant, antibiotic resistant bacteria is becoming more and more prevalent. I can just from my own experience with one disease, Wiskott-Aldrich where it was known for a long time that splenectomy made these children exquisitely sensitive to sepsis with encapsulated organisms and then the observation was made that simply putting them on

prophylactic antibiotics eliminated that potential risk, and that observation was made in 1980. By 1990, children that had previously done very well on antibiotic prophylaxis started having septic episodes with resistant organisms too the point where it became frightening to just splenectomize these kids and try to use antibiotics.

Then it became routine for most institutions too use IVIG and since that time at least in the experience that I have had with my patients we have not seen septic episodes occurring. So, it has been an effective prophylaxis but I don't know about the general experience with that but I think in general that is a case where IVIG prophylaxis has been very effective. I guess the concern has always been for those serotypes that are not represented at high levels in the immunoglobulin products whether the patients are going to be at risk.

DR. OCHS: Since you brought the Wiskott-Aldrich question up what are we going to do with those who were splenectomized and then received bone marrow transplantation?

As an example we had one adult who was splenectomized who was on prophylaxis. He had a mild form of XLT, was on antibiotic prophylaxis,did well. He got his transplant, did well, was first on IVIG, then on prophylaxis from the transplanters and they forgot to put him on

prophylaxis for his splenectomy. He didn't get the prophylaxis and within 6 months he was dead of overwhelming sepsis in Alaska.

We have another one who got splenectomized before bone marrow transplantation. We don't know for -- he is still in IVIG. He has a perfectly normal antibody response now. So, we take him off from IVIG but now what you said, should he be continuously on both IVIG and antibiotics or can we trust the antibiotic to prevent?

So, there are situations where we really are stuck.

DR. BAESE: Certainly that is a disease that doesn't respond to the unconjugated vaccines but generally do make protected titers of antibody if you use a conjugated pneumococcal vaccine and I guess the question is did either of your patients have a conjugated vaccine; did they make antibodies to it and then if they made antibodies normally.

DR. OCHS: The one which is now still alive, he makes antibodies to polysaccharides. He is perfectly like a normal guy but he is splenectomized.

DR. BAESE: And that has always been the observation and not to drag this out too much but kids driving their motorcycle and having an accident and having their spleens removed have always been shown to be at increased risk for sepsis from that same group of organisms,

and we have generally recommended prophylactic antibiotics in that setting but again now with the bugs becoming more and more resistant to the antibiotics we choose it is a true dilemma for us in trying to figure out how to deal with that.

DR. GRIMBACHER: Hans may be also alluding to the IgM, IgG issue. So, if there is no spleen you may also miss the IgM response.

DR.OCHS: Plus you are missing certain B cells. Splenic B cells are very important for polysaccharide antibodies.

There is another organism which we haven't met which is a problem for X-linked type of IgM and that is cryptosporidium and IVIG doesn't work for the IV. I don't know if it would work orally but that is a real killer for X-linked type of IgM syndromes that go on and develop sclerosing cholangiolitis and liver failure and usually die after liver transplant.

DR. STIEHM: But gamma globulin doesn't prevent that.

DR.OCHS: Gamma globulin doesn't prevent IV, doesn't prevent cryptosporidium infection but I wonder you know how do we locally treat them? You had some ideas in the past. Do we take colostrum, human colostrum, cow colostrum, oral gamma globulin and this was presented this morning that

in Europe they have used or we use oral gamma globulin for SCID patients with diarrhea and it works in half of them . We don't know what works and we don't know what the organisms are but only anti-inflammatory. That is another thing that one needs in the future to address, non-conventional use of gamma globulin and one is oral gamma globulin which we know very little about at all.

DR.BAESE: And so we have the question about, oh, Dot, go ahead?

DR. SCOTT: Actually I wanted to get to the question about the pathogens of greatest concern and I think that one of the things that has been apparent this morning is that we still have the old players which are Strep pneumo and H. influenzae and that people are still getting some infections even in spite of having intravenous immune globulin.

I think it would be useful to know, I mean obviously the IGIV based on the historical data that we have and data from patients pre-treatment and post-treatment is doing a lot of good and so in terms of how do you think about potency testing you also think about maintaining at least the levels that we already have in our current immune globulins that were all studied and proven to be effective.

I think some of the other concerns seem to be the meningoencephalitis causing organisms and the viruses and I

would also say with respect to antibiotic resistance the whole conception of antibiotic use, how frequent it is and whether we are getting as much out of the IGIV as we can is a separate question from this workshop that is very important and it would be nice also to address that and it is not clear to me and I would like to ask the treaters that are here although patients aren't getting as many infections how many of those are chronically on antibiotics to prevent infection proportionally, you know, like 10 percent or 80 percent.

DR. OCHS: That is a very difficult question because our friends from infectious disease, they are worried about persistence. We think we have to prevent infection but in our clinic we use it usually if they have already started to get infections, if they have sputum for instance and a very effective way is an intermittent treatment and I have that recipe from my neighbor to the left, from Dick who picked it up from England to give citromycin(?) 4 days on or 3 days on and 11 days off or you can use any other antibiotic and many patients do very well on this regimen. So, you just reduce the load every so often and of course they are all on IVIG but there are no studies as far as I know that really address the issue does early intervention with IVIG and antibiotics prevent chronic lung disease. I remember when I was a fellow that almost all of

our XLAs had lungs removed because they had so severe bronchiectasis and this doesn't happen anymore. So, I think we do some good but there are still patients who develop chronic infections and they develop bronchiectasis. If you do CT scans you can see them and they have chronic sinusitis and how to prevent this in patients with antibody deficiency by a combination of IVIG and antibiotic is not known, but we should try to get trials under way.

DR. BUCKLEY: I would like to get back to the study that Charlotte did earlier when she took patients who were not having recurrent infections and I think the same thing needs to be done with those who have bronchiectasis and those who have pansinusitis chronically because they don't have anamnestic responses. So, you give them a fixed amount of antipneumococcal antibody but you really don't know how long that lasts and so if you could do antibody titers in a group of patients who are chronically infected and antibody titers in a group not chronically infected using the same IVIG and then measuring titers I think then you would have an idea about how fast they are consuming these antibodies and which antibodies will be necessary to really focus on getting high titers for.

DR. STIEHM: I think that is a major problem and is there a good assay to measure the antibodies to this non-typable or are there so multiple different antibodies you

can't approach this?

DR. CUNNINGHAM-RUNDLES: I don't know the answer to that. I think that the best data on that was Samuelson and they ended up thinking that they didn't know the assay and they weren't positive that that organism wasn't to some extent living intracellularly as well. It sounds bizarre when you think about a bacteria and so that is the reason I think that your zithromax(?) recipe works and that is why we use that sort of macrolide therapy a tremendous amount.

The other bang for your buck that you get from the macrolides is that they are individually anti-inflammatory. There is a lot of data. There is as much data about the macrolides being an anti-inflammatory as there is an anti-infective and I think that that is why we also succeed. It is partly one and partly the other but I don't know what good assays they are. I think you are stuck with antibiotics with those mycoplasmas.

DR.SCOTT: I know that we have someone in the audience who may be familiar with these kinds of assays. Carl, I wonder if you would like to say something?

DR. FRASCH: Carl Frasch. Regarding the non-typable H. flu one antibody might be anti-protein D and the reason for that is some of you may be familiar with the GSK pneumococcal conjugate vaccine which was recently tested at our trial in the Czech Republic and found a rather

remarkable protection against non-typable H. flu, otitis media and so anti-protein D seems to be protective. So, it might be interesting to use that as one of the measures if you wanted to look for antibody in IVIG against non-typable H. flu.

DR. BLAESE: Dr.Orange?

DR. ORANGE: I would like to emphasize one of the points that Charlotte made and in particular call to attention the study in Annals of Internal Medicine from Helen Ikow et al which does measure two different dosing regimens of IVIG and looks at the residual protective titers and the surprising thing they found is that with the higher dose of immunoglobulin even though they had a 50 percent increase in IgG trough level there was a 102 percent increase in the specific antibody against type 14 pneumococcus,84 percent increase in type 9 and 93 percent in type 3 but when they looked at non-typable H. flu or Hemophilus influenzae B it was concomitant with the increase in trough level.

So, I think there is a non-linear relationship between some of the protective antibody titers at the residual trough with the total IgG dose and trough level.

DR. BLAESE: Dr. Berger?

DR. BERGER: I would just in both the sort of issue that Jordan just addressed and the issue that Dr. Scott

brought up a few minutes ago about the use of antibiotics, I think we need to distinguish between patients who are already chronically infected and patients in whom we are trying to prevent or at least prevent detectable infections and so many patients with established bronchiectasis and progressive lung disease I think are on continuous rotating antibiotics and certainly in our clinic we have CVID patients and XLA patients who were treated basically like cystic fibrosis patients.

DR. OCHS: That may address the issue of anatomical changes which you have in chronic bronchiectasis but also in sinusitis. There is probably no cilial epithelium up there in the sinuses and it is just a nuisance. In IVIG they don't get invasive infection. They don't get osteomyelitis but they have consistently their sinusitis and the quality of life is markedly decreased but it is, once you have the anatomical defects and abnormalities nothing works except reducing the amount of bacteria by both IVIG and antibiotics.

DR. BAESE: Dr. Siegal?

DR. SIEGAL: I have a question about the use of subcutaneous versus intravenous gamma globulin. Does anybody know if the difference in the peak level of specific antibodies makes a difference in terms of clearing infections? I mean is it just as well to have a chronic

persistent level of non-antibody excess which you might achieve in some infectious processes with subcutaneous gamma globulin rather than giving a big dose every 3 weeks, any information?

DR. STIEHM: Certainly in the patients who have central nervous system enteroviral infections that peak is very useful to get immune globulin across the blood-brain barrier. Similarly you can get some immunoglobulin into the mucous membranes and into the sinuses by having that very high peak that may not be achieved by using the lower peaks obtainable and when you are dealing with chronic sinusitis it is really important to have antibody get into the sinuses. So, perhaps the peak is useful.

DR. OCH: But in practice this doesn't pan out. So, if you take the study results from the subcutaneous trials which were done in Europe independently from the United States they all show a significantly decreased incidence of severe infections, more than on IVIG. So, practically it is not the case but if you, theoretically if you have a low level a minimum level against pneumococcal for instance you may get something with a peak if you give it IV but not if you give it consistently subcutaneously, but practically I don't think it is, but there are no data, again.

DR. CUNNINGHAM-RUNDLES: We like subcu but frankly I haven't seen any data about antibodies in subcu patients

and I would like to know that.

DR. OCHS: I think we have a representative from CSL Behring here and he will present the data you just mentioned tomorrow.

DR. CUNNINGHAM-RUNDLES: In blood.

DR. OCHS: Yes.

DR. CUNNINGHAM-RUNDLES: Not in the tube.

DR. OCHS: In blood.

DR. BLAESE: Dr. Orange?

DR. ORANGE: Thanks. One other comment. So, there is probably a difference in terms of preventing infection versus the use of immunoglobulin as an indication for treatment of infection. There are several useful indications.

With that I would like to perhaps bring up one other organism that I would like to hear people's opinions about which is Clostridium difficile. Given that to address, help address the antibiotic question the IDF physician survey showed that almost half of people who use IVIG are using antibiotics as an adjunct therapy to IVIG clearly Clostridium is an important concern and there are an increasing number of Clostridium antibiotic treatment failures for which IVIG is being increasingly turned to.

DR. BLAESE: An excellent point.

Also, our charge was to talk about the registries

and how we might design issues and maybe that is beyond the scope of what we can do now but I was wondering if anybody has any burning comments about the kinds of issues that we could address using these new tools that we have with the registry and if you don't want to speak up in public, Dr. Ballow?

DR. BALLOW: I can speak up in public. This may be related or not related but I was just thinking about this pneumococcal issue that keeps coming up in our conversations. We don't have enough data in our patients as far as culture results. Where can we get serotype testing; how do we know the same serotypes that are important in otitis media or in normal individuals with sinusitis is important in our patients who are not only on IVIG but chronic antibiotic use? Maybe there are some other pneumococcal serotypes that we are not recognizing as being important certainly and may not be in the pneumococcal vaccine or the pretnor(?) vaccine.

So, I think you know by having the registry maybe you can almost force the issue perhaps in partnership with the CDC that would be more aggressive in culturing our patients and if pneumococcus, for example, is cultured out to be able to have a resource to be able to send the culture for further serotyping.

DR. PIERCE: Dr. Pierce. I would like to also

reinforce the importance of the culture results and in the databases that I have seen of clinical trials of immune globulin products submitted for registry in the United States we have a certain low number of serious bacterial infections that are being reported despite the use of the products but there is very, very little culture data coming in in those trials in those patients who are deemed to have a serious infection and I think if somebody is enrolled in a clinical trial I would like to plug for the investigators really trying to go the extra mile to get an organism when they possibly can.

DR. BLAESE: Certainly the registries can play a role. I don't think the registries are set up at the moment to organize clinical trials but I think if there is a clinical trial that is being organized the registries could participate as a way of collecting the critical data. At least I think the USIDNET one would be delighted to be involved which would involve again the investigators coming to the registries with a protocol that they would like to include and then we would have to have the committees approve it but I think there is great interest in making these registries living facilities and tools that can address the kinds of questions that we are having trouble answering in general.

DR. SCOTT: For the registry I wasn't sure if you

were going to ask about antibiotic use. I can understand that could be a complex question or a simple question but it seems that it gives us a read on how well clinicians think their patients are doing and it is sort of an indirect measure of infections.

DR. BLAESE: There certainly are in both of the registries questions about antibiotic use. I am not so sure they are designed at least in the USIDNET registry in a way that would track very effectively association with certain infections and I mean it is a good point. It is another matter of the details about how the registries are structured.

Dr. Grimbacher, do you have a comment?

DR. GRIMBACHER: For the CVID study there is data collection for antibiotic use with respect to what type of infections and the severity and the kind of antibiotic.

PARTICIPANT: I think you have data on antibiotic use in every one of the licensing trials.

DR. SCOTT: I think it is always very useful especially because this will be living registry to look forward because we might be able to ascertain changes in the patient population with respect to infections and also the clinical trials obviously are limited in terms of time and we do have that information of course. I am not sure how representative it is of what goes on in the field as a

whole.

DR. BAESE: We have two more questions out there but I just wanted to reiterate that if you have suggestions or thoughts about the registries we would be delighted to hear from you.

PARTICIPANT: With the use of antibiotics I think it might also be useful to collect information on prophylactic antibiotics because that way you might see a difference in patients who, you know, infection rates and that type of thing in patients who are on prophylactic antibiotics compared to those that may not be at the time they got an infection and also the type of prophylaxis they were on and the type of infection they get.

PARTICIPANT: I think it has been clear from many of the presentations that the more data that we can get about the dosing regimens the better use we can make of the registry and additionally I wonder whether there is any potential to link it to efforts to get blood samples that could be either banked for future study or directly tested particularly to get trough levels. I am not sure what to say about peak levels but at least trough levels because then you have some ability to correlate with the levels in the patient with whatever phenomena are being seen clinically and that seems like a missing link right now.

DR. BUCKLEY: I would just like to emphasize again

not just necessarily trough levels of the protein but also the specificity. You have got lots of blood that has already been banked that actually you could go back and try to look at titers and then you could break them down as to whether they are chronically infected or not and find out how much of it is being consumed.

PARTICIPANT: As suggested earlier I think it would be very interesting to have data on the immunization experience with children from the registries, from the US registries and European registries.

You know there is very little published data on that with denominators and I think that would be very important to the advisory committee as they consider recommendations for specific groups for all new vaccines and rotavirus is a good one. I think you are all anticipating there might be problems with that. It is given very young before severe combined immune deficiency is diagnosed.

DR. BLAESE: Maybe we should call this to an end. We are getting behind.

DR. CUNNINGHAM-RUNDLES: I am going to make a comment. I have just been sitting here thinking about making this comment. The USIDNET budget is really quite okay and we have been blessed to be able to even get this off the ground, but all the people here probably know that budgets are contracting at the NIH and the USIDNET budget is

contracting as well and to be honest with you for the additional data we need an additional partner and I think that we just have to bring that out in the open.

So, all of you who have an advocacy position to say that we need data, then frankly we need some help to gather it because this is a wonderful chance to do it but we can't add on an infinite amount of more work for people who are already struggling too do what they are doing now in the budget that is going to shrink. So, I just mention that now because in this room there are a lot of people who know the exact situation and may have some thoughts about how we could proceed.

DR. BLAESE: An excellent way to end the session.

Agenda Item: Antibodies to pathogens in current Immune Globulin products

DR. SCOTT: We are going to begin the second session with Don Baker as the moderator.

DR. BAKER: You know conscious as I am that this is the session that stands between this group and lunch I am going to make my introductory remarks mercifully short.

You know in 2007, we will utilize in this country approximately 10 million grams of IVIG in the management of various immunodeficiency syndromes. That is truly a remarkable achievement and I think everyone in this room has contributed in some way to that achievement either as a

patient, a patient advocate, physician, researcher, manufacturer, regulator or most importantly as plasma donor and I think we can all take great pride in what we have achieved.

Having said that the key challenge that we face in this workshop is how do we make a better therapy and this is particularly complicated because we don't face a static threat.

As has been discussed in this meeting the threat evolves both from the pressure of the therapies that we have particularly the antibiotics and their change in infectious diseases and in new and emerging infections.

Now, any robust program of continuous improvement no matter what you are trying to improve has three key elements. There is a planning element. There is a "do" and there is a check and in this workshop we have tried to bring together speakers to address particularly the elements of the planning and the checking. Planning you try to understand the gaps in your therapy. You try to understand what is possible, things that could be done. You try to understand the characteristics of your current therapy.

The checking component, clearly that is the registries, what we changed, does it have any impact? What as organizers we want to have this audience do is give us guidance on the do part. It is tremendously easy to be

paralyzed by analysis but the next step and the most critical outcome of this workshop and one I would like to challenge us to do is to come up with at least one actionable step that we can commit to that will be directed towards improving this therapy.

Considering how much we have already done one step would seem a relatively modest achievement. However, I can tell you we have had workshops in the past on similar topics and not achieved that one modest step.

So, that is the challenge for this group. One final reflection on doing this and my industry colleagues are going to problem beat me with a stick about this but don't listen too closely to industry because characteristically what we do when we are proposed to make a change in something we say, "It is too expensive. It will take too long and it will be the end of western civilization as we know it," and then what do we do? We promptly do it. So, don't be constrained in the suggestions. We are really looking for some actionable items here and oh, one little rule, the actionable step cannot be to have another workshop. That cannot be the only actionable step.

All right, as part of understanding our threat I am very pleased to have Dr. Jane Seward address us on current epidemiology of some of our old foes, measles, polio and diphtheria.

Agenda Item: Current epidemiology of measles polio and diptheria in the US

DR. SEWARD: Thank you. I would like to thank the workshop organizers for inviting me today. I am presenting as you see on measles, polio and diphtheria. I am not a detailed expert on all these diseases, but hopefully can do them justice.

I will start with measles which I do know a fair amount about. Our strategies to control and eliminate measles in the United States have been to maximize population immunity to measles through delivering the first dose on time, and that first dose is administered at 12 to 15 months, to increase the second dose coverage in school and college students. The second dose of measles which is delivered in this country as MMR vaccine is delivered at 4 to 6 years but it is recommended for all age groups up to through college and then to vaccinate high-risk adults including health care workers, secondly to ensure adequate surveillance, to respond rapidly to outbreaks and to work to improve global measles control.

This slide shows measles in the United States since the vaccine was licensed in 1963 and as you can see, this is on a log scale, there has been a dramatic decline from an average of 6 to 7 hundred reported measles cases a year although about 3 to 4 million cases did occur back then

but from our passive surveillance system as you can see a dramatic decline.

At the start of the program only one dose of measles vaccine was recommended. One dose of vaccine administered at 12 months or older is about 95 percent effective in preventing measled but in high contact situations such as schools we continue to see some outbreaks of measles in one-dose vaccinees and so in 1989, a second dose measles vaccine was recommended by the advisory committee.

As you will see right after that time there was quite an increase in measles and that measles resurgence that occurred in 1989 and 1990 was primarily due to low vaccine coverage, so absence of vaccination in our pre-school population and there were outbreaks. There were about 120 thousand cases of measles at that time, about 100 deaths and as I said low coverage in our inner cities, coverage rates of 50 or 60 percent which was rather appalling,

Following that there was increased funding put into immunizations and we regularly now measure the coverage in children 19 to 35 months, the age group that was affected by the resurgence by school.

We always had very high coverage. As you can see since the second dose policy was implemented we have had extraordinarily low measles in the country down to below 1

case per million really since 1997, and it has continued.

Measles elimination or absence of endemic transmission of measles virus was declared in the United States in 2000 and we have had consistent epidemiology since that time.

Large, as you see here it is not very large but these are the largest measles outbreaks that we have had since 2000 in the era of elimination of measles and so all the sources for these outbreaks are imported virus. That is the only way you get measles in this country now and so outbreaks really depend on where the virus lands and if it does happen to land in a susceptible population then you can get a small outbreak and just to highlight some of these outbreaks these were infant adoptees from China and there was an outbreak in an orphanage in China and these children got measles and in about 10 cases I think there was very limited spread to family members.

The last 2 years we have seen outbreaks. This was in a church group that were exemptors(?). They objected to vaccination and so they were a pretty much unvaccinated population. One of their members came back from Rumania, developed measles on the day she attended a church gathering and there was really explosive spread from that one church gathering with about 10 cases in the first generation and most of these cases were unvaccinated people in this church

group.

Reassuringly this paper was published in the New England Journal in January of this year and reassuringly there was just no spread to the surrounding community. So, our high two-dose coverage in our school-age children particularly is highly effective in preventing spread.

This outbreak again was an imported case from India who was a young adult in his thirties. He came to work in Boston in a computer company and most of the cases were unvaccinated adults or adults where there wasn't any evidence of vaccination and again no spread to younger populations.

The age distribution of these cases really reflects mainly these outbreaks, as you can see and so we don't get much disease anymore in young children. These are the adoptees. There was an outbreak in Alabama. I think it was in this year where a baby who was visiting India with his mother came back to a child care center in Alabama and they are all children under 1 and he was in the baby room and none of them had been vaccinated because they were too young. So, we got, I think the attack rate in that classroom or child care class was 90 or 95 percent. So, measles was highly infectious but we don't have many situations where babies are exposed anymore and this reflects the same information I just showed you in the outbreaks. Most of the

outbreaks now do occur if an imported virus happens to land in a susceptible population and it was babies this year, adoptees and then these last 2-year outbreaks in unvaccinated persons, the former in 2005 who objected to vaccination and in 2006 had just missed out on vaccination and this shows the same information that almost all our cases now over the last decade increasingly it is every case but one in 2005 were import associated. That means the Indiana outbreak they were all a result of an imported case.

This shows measles genotypes which is just another piece of information that was considered by the expert panel when they reviewed the information to declare in 2000 that measles had been eliminated or endemic transmission had been eliminated in this country.

During the resurgence when there were a number of cases as I told you all the isolates were D3 genotype, really since the early nineties on there have been a tremendous number of different viruses and our surveillance is good enough now that we can for every measles case now that is confirmed by lab, we do get viral specimens and we are able to say that that is a B3 from India. That is a D6 from somewhere else and so we are highly confident that we are capturing all cases.

So, just to conclude measles has been eliminated or endemic measles transmission has been eliminated in the

United States. We have maintained an extremely low incidence, less than one case per million population per year. The majority of cases are internationally imported or import associated.

The surveillance system is adequate because we detect all these imported cases that come in from overseas. Our population immunity is very high and we see there is no endemic strain of measles virus circulating in the country.

So, that is measles. I guess I will just go on and do all three presentations and take any questions at the end.

So, now on to polio epidemiology. For many of you who remember the photo that we saw this morning of children in an iron lung polio vaccine was very much appreciated when the IPV was licensed in 1955. That is the inactivated polio vaccine and that was followed by oral polio vaccines becoming available in the 1960s, first monovalent types and then the trivalent OPV.

These vaccines were given in a three-dose primary series where they are recommended in the first year of life and second year of life with recommended boosters at 4 to 6 years and then every 10 years for adults who are at risk of exposure.

More than 20,000 paralytic polio cases were reported in 1952. In the decade of the fifties between 5 and

22 thousand paralytic polio cases were reported. So, it was a tremendous burden and that burden has dramatically declined as I will show you in the next few slides.

The last case of indigenous wild polio and that was a small outbreak in the Amish people who object to vaccination occurred in 1979, and the last imported wild poliovirus case in this country was in 1993. I think that was from Nigeria.

There have been some adverse effects of the oral polio vaccine that you are all familiar with, this particular audience. It was a live virus vaccine and it could cause vaccine-associated paralytic polio, on average nine cases a year and while polio was common that was accepted as a necessary consequence of OPV use to reduce the risk of imported wild polio but that perception of risk/benefit changed as polio disease declined in this country and this is a paper from CDC that was published in 2004 really showing the elimination of vaccine-associated paralytic polio in the United States with a change in vaccine policy that occurred and just to orient you this is a slide on a log scale showing decline in polio over time from the sixties through 2003 and this shows total paralytic polio cases, so really off the scale here in the sixties the number of cases still occurring.

These are the vaccine-associated paralytic polio

cases and as you can see by the seventies essentially all the cases being reported in this country were VAPP or vaccine-associated paralytic polio caused by the vaccine and I will just show you a little bit more of that by decade.

So, in the 1970s still we were seeing some polio. This was the last indigenous outbreak in the Amish people population but as you can see vaccine-associated paralytic polio which wasn't really recognized -- it was recognized in the sixties soon after OPV got licensed.

By the eighties these are imported cases now occurring of wild virus and these are all the vaccine-associated paralytic polio cases that kept occurring in the nineties and then in the eighties, sorry and then in the nineties this information was considered by the Advisory Committee on Immunization Practices and OPV use was stopped in the United States because of this risk/benefit changing and things that were considered at the time were the declining risk of importation of polio because of the success of the global polio eradication program and so there was a transition to IPV or inactivated polio vaccine first with a sequential schedule of two doses of IPV followed by two doses of OPV and then finally to an all IPV schedule that has been in place since 2000 and this shows the success f that change in policy in the yellow bars here. These are the vaccine-associated paralytic polio cases that were

occurring. There were two imported cases of wild virus and one in 1991, the last on as I said in 1993.

This shows OPV doses in millions and when the ACIP actually made the decision in 1996, and the sequential schedule started in 1997, we still has some polio cases but none of these had followed the schedule. There was still a lot of OPV around and none of the cases that occurred after this got two doses of IPV first. They got OPV first.

By the time there was no OPV then that just disappeared. There were no cases at all. Interestingly as I will show you in a later slide we had an imported case of VAPP reported in 2005 but was not acquired here in the United States because there is no OPV around anymore.

So, in the post-cessation era, OPV era we have got high vaccine coverage being maintained greater than 95 percent coverage in the national immunization survey that measures coverage in children 19 to 35 months and high sera immunity to all three polio serotypes after the change in schedule and that was a paper that was published by Prevo et al in December 2004 in PIDJ and so paralytic polio, there are some risks although they are low. We could still get an imported wild virus. The world hasn't yet managed to achieve polio eradication. Last year 2000 wild poliovirus cases were reported globally and those are concentrated in a few countries mainly Nigeria and Northern India but we haven't

seen any of those or if they have come in they haven't transmitted and spread.

Vaccine-derived polioviruses have to be acquired outside the country but as you will see in a minute they can occur nd then you have got immune deficient poliovirus excretors but not many of those and the risk groups we worry about mainly are under vaccinated children in urban areas and vaccine refusers in the religious communities and we did have some important things happen in 2005, as you see here with an imported vaccine-associated paralytic polio case and also some vaccine-derived poliovirus infections that IVIG was used for.

So, first the imported VAPP case, it was the first imported VAPP case ever identified in this country. It was a 22-year-old woman college student from Arizona who had acute onset of acute flaccid paralysis, fever, meningitis while she was in Costa Rica. She was unvaccinated because of a religious exemption. She was on a study abroad program to Cost Rica. She was staying with a host family and next door the daughter lived of the host family who had two young children and the baby who was 2 months old when she arrived received his first and second OPV doses during her stay. So, we are assuming that this was contact vaccine-associated paralytic polio. So, she was extraordinarily unlucky but it occurred.

She got bilateral areflexic extremity weakness and respiratory failure. The stools were positive for Sabin strain polioviruses 2 and 3 and her clinical picture was absolutely consistent with polio. She survived, was taken off the respirator but she does have residual severe weakness at 60 days and finally the vaccine-derived poliovirus type 1 infections that were first again in the country that occurred in an Amish community in Minnesota in late 2005. In total eight infections with this virus were confirmed among children and adolescents in one particular unvaccinated Amish community in Central Minnesota. There were no cases. There were no cases of paralysis or other neurological manifestations of the polio. The index patient was a 7-month-old unvaccinated infant who had been hospitalized continuously since August and with investigation of failure to thrive, diarrhea and recurrent infections and when this child finally got to the university hospital in Minneapolis she was diagnosed with SCID.

At type 1 poliovirus was identified on September 29, and further characterized to everybody's surprise first to even have a poliovirus here but then to characterize it as a vaccine-derived poliovirus with 2.3 percent divergence from the Sabin type 1 strain and it showed characteristics of being in an immunodeficient person. There was no recombination with other polioviruses or species C

enteroviruses.

So, it was characterized as an IVDPV, not a C VDPV and this shows the virus and there was some spread in the community as I will show on the next slide but this is the child with severe combined immune deficiency sequential viruses that changed slightly with time and then another family and then yet another family and so this child apparently wasn't the first infection in the community. Probably this child was and from molecular clock information that was done by our labs at CDC this OPV dose had likely been administered to someone about 18 months before the child with SCID got infected.

The child was treated. She had continued excretion of poliovirus and there was a lot of concern that she would develop paralytic polio. Dot and others at the FDA were tremendously helpful in rapidly identifying IVIG lots with the highest titer poliovirus type 1 antibodies and she was treated with them weekly for about 4 months.

Virus didn't clear but it probably did decrease her risk of paralysis substantially and then finally on a second bone marrow transplant it was successful and she cleared the poliovirus excretion.

Public health investigations at the time in the particular community she was in with 150 persons with very low vaccine coverage only three families out of 24 submitted

stool and serum specimens and three out of five of those showed evidence in their children of poliovirus infections.

So, this to us even though the numbers were small showed fairly widespread transmission of this virus in the community. The four unvaccinated children that you saw n the previous slide, age 2 to 14 years from two families had the same immune deficient vaccine-derived poliovirus in stool specimens and then three unvaccinated siblings of the index patient showed serological evidence of just high titers t type 1 but not to the other two types, again indicative of infection with this virus.

There were no other of these infections or cases identified in Amish populations or any other populations in Northern US or in Canada and Ontario that is close by and where there was a lot of interaction and response to vaccination efforts in these communities varied from being as high as 100 percent in some to being very low in others.

So, that is polio.

On to diphtheria. Global threat persists as it does for measles and polio with importations due to diphtheria being present in countries still. I will mention that a little. The US vaccination schedule, US epidemiology and then I will touch on the antitoxin.

This is incidence globally from 2000 to 2004 showing areas in red that have the highest incidence and so

this sort of gives an idea of where cases might come from. The most recent lab-confirmed case in the United States that I will show you in a minute came from Haiti where there is still ongoing transmission of diphtheria.

The reservoir as many of you know is humans from asymptomatic carriers or respiratory lesions. Skin diphtheria is no longer reportable in the United States.

So, the risk of exposure to diphtheria in the United States is very low. There are less than two reported cases a year in the 2000's and none of those cases have ended up being lab confirmed.

The immunization schedule, a primary series of three doses at 2 to 6 months using DTAP and then boosters are needed to sustain protective levels and I will show you some data later that is a little concerning about decline in antibody levels over time.

The boosters are given one at 18 months and one at age 4 to 6 and now that we have an adolescent and adult acellular pertussis vaccine instead of TD people should get Tdap at age 11 to 12 and then every 10 years.

Here is the same graph for diphtheria as I showed for the other two with a dramatic decline in cases with implementing the vaccination program. In the little insert up here you can see that there have been five or less cases reported from 1980 on, only 55 in total and almost all those

are probable cases that were not lab confirmed, but we still count them.

This shows the age distribution with most of them being over 50. This is not incidence but seeing that we are showing the data here in decades it probably pretty much translates into incidence.

This is the last laboratory confirmed case in the United States as I mentioned. It was a healthy 63-year-old man who traveled to rural Haiti, was reported to be unvaccinated. He had a sore throat one day before he returned to the US. He presented to an emergency room 2 days after he returned with a sore throat, difficulty swallowing. The diagnosis wasn't considered. He was put on antibiotics but not the correct ones and he came back a few days later with membrane. Culture was negative at that time. The diagnosis still wasn't considered and he finally didn't get diphtheria antitoxin and he died after 17 days of illness. PCR was finally positive for C. diphtheriae.

Sero-immunity data from NHANES, this is the National Health and Nutrition Examination Survey, I think that is what it stands for done then and NHANES is ongoing; so, I hope somebody will look at more recent data from NHANES II as well and here are the diphtheria antitoxin levels.

I think this paper looked at levels above .1 and

this shows seroprevalence to both tetanus and diphtheria. So, it is males tetanus, females tetanus, males diphtheria, females diphtheria and six is the youngest age that have bloods drawn in NHANES and as you can see there are very high levels for all these in children 6 to 11 but they are starting to drop in adolescents and then they do drop continuously. This is a cross-sectional survey but in 20 to 29 much the same with an increase in males that is probably related to military, being in the military but it appears that tetanus levels are maintained better than diphtheria levels such that by the seventies only 30 percent of people have seroprotective levels for diphtheria and by race this is white, Mexican-American and black and we see there is quite a difference in the adult, young adult age groups but by elderly they are all 50 percent or less have protection levels.

Finally in management of the suspected diphtheria patient and this guidance is on the CDC web site related to release of diphtheria antitoxin, isolate the patient and notify the health department, obtain specimens for diagnosis, start antibiotics, penicillin or erythromycin, obtain and administer diphtheria antitoxin and that is obtained through an IND held at CDC, provide supportive therapy, immunize during convalescence.

Diphtheria antitoxin is produced from horse serum

as you know. There has been no licensed product since 1997. Here is the web site where it is available through CDC under an FDA approved IND protocol.

CDC receives about 12 to 15 requests for DAT per year. It is released on the basis of a probable clinical presentation. We don't wait for cultures or PCR positivity and so it is released at that rate a year and none of these cases or very few of them turn out to be diphtheria. Unfortunately the one that was a few years ago it wasn't requested or suspected.

Dosages are as shown here.

I would like to acknowledge people at CDC who shared slides for this presentation.

Thank you.

(Applause.)

PARTICIPANT: May I ask a question? That was a wonderful presentation. You didn't mention pertussis and pertussis is sort of becoming a mini epidemic among adults. In the old days babies gave it to adults. Now, the adults are giving it to their children and this has tremendous pertinence to patients with immunodeficiency. Could you comment on that?

DR. SEWARD: Yes, I can. I wasn't asked to present on pertussis but I agree with you. It is a real problem. We are hoping, it is not exactly clear how much of the increase

over the last few years is higher awareness, better diagnostic tools.

As many of you know the diagnostic tools are not very good for pertussis. We, also, have PCR. There was a supposed pertussis outbreak in New Hampshire last year in health care workers that turned out not to be pertussis at all and PCR had diagnosed about 50 cases but there is certainly circulating pertussis. It is endemic.

We are hoping that with the acellular pertussis vaccines now available and recommended for adolescents and adults that we will see a decline in this country.

You know we haven't yet had much time for implementing and seeing a program effect but we are very hopeful that those vaccines will make some difference. Meanwhile we are working closely with a lot of partners on trying to improve still further diagnostics because it is a big problem.

You know, pertussis presents with a very non-specific clinical presentation that can be mimicked by a lot of viruses and other diseases and it is really difficult.

DR. OCHS: In regard to measles what happens if you get live measle vaccine and you have protective levels of antibody? Does that take? Do you get a boost? With the second immunization how many get a take?

DR. SEWARD: Right.

DR. OCHS: And in the old days when measles was around did we constantly get boosted or why is there this difference in antibody titers?

DR. SEWARD: Right. I brought with me and I am going to download it tonight and reread somebody in my division, Charlie Lebaron has published on that last year. We had a prospective study in Marshfield, Wisconsin looking at children immunized with their first dose in infancy and then getting second doses either at 4 to 6 years or at 11 t 12 years because in the early nineties ACIP, the Advisory Committee on Immunization Practices recommended 4 to 6 years for the second dose and the American Academy of Pediatrics recommended 11 to 12 and so some states were following both those recommendations.

There is about a 5 percent vaccine failure rate. I think in the Lebaron paper it was more like 3 percent didn't have antibodies when they had their second dose and then they boosted and not very many four-fold rises in children who had immunity already but did have boosts in their geometric mean titers.

So, the second dose has been considered to be primarily to cover the primary vaccine failures but it also does boost somewhat but you have antibody levels declining again although remaining above the protective levels when measured in this study at age 15.

We don't see any evidence epidemiologically of immunity waning to the point where adults are having cases but we think we need to watch this very closely because measles is a big concern. In the mumps outbreak last year I don't know how many of you are aware, we had a large mumps outbreak in the United States last year, 6000 cases reported, we see a lot of four-fold boosts in vaccinated people with their second dose of mumps.

So, mumps virus even if you have antibodies half of them get a four-fold rise with their second dose and we saw a lot of two-dose vaccine failures with mumps. Two doses of mumps vaccine is not nearly as effective as two doses of measles which is 99 percent effective.

So, we think we have to watch very closely for levels of immunity. We are still trying to understand waning of immunity for mumps and how much of a role it played in that outbreak and follow that on into the future.

I saw on one of the slides this morning protective level of immunity for mumps. I don't think we know that. We have a much better idea for measles than we do for mumps.

I guess it is lunch time.

DR. SCOTT: I just want to have one last word. I think it has been very helpful to see where we are in terms of the success of the vaccination programs and also the level of threat that these diseases may pose to primary

immune deficient patients in the context of what we test for in our products. So, I just wanted to thank you very much for making the trip because it is very helpful.

DR. SEWARD: You are welcome.

(Thereupon, a recess was taken for lunch.)

AFTERNOON SESSION 1:00 PM

Agenda Item: Antibody levels in current Immune Globulin products, including levels relative to estimated protective levels needed against significant pathogens

DR. BAKER: Okay, if we could take our chairs now I would like to welcome you to antibodies, part 2, the sequel. You know in listening to the conversations at lunch I did want to comment on a couple of points because there are sort of two different themes going through this workshop. One is a question around what of course is near and dear to my heart as a quality professional, quality assurance and quality control assays and you know what the specifications ought to be and this will come into place particularly tomorrow when we are discussing the measles titers and that is one component and a very important component assuring the quality of our products and consistency.

The second sort of theme that is running through is antibody specificities and clinical relevance thereof and these are two separate themes, each of them very important to these products but they are different and the bottom line I want to encourage discussion on both of these topics and we understand that there is little cognitive dissonance to make sure which one we are talking about but it is both our quality control and quality assurance and product improvement.

All right then, as part of our continuing discussion around antibody levels in our current products I would like to welcome our first speaker, Dr. Steffen Gross.

This is part of our pluralistic community here where we are having input from our European colleagues with respect to their perspective, and so I am very glad to welcome Dr. Gross?

DR. GROSS: Okay, first of all I want to thank the organizers for inviting me here to give me the opportunity to present some data and I have to combine the two topics you just mentioned because originally I was asked to present some data on the testing of IVIGs in Europe or in Germany, but at a certain time point I was told that I was delegated to this workshop and therefore I had to present also some regulatory stuff. So, that is why I have divided my talk in two different parts.

One, I want to tell you something about the development of the European regulatory framework and the second part I want to tell you something about the requirements for IVIG testing in Europe and also about some results we obtained at our institute.

As you might know there are current guidances given by two documents in Europe. There is one, the Note for Guidance on the Clinical Investigation of Human IVIGs and the other one is the Core SPC for Human IVIGs and the

European Note for Guidance is in principle an agreement of a list of established indications for all countries in Europe and so these indications have to be demonstrated for proof of principle and it is enough to submit a limited set of PK safety and efficiency data.

For all other indications outside this one there are well-controlled studies required.

Indications which I have mentioned here, these are defined by the core activities and all these indications, they are valid for all IVIG brands which are on the market at the moment, but as you might know besides all these established indications listed here in the blue box there is an off-label use of IVIGs and a number of other indications and for some of the indications this might even be justified.

Therefore since almost 2 years now both guidances have been ongoing and the original guidance consists of data which are necessary to support the safe effective use for IVIGs and core indications and this is for harmonization with the FDA's aims. For ITPs there is some suggestion for use for models ongoing and also there is the question what are the requirements with dealing with children and the second point which data are needed to support the indications.

The origin of the core SPCs discusses changes to

currently already established indications such as CLL or pediatric AIDS. It discusses also changes to the posology and a general review of warnings, contraindications and maybe adverse events but also possibly new indications are discussed for original chronic disease.

The first-line therapy is the CIDPs and for second line therapy severe myasthenia gravis, dermatomyositis and MMN are discussed.

As for new indications quite often you have all those changes or developments in your manufacturing process and here the problem really starts how to really characterize polyclonal immunoglobulin and how to investigate the impact of changes in the manufacturing procedure on that molecule.

The question is are the IVIGs individuals or generics and the guidelines are quite strict in this manner because the tell IVIGs are individuals and this is true to the effect that they might interchangeable as far as efficiency is concerned but this is not necessarily true for safety.

Also, standards for the viral safety are increasing and being implemented for each IVIG and for each IVIG the quality specifications ensure they are typical properties.

Furthermore not all IVIGs are created equally. We

have this really large donor pool of more than 1000 donors and this is a wide range of epitopes and these epitopes again depend on the donor population and possibly on regional differences. We have also some difference in batch to batch manufacturing process. We have different kinds of fractionation. We have several sets of viral inactivation. We have no pH treatment. We have refrigeration and of course all the different IVIGs; they have all the different excipients. Therefore every IVIG preparation should be considered as an individual and despite the core SPC agreement the applicant is forced to file a complete application with data on clinical efficiency and safety for the agency and this can be done by all these different procedures. IVIGs at the moment were approved by national procedures but more and more there are mutual recognition procedures, decentralized procedures and centralized procedures are coming to the light.

One should keep in mind that not all products are open forum centralized procedures. This is just optional for products that an applicant can show that the product constitutes a specific or authentic innovation as for instance for virus safety innovation or that the authorization is in the interest of patients or animal health at the community level.

Standardized procedure is mandatory for medical

products or when the product is developed by means of biotechnological processes as is the case for monoclonal antibodies.

These are the products which are at the moment on the market in Germany. We had 14 last week, we had 14 products on the market and 10 are approved by national procedures or by mutual recognition procedures. One is approved by a decentralized procedure in 2006. Two more are pending at the moment and we have one product pending which should be approved by decentralized procedure.

These are the products which are on the market and as I have said before each IVIG has to be considered as an individual because of the manufacture, composition and there are virus inactivation and elimination tests. Especially the later ones are quite important because the manufacturers are always obliged to optimize their blood products' safety by rigorous selection of donors by screening of donations quite early in the manufacturing process. That would be at the level of donor pool or even single donation testing by CPR and they try to improve their inactivation and virus removal methods.

So, many companies have started now to include non-refrigeration by the manufacturing process.

How should now the IVIGs be characterized? They can be characterized on three levels. There is the general

level which includes the molecular size distribution, quantification of monomers, dimers, etc., and impurities, we do have some very important characterizations by observed therapeutic activities and other biological characteristics such as IgE antibodies. It is a new requirement. They all have to be tested for IgG antibodies. They have to be tested for prekallikrein activator proteins, haemolysins or anti-complimentary activity.

Very important is the biological activity and this cab take place by in vivo and in vitro quantification of neutralizing antibodies. It should be demonstrated that Fab and Fc functions of the antibodies are still okay and of course for immunomodulatory and anti-inflammatory activities are to be demonstrated just by all the auto immune models or by the ability to inhibit auto-antibody activity in vitro.

As I said before specific preparation is prepared from pooled material from no fewer than 1000 donors by a method that does not transmit infections but contains antibodies for at least two pathogens, the concentration of these antibodies being at least three times that of the initial pool.

The strange thing is that the companies have to demonstrate this only during marketing authorization application. There is no requirement perpetually. Furthermore IVIG preparations have to comply with IgG

subclasses and they should comply with the test for Fc function.

What is required through the EU monograph is listed here and just to mention the last point antibodies to hepatitis B surface antigen should be tested for batch release.

Fortunately the companies complementary perform additional testing. We have five products tested for anti-HAV and anti-parvovirus B19 but this might be because of safety reasons because normally for these two antibodies already at early stage of the pool and testing is performed by PCR but as required by the monograph all 15 products are tested for HBV, two for anti-CMV, two for anti-polio and interestingly 10 products are tested for anti-diphtheria and interestingly no one of these products is tested for anti-varicella. I will come to this point in a second.

Actually this does not require any testing for antibody titers in normal IVIGs. We just measure from time to time levels of or we try to confirm the titers which are given by the companies.

As I said before five products will be tested for HAV, anti-HAV titers and if we perform tests at our institute almost we always confirm the results obtained by the manufacturing. Another thing we can observe for the anti-diphtheria titers as I said, 10 products are tested for

anti-diphtheria and we can confirm these titers and at our institute, at our lab we established a test in 2005 and if you compared titers which we obtained in 2005 to titers we obtained in 2007 then we can give the levels of anti-diphtheria antibodies. They are more or less constant in these products.

Just to do some work on the importance of antibody titers for therapy because measles is a topic of this, measles seems not to be a problem because the immunizations are in Europe and all European countries use vaccination against measles. I am not completely sure about the new member states but what seems to be more important is chickenpox especially for immune deficient and immune depressed patients. There is no routine varicella immunization in our countries and we have just started last year to check all the products in the German market for their levels of anti-varicella antibodies and what we could observe is that there is an enormous difference between the products ranging from almost no antibodies against varicella to levels which come close to levels of a specific anti-varicella products.

To conclude this talk the conclusion of the first part is quite easy because both guidelines are under revision and under discussion and hopefully they will be finalized in 2007.

To conclude the second part of the talk the potency testing as effective with respect to specific antibodies titers only to be demonstrated during marketing authorization application and the determination of specific titers is a criterion for the manufacturing process development which means enrichment of the plasma.

The testing for viral safety is in many cases of the products specific to applications and the last point which may be the most important point the future determination of specific titers might depend on indications, and also on regional characteristics, let us say vaccination.

Okay, thank you.

(Applause.)

DR. SCOTT: It is of interest how your requirements differ from ours with respect to lot release and as you saw this morning essentially we make these tests and these are a requirement in our Code of Federal Regulations, but I am wondering what was the rationale for not requiring any particular potency test for lot release?

DR. GROSS: I don't know. I really don't know.

DR. SCOTT: It is okay because I don't know what the rationale is for us not looking at Fc receptor function either. So, I think we are even.

DR. GROSS: No, in contrast. I am only thinking

since 1 year to include at least maybe not to test every batch for specific antibodies but to check from time to time to see a trend in the development of antibodies. So, this is a thing to discuss in our labs but not for EMA levels.

PARTICIPANT: Are you trying to get rid of the anti-big D and the anti-AVL antibodies?

DR. GROSS: Pardon?

PARTICIPANT: Are you trying to use gamma globulin, prepared gamma globulin that is depleted in anti-D and anti-AB antibodies?

DR. GROSS: Yes.

PARTICIPANT: Why? I mean the implication of your talk was that you were trying to prepare gamma globulin that is depleted in anti-red cell antibodies; is that wrong?

DR. GROSS: No. Which slide do you refer to?

PARTICIPANT: I didn't count.

DR. SCOTT: I think what he intended to show is that this is one of the lot release specifications. You want to minimize the amount of IC grutments(?) in their product because this can be associated dramatically.

PARTICIPANT: But of course probably treatment of ITP works in Rh negative people through those antibodies.

PARTICIPANT: Could I ask you to elaborate on the differences you saw from product to product on hepatitis A antibody, diphtheria and varicella virus antibodies?

DR. GROSS: There are not huge differences. With the HIV especially we have specific antibodies. We don't have to check this just for virus reasons but it ranges from 1 to 6 units. So, it is not a big range.

PARTICIPANT: Which one was that, I am sorry?

DR. GROSS: Diphtheria. We have levels from 1 unit to 6 units. That is not a big difference.

PARTICIPANT: What about varicella zoster?

DR. GROSS: Varicella zoster is a bit different. We haven't checked. The program just started end of last year and the preliminary data we have indicates that we have products which have almost no antibody against varicella zoster and we have products which almost have levels which reach a specific antibody varicella zoster antibodies. So, there are really enormous differences between these products. This might be maybe a reason to use this one or this one but as I said, it is just preliminary data. We have to follow this up and then we might be able to present data.

PARTICIPANT: Can this be due to difference of plasma origin because we have looked at different sources and --

DR. GROSS: No, we went into this and it is unlikely that this is a plasma origin because the plasma pools were coming from the same countries. So, it seems to be a difference in the plasma pool. So, the plasma pool

appears to be the reason for that. We didn't go into the vaccination methods. Maybe it is vaccination.

PARTICIPANT: Of course you mentioned enrichment. My question is for products that are not labeled as specific immune globulin do you allow any labeling with regard to levels for other antibodies that may have been enriched?

DR.GROSS: No, we do not. This enrichment as I said has to be demonstrated to the original application. They had to demonstrate that for any method they choose they have to show it is enriched at least three times and then the enrichment is located. The product is located, but we do not label this as a specific or enriched for that antibody. The physical outline, I don't know what is in there actually.

It would be a good idea maybe if we have especially for varicella zoster if we have high levels of anti-varicella antibodies maybe the manufacturer has indicated this.

DR. BAKER: This is a very interesting presentation, but I am very conscious of the time.

So, thank you.

In preparing for this conference I would poll my clinical colleagues about what were the most important pathogens in the primary population and I found out that my clinical colleagues were both very definitive about what pathogens were and very different in their determinations as

to which were the most important. So, I have decided to adopt the terminology that you will find in law enforcement and rather than speak about the most important pathogens I am going to speak about the pathogens of special interest and so for two of the pathogens of special interest I am delighted to have Dr. Dot Scott who is going to talk to us about Strep pneumoniae and flu B.

DR. SCOTT: Before that I have an important announcement to make. We found a button up here. So, if anybody is missing a button please see me later.

I hope this will be pretty straightforward. What I am going to talk about is some data that we published mainly a couple of years ago where we looked at antibodies to Strep pneumoniae and Hemophilus influenzae type B in the US licensed immune globulins and the rationale for doing this is we really wanted to know what kind of antibody levels we had across products and from lot-to-lot within products for these very important pathogens in primary immune deficient patients, and I would point out that a priori all of these have been licensed based on clinical trials so that we know they are effective in preventing a lot of these kinds of infections.

So, the question was not is a product low or high or not good or good. It was rather just where are we and we have a precedent for that in how the measles antibodies were

set that I will talk about later.

So, the goal was simply to define the current range of anti-pneumococcal and anti-HiB antibody levels in our licensed products.

So, we looked at five lots each of seven licensed products and those were lots from around 2000 to 2003. This is in connection, in collaboration with Carl Frasch's lab and he actually taught our folks how to do the ELISA assays which are very well controlled and in his laboratory they did the opsonophagocytosis assays for the pneumococcal serotypes.

Just very briefly about the methodology CBER reference standards were used to quantitate the antibody levels and the S, pneumo serotypes that we looked at were the 4, 6B, 9V, 14 and 19F and these are some of the more prevalent serotypes and in fact the infant vaccination Prevnar(?) is against these serotypes.

The IGIV samples are absorbed with a capsular polysaccharide and also the 22F polysaccharide and this increases assay sensitivity.

I will mention that a little bit later as well and we also looked at antibody subclass findings from these different products to the S. pneumo serotypes. We also looked at opsonophagocytosis assays and that of course is a functional test.

It is believed to be the primary protective mechanism against invasive pneumococcal disease and also very important for HiB which is encapsulated.

For the opsonophagocytosis PBMCs were used. There is also a cell line HL60 that Carl has worked with and I think it has undergone various validations studies since which can be differentiated to PBMCs and might be easier to control and the IGIV samples were really selected at random.

So, this is the kind of graph we are able to generate and it gives us a couple of kinds of information. Just very briefly these are the products. So, they are blinded. These are the seven products A through G and this is a microgram of specific antibody per milligram of IGIV and what I have done here is just shown you where the mean is for all of these points and two standard deviations below and above and you can see right away that nearly every lot is within two standard deviations but if you look at any individual product it tends to cluster pretty nicely around a certain mean of its own and we have often found this when we look at antibody levels for the different immune globulins for other specificities and it is not perfect but you can really see that this is a cluster and this is a cluster and we are only even looking at five lots.

So, it is kind of nice to think about lot-to-lot consistency when you look at tests like this. For the anti-

HiB antibody subclasses they also looked at the binding and what you can see is what we would normally expect and that is a predominant subclass is IgG 2 but there is also some IgG 1 and kind of surprisingly a little bit of IgG 3 and here we are just looking, whoops. I don't know what this means but I think I must have leaned on the computer. This talk could take a lot longer than I thought, and so we have this funny IgG 3 level and we really only looked at one lot of product for each of those three products that were representative there.

This is just an example and I am not going to show you all of the data in this format of antibodies to S. pneumo serotype 14 by ELISA and again you see some sense that these kind of cluster from product to product. You are looking at essentially the same kind of graphs with the different IGIV products here and the micrograms of specific antibody per milligram of IgG here, the mean for all of these points and two standard deviations. Again, nearly all of the lots fall within two standard deviations. It is impossible to really look at all of this data in one graph but I am showing it to you anyway because there is a point that I wanted to make. So, again, here is micrograms of specific antibody per milligram of IgG and these are the different serotypes that we tested in all of the IGIV lots. These are the products A though G. So, essentially this

represents product A, all those five lots that we assayed for this particular specificity but what we learned from this or what we questioned really is are there some immune globulins that have really all of the highest titers for all of these serotypes or lowest for all of these serotypes and the answer is no. There was no product that was consistently higher or lower for all of the tested serotypes. The other thing that you can see is that for these specificities you have higher levels but this is something apparently that would have been expected anyway from what people know about epidemiology and serologies for these antibodies in the population.

So, in Carl's lab they went on to do the opsonophagocytosis assays for some of these products and lots and this is a very simple schematic but in this particular assay human polymorphonuclear leukocytes were isolated from peripheral blood and therefore they didn't need to be activated. They were exposed to the pneumococcus in combination with the IGIV antibody and what is supposed to happen is this antibody complex is here. It is taken up by the Fc receptors. The bacteria is engulfed and it is killed in the phagolysosome and the assay readout for these is how many bacteria do you have left. So, it is simply colony counts.

I put this into graph form. Basically again here

are the products A through G. Here are the serotypes that were looked at and what you can see from this is that there is quite a variety here of titers that one gets for the different products and actually this is not the LD50; this is really the reciprocal of the titer and I thought I would put it there.

So, what did we learn from that? First I am going to go to the general conclusions and then I would like to say a little more about the functional assay, but the lot-to-lot variation in ELISA titers for HiB and S. pneumo were low within any given product, about two-to-threefold and the lots that we looked at generally were within two standard deviations of the overall mean. Why is that important? Well, it is one way that you can imagine you will get pretty good consistency across products. It is one way you can imagine if a specification were going to be set that you could set it and historically the way the measles antibody titer specifications were set for neutralization and those are the same specifications we have today is that 60 lots were looked at in the early 1960s by neutralization and the mean of that was taken and statistically it was determined where the 95 percent cutoff was and that was how the specification was chosen.

Now, in that case of course these immune globulins or those products had already been tested for their ability

to prophylax against measles in the field because of course that was before vaccination, but my point, the point I mean to make is that one of the ways you can set a specification historically has been that in the case where you know that your products are already deemed to be effective.

We, also, did some calculations which are in the paper to look at what would be the estimated trough level titers achieved in patients receiving 300 to 400 milligrams per kilogram of immune globulin every 4 weeks and estimated that those for the HiB and for the Strep pneumo would be at or above the identified protective titers in normal subjects from vaccine studies and this is generally accepted to be .15 micrograms per ml for HiB in the serum and there is sort of an aggregate okay level that has been identified by WHO and adjusted by a different assay using the 22F but it is .2 micrograms per ml for S. pneumo but really each serotype is a little bit different and the range for specific serotypes has been about .015 to 1.15 micrograms per ml, but what I am telling you is that you would guess that in most patients infused with a typical dose of immune globulin that you would at least reach this level of protected titers by the trough time.

In real life I think we all understand that all patients are different and that PKs can vary quite widely depending on the patient and their condition and their

catabolism of IgG but I think it is useful to do these kinds of calculations to see if we are at least in the ballpark. It is also possible that immune deficient patients need higher levels of antibodies than people do who are being prophylaxed by vaccination than normal subjects.

The other thing we learned at least for us that the opsonophagocytosis assay did not necessarily correlate that well with the ELISA assays and this has not only been something that we observed but others have observed.

There is interference still in the ELISA assays from non-type specific antibodies in serum and in this case perhaps in our IGIV that are not opsonophagocytic.

So, in other words there are antibodies there that can bind an ELISA so it may not have that functional ability that is needed to clear the bacteria and that is in spite of the absorption protocols to try to get rid of some of those non-specific antibodies.

There is evidence in the literature that the opsonophagocytic assays better reflect the clinical efficacy against invasive pneumococcal disease but these opsonophagocytosis assays have historically been difficult to validate. Recently and I think it is published in the March 22, Vaccine there has been a validation study reported for S. pneumo opsonophagocytosis and they did a lot of work to control the cell line which has to be differentiated as I

mentioned, qualify the complement source and figure out how to change over the complement sources and control of the bacterial feed. It has also historically been a labor-intensive assay with lots of colony counting but of course there are automated methods now that make that easier and in general studies at least in clinical trials they have shown that titers in patient serum greater than 1 to 8 for opsonophagocytosis are correlated with vaccine efficacy. So, there is at least a ballpark range of opsonophagocytic function that has been correlated with a good clinical result.

This comes from that paper. It is the last point I am going to make from that but I wanted to show it to you because what it does is it compares the ELISA test with the opsonophagocytosis assay and just to explain these are simply two different serotypes, and I am making the same point with both of these graphs.

These people were immunized with Prevnar which is one of the pneumococcal vaccines and after that and I can't remember how many weeks or months their serum was taken and it was assayed both by ELISA including the 22 F absorption and also by opsonophagocytosis here and what they did is they took that 1 to 8 cutoff for opsonophagocytosis which has been correlated with efficacy and that .2 cutoff which has been for ELISA in micrograms per ml that has also been

correlated with efficacy and compared these two assays for the same sample and you can easily see and I confess I selected probably the worst case that you have some samples with good opsonophagocytic activity and what would be considered very poor ELISA activity and over here to go to this graph you see very good ELISA activity and very poor opsonophagocytic activity.

So, even here the assays didn't always correlate. Which one is right, I don't know if I am qualified to say but I think that functional assays give you a lot of information that binding assays can't always give you and they also eliminate the non-functional antibody confounding factors.

So, I would like to acknowledge all of the people that contributed to the CBER end of this work including Carl Frasch who has kindly come here today to help us out and my boss, Basil Golding, Nelidia Conception in Carl Frasch's lab, Margaret Mikolajczyk in my lab, Doug Frazier and Theresa Wang at FDA.

Thank you.

(Applause.)

PARTICIPANT: One of the things that we have noted is that very often some patients make an initial good antibody response to pneumococcal vaccine and then after 6 months it disappears and have you had a chance to look at

this, particularly because the opsonophagocytic assay may be very responsive to IgM and then later on it disappears and the opsonophagocytic titer may decrease dramatically.

DR. SCOTT: It seems like a very good point. We haven't looked at that because of course we are looking exclusively at IgG and I don't know if Carl would have any additional insights to that or not.

DR. FRASCH: For some reason it turns out that most of the opsonic activity is in the IgG fraction. Why not so much IgM I am not sure

DR. BERGER: Mel Berger, Cleveland. The opsonic activity you observed is very likely related to the expression of receptors by the cells you use and on the one hand I very much appreciate the desire to have a standardized set of cells which the HL60 cells is a good approach to but then they display a particular set of FC gamma and complement receptors which may be different from activated neutrophils or monocytes or alveolar macrophages, and we know that in vivo there is tissue-specific receptor expression which will vary the results of this assay.

DR. SCOTT: Yes, I think like any lab assay for potency that we are somewhat limited by having to select a cell line and sort of standardize that and just like for the measles assays it may not replicate the cell that is actually being infected or is most susceptible.

With the HL60 in that particular paper that I referenced they did look at the effect of the passages of cells and they had looked at Fc receptors.

I am not sure if it is in that paper or a different one to try to standardize it as much as possible and complement receptors and the complement which depending on how much you add you get a different result.

So, it really isn't exactly simple.

DR. HOOPER: My name is John Hooper. On the opsonophagocytosis assays versus ELISA did you do any of these?

DR. SCOTT: No, that is from the Henkert's paper which I have if you want to look at it.

DR. HOOPER: It looks like you would get a similar result with Type 14 that you did with Type 19. That is the one that gives you the highest ELISA and well, you don't have any data on opsonophagocytosis. Well, you do; it was on the next slide, but you don't say what type you studied.

DR. SCOTT: If you want we can talk about it after.

DR. BAKER: You know at several points during the day we have mentioned that one particular conundrum that we face with IVIG products is that the antibody titers can vary with time and vary across products and I am very pleased to have Dr. Peter Lerch who is going to provide us with, make sense of data sets that will demonstrate this point.

DR. LERCH: I would like to thank the organizers for inviting me to this workshop. My presentation will be in two parts. The first part will address the trends of antibodies in one product over a period of approximately 20 years and in the second part I would like to show you some data on various immunoglobulins from different manufacturers, from different countries and show some data on antibody titers of such products.

We have analyzed Sandoglobulin 6 percent solution. These are released data and we started in 1986 and the last batches are analyzed from this current year.

We have looked at antibody titers from different regions and different plasma types and have compared mean plus or minus one standard deviation.

Most of the lots are recovered plasma either from US or from EU, more than 4000 lots of US plasma and more than 2200 lots of European plasma.

Recently we have also fractionated source plasma but much less only something about 300 lots from source US plasma and roughly 100 lots from source EU plasma.

Of course, during that long period of time there are some caveats which have to be considered.

The test systems might have been changed slightly which has of course or can have impact on absolute values and also variability.

Changes of standards, we have changed 175 to 176 I think in 1993. For instance we have taken test kits. Automation might have an impact but also possibly pool size restriction. We have now pools of on the order of 10,000 to a maximum of 60,000.

Of course, also, the test system has an influence on the variability and you see that the variability or precision is quite different if you compare functional assays such as neutralization with ELISA or nephelometry. There is a huge difference in precision in these assays.

We have used an ELISA for the CMV diphtheria with the neutralization assay, polio as well, HIV and ELISA, HBs ELISA, measles, the hemagglutination inhibition and the Strep with nephelometry.

Here are the data on CMV. There is a slightly higher level of CMV antibodies in US recovered plasma compared to the European plasma.

Unfortunately we have no data on the EU source plasma so far. Comparing diphtheria US recovered and Eu recovered again a higher level in the US-derived plasma.

The specification limit is shown here. There is probably no significant difference between recovered and source plasma. HAV shows a very nice trend from the originally high levels. There is also a difference between, a clear difference between US plasma and European plasma and

also a difference in the variability between the US and the European. I will get back to that later on.

An opposing trend is the HBs antibodies in these immunoglobulins. There is an increase in the mean titer most likely due to the immunization that contains. The titer again is shown here at a very low level.

Measles, we have been discussing that and will still be discussing that. It has been showing a trend towards lower titers over the years. There is quite a striking difference between recovered and source plasma. There is also a slightly higher level in EU compared to US plasma.

Polio, probably not a significant change over time, slightly higher in EU plasma compared to the US. Streptolysin we don't have complete data on source plasma but on the recovered levels there seems to be a little bit higher level in US compared to EU again. Here is our specification level for case type.

I am now coming back to the HAV antibodies and the variability. If we look at products derived from Polish plasma and compare those with either US source or EU source recovered or even Danish plasma we see a difference from here to here may be about four-fold.

The Swiss partner or Swiss product here is also somewhat higher but I don't have an explanation for that at

the moment.

So, I would like to go to the second point and show some data on various products which are licensed but also products which are in development. We have tested US, EU, Australian and Japanese products between 2002 and 2007, and up to 28 liquids and lyophilized products were also included, not only IV but also subcu or IM products.

It is important to realize that all these tests were done with in-house assays which have been validated for our products but not for other products. So, we cannot really tell that these are absolute values.

I tried to calculate for a 5 percent solution or the results are expressed per gram of IgG. Especially for liquid products it is possible that during the shelf life some titers may change. Since we don't have data on the production date the effects are not considered.

I can flip quite rapidly through these graphs and P means powder or lyophilized, IV of course intravenous. If there is no indication it is a liquid product and there are two products here, subcutaneous or IM which are also included.

Ninety-one products are here shown with very high titers. We have a recent case that with this special product combined with this test there are these values. These values might not be quite correct.

Diphtheria, I mean you see quite a large variability throughout all these products and that is basically the picture from all the specificities. We have tested the antibodies in these various products.

With measles here the specification limit is seen here around eight. So, we can see that several lots here from several manufacturers would be very close to the specification limits or even below but again these are not absolute values.

There is variability here Streptolysin, Hemophilus and Staph enterotoxin B.

So, I would like to summarize. We see a significant lot to lot variability within 1 year. We, also, see differences between regions for most of the antibodies we analyzed.

There are differences between source and recovered plasma and for some of the antibodies we have analyzed we see clear trends which might be influenced by incidence or vaccination programs.

There is a clear decrease for measles and HAV antibodies over time and an increase for HDS antibodies and we can detect lot-to-lot variability in all the products we have tested from various manufacturers.

With this I would end. Thank you for your attention.

(Applause.)

PARTICIPANT: Is the difference in hepatitis A titers, is that possibly due to the change between having natural disease or exposure to hepatitis A versus immunization?

DR. LERCH: I have to pass. Maybe a clinician could answer that. Incidence, certainly there is an effect of vaccination I would imagine.

MS. SEWARD: Hepatitis A has declined dramatically in the states that are using the vaccine, high-incidence states so that they now all are down to the same incidence as the low-incidence states in recent years in 2005. So, hepatitis A vaccine was recommended for children. So, incidence has declined quite a bit and there are still cases in adults and quite a lot of it around.

DR. OCHS: There are also many more naturally infected in the older age group. In Europe, for instance after the war hepatitis A was rampant and those are the ones which were donors in the eighties and nineties and maybe they are replaced by ones who never had naturally-occurring hepatitis A.

I was intrigued by your comment that there was one gamma globulin that falsely had high titers.

DR. LERCH: Yes.

DR. OCHS: How can this happen?

DR. LERCH: I don't know yet. We have observed actually a similar, well, we have observed an effect in stability studies at high temperature. We observed that there was an increase in titer over time at high temperatures. So, we believe that this specific assay is not appropriate for such products if exposed to high temperatures.

DR. OCHS: Does that that pasteurized products have high titers and are they in any way useless or would they mean something? In other words is pasteurization a false positive or is pasteurization inducing better antibody activity, maybe by breaking up aggregates or actually I would have thought when you heat it you will get more aggregates.

DR. LERCH: It is probably not the effect on IG only. I think we have a problem with this assay, with the kind of assay. We have changed the assay and we are taking a different assay and there we don't see this.

DR. BAKER: As we discussed we have seen variation in antibody products with time, with pathogens, with plasma source, plasma type and next we will continue with discussion comparing plasmas of different geographic origins.

DR. JORQUERA: Good afternoon. First of all, thanks to the organizers for considering the data worth

presentation, and I am going to present some data we have on different antibodies to different pathogens.

It is probably not as sustained in some cases as the ones you have seen here, but allows, also, comparison in a specific product under the same type of assays and under the same production process of products or lots derived from source plasma coming from the United States and recovered plasma coming initially from Spain or the Czech Republic.

One of the first I would like to present has been spoken of, the relevance of it. It would be Staphylococcus pneumoniae. We have studied the titers to this pathogen by the enzyme immunoassay from cold vaccine which was the same to measure antibody responses to pneumococcal vaccines and it incorporates 23 polysaccharides isolated from Staphylococcus pneumoniae.

These polysaccharides represent approximately 80 percent of the commonly encountered virulent serotypes which are listed.

These are the results that we have found in different years coming from source plasma, again coming from USA. With these comparisons we will not not know if it is sometimes because of the content because of the type of plasma.

We found some differences in the titers, in the titers, in the average titers that we obtained in the years

that we studied and you see that the number of tests is relatively low, and I think in this case the assay is influenced by this particular box here and probably t he relevance of this, the statistical difference is questionable.

The same assay for the product coming from recovered plasma from Spain, again, the number of batches is low in some cases but still we see some differences among the years, but there is no clear trend because the average would increase here but would rebound in the following year. So, it doesn't look like there is any obvious trend of going up, rather than downward.

So, we are pulling together all these data and comparing the titers from US source plasma versus Spanish recovered plasma and in this case yes, we found some differences consistent through and perhaps even relevant.

Coming to vaccinia we tested also, anti-vaccinia. I mentioned earlier that the previous tests were tests were done by enzyme immunoassay.

In this case that was on neutralization assay, and the results are explained as international experimental work was compared to international standard, parameter of 5 percent product and in this case in the slide there are no statistical differences between the other titers of the different batches coming from source plasma or recovered

plasma.

We did some comparisons also for measles, poliovirus type 1 and in this case the first one the test set of data comes from immunoassays and all three tests from neutralization assays that we do for batch releasee and while we have a relative high number of batches tested for the US source plasma we don't have so many for these kinds of plasma because this is not a requirement for the batches to be released in the European market that you heard before.

So, you can see here we find that by ELISA there is some significant difference between the Spanish plasma and the US plasma but this is not confirmed by the neutralization assay although the number of batches in the case of the Spanish plasma is lower. Still the averages are quite similar. So, we did not see any difference in the neutralization assays although there are in some cases slight differences in the average values but the variability of the assays probably is influencing the statistical results.

We will probably need more data to reach a more conclusive conclusion. We, also, tested viral antigens by enzyme immunoassay. These are expressed as units, arbitrary units per milliliter final product 5 percent.

As you can see here in some cases we find that the results are clearly higher for US source plasma while in

other cases it is more relevant or higher for the Spanish plasma.

In this case the standard variation between batches was quite high but if you are running some parametric tests they appear to have a significant difference between the source, the US plasma and recovered in Spanish plasma.

We, also, measured more titers by enzyme immunoassay. In this case these are compared to international standards. So, it could be helpful for follow-up comparisons in the future and as you can see in some cases the Spanish plasma well, in this case the number of data for some of the tests is different, in other cases is more relevant.

As you can see in some cases the US plasma did have significantly higher titers while in others it was the Spanish plasma.

I think that is the last set of data. Again, enzyme immunoassays against different pathogens in this case are, essentially all are viruses and with the only exception of mumps or parainfluenza type 1, these are all new cases, again by ELISA. The US source plasma yielded higher titers when tested by the same assay.

There are two other viruses, the respiratory virus and the parainfluenza type 2 virus which were both aligned

or negative in the recovered plasma from Spain but possibly in the source plasma from USA.

So, in summary we found some statistical differences among US for anti-Streptococcus pneumoniae but there was not a clear upward or lower trend.

The recovered plasma from Spain resulted in 1.3 times higher titers for Streptococcus pneumoniae on average than source plasma from USA. There were no statistical differences between plasma origins for measles, poliovirus type 1 or diphtheria toxin when assayed by neutralization assays.

However, the IGIV titers of antibodies to measles were statistically different when assayed by enzyme immunoassay.

All the statistical evaluations might be affected by the high variability especially for neutralization assays and the low number of lots from recovered plasma and that is the summary for some of the pathogens for which the recovered plasma was higher for Streptococcus pneumoniae, measles, T. gondii, Candida albicans, rubella, hepatitis A and although titers were higher in the plasma coming from USA. These all were tested with the same ELISA.

So, apparently there is no obvious general association between the type source versus recovered or origin USA versus Spain of plasma used for IGIV production

and increased titers versus all pathogens.

We may have some higher titers in Spain or Europe and United States for source plasma we have higher titers for all the pathogens, and that is it.

Thank you very much.

(Applause.)

PARTICIPANT: Do you have any data looking at source plasma in Spain? I mean is there just a very simple explanation for the higher titers in Spain for recovered plasma that the donors are just donating lesser amounts of plasma so they become less depleted of the --

DR. JORQUERA: I am sorry I am not hearing you well. Can you speak a little louder?

PARTICIPANT: I am just wondering if you have data from Spain with source plasma and if the difference between source and recovered is for the most part simply because when you have donors who are giving recovered plasma they are donating this plasma per donor and they are depleting their own immune globulins less. I don't know how well documented that is but I have heard that as an explanation for the difference between source and recovered plasma in the United States.

DR. JORQUERA: We do not collect source plasma in Spain. I don't know. If I had to improvise and answer I would say that yes you would be depleting all specificities

similarly. I don't think you would be reflecting it in plasma donors specifically in some and not others.

So, once you have gone to the final concentration and the final product that should be corrected, but that is only a guess.

DR. OCHS: I think you could also argue that it is the source of the donor. In Spain it is probably the upper middle class that donates and in the United States if you use source plasma it is those who maybe are more exposed to certain diseases than the upper middle class in Spain and there is an anecdote that in the days when they produced hypo-immune serum to tetanus they had a pool of people who were hypo-immunized against tetanus and when they plasmapheresed actually their titers went up rather than down. This is an observation which is at least 20 years ago. I don't know where this came from, but it is documented.

PARTICIPANT: So, the upper middle class in Spain have Ketz(?) or Spitz(?) and that is why you have the toxic load levels.

(Laughter.)

DR. OCHS: At least they feed them.

DR. SCOTT: I think, also, just from Dr. Lerch's talk there are some cases where the source plasma probably has somewhat higher titers in the recovered plasma product for anti-streptolysin 0, it looks like and for CMV

antibodies. There weren't very many points that I think that it is more likely the case that it depends on the donor population largely.

DR. BAKER: Well, we are not sufficiently confused now where we have seen that antibody titers can depend on products, can vary through time, vary with geographic location and vary between lots. We have now been looking at the question of what happens when we are faced with an emerging pathogen. So, Thomas Kreil is now going to talk about what happens to our IVIG products as a pathogen emerges.

Agenda Item: Emerging pathogens

DR. KREIL: Good afternoon, everybody. I really appreciate the opportunity to share with you some data that we have recently generated on antibodies to viruses that are contained in immune globulin products specifically for the treatment of PIDD.

The two examples that I would like to discuss with you are, one, an example of an endemic virus, a widely prevalent virus that being parvovirus B19 and then the other as Don has suggested a rather interesting example and that is the antibody to West Nile virus which at least here in the United States has been an emerging virus.

Starting off on B19 virus as everybody knows this virus has been around for a while, discovered already in

seventy-five. There are a number of disease associations well established such as fifth disease, a rather mild but rather frequent infection than more rare but more significant hydrops fetalis.

We will see what the final verdict on some of the recently reported emerging disease associations that I would like to call them will be but it seems like B19 virus is also capable of in certain instances at least to cause fulminant hepatitis or maybe even myocarditis cases and that may cause us to rethink some of our concepts about B19 virus as suggested by the fact that the virus is widely prevalent in the population. Here you can see the presence of B19 virus antibodies in approximately 1100 plasma pools that we have tested and obviously there is antibody in all of these pools present which is again not unexpected.

It is important to keep in mind that all of these 1100 pools roughly that we tested the lowest two that we ever found were roughly 11 international units per ml and then the highest that we ever found was something like 71 which seems a drastic difference but really is always in the same order of magnitude and probably that is, also, a consequence of the virus being widespread and therefore there is a lot of antibody in all of these pools, but what does this tells us in terms of antibody function? Function you can only investigate when you can work with infectivity

and that has been rather difficult with B19 virus at least historically.

Through the help of two gentlemen that I would like to acknowledge here we were able to get UT7/Epo-S1 cells into our laboratory and as you can see here they are nicely infectable with all genotype 1 parvovirus, B19 S, genotype 2.

Now, when that occurs what you can do is you can actually use that to establish an infectivity assay, not the classical one where you see cell lysis or physiogenic activity between cells but you need to have a little molecular biology help here.

After infection of the cell the genome is transcribed into RNA here and then it is spliced into messenger RNA. That RNA you can actually isolate and then you can use an RT PCR assay with a probe spanning the splice site here so that you can discriminate between the input virus that would not give a positive signal because you would still have the intron in there and infectious virus that has replicated within the cell that would actually result in a positive fluorescent signal here in this RT PCR assay, and when you do that you get a number that is the number of cycles required for you to get a positive fluorescent signal here and that number is a numerical correlation to the amount of infectivity that you have.

Now, when that is established you can actually take different levels of input virus as determined by classical PCR, put these different amounts of virus into your cell culture and determine for all of them how many cycles of RT PCR are required to result in a positive signal.

That will establish for you the standard curve between RT PCR infectivity correlates and here PCR titer. So, that is a correlate for virus particles and using that standard curve you can then go on to analyze any specific sample which you are interested in the infectivity of and you can use that curve to establish how many genomes or how many particles for that purpose this correlates to.

So, as I said before ELISA, the presence of antibody has been established. Now, with the infectivity assay we can actually determine how much neutralization this antibody is able to give you and this here is a comparison of a control TCID 50 titration of parvovirus B19 using the assay that I just explained and here that same assay in the presence of an antibody concentration of 11 international units, in other words that it is the lowest antibody concentration we ever saw occurring in a plasma pool for further fractionation and what you can see here is that the TCID 50s are roughly five log steps apart or in other words the lowest concentration that ever occurred in the plasma

pool that we have seen already neutralizes 5 log steps of the virus.

Now, there is a dose-response effect to that neutralization that does occur. Upwards here there is no further dose response because this is the limit of the assay's dynamic range but if you go ahead here and dilute the plasma pool at 11 units artificially that means to say we have deliberately chosen negative anti-B19 virus plasma further downwards.

You can see that roughly at around 4 units you see that the neutralization efficacy of that plasma starts to wear off.

This is another interesting thing. When you compare plasma from different sources, that being source versus recovered you do see some statistically significant difference here between source somewhat lower and recovered somewhat higher which is very likely an effect of the different ages of the donor populations.

What I would like to emphasize though is that still for all of these populations this is always in the same order of magnitude. Why is all of this maybe important? IVIGs are indicated for the treatment of B19 infection under certain circumstances, particularly chronic B19 infection of immunodeficient patients and therefore it might be an opportunity to see specific high titers, B19 antibody lots

but given the fact again that all this occurs within only order of magnitude the clinical meaning of that is I think not established at this point.

So, summing up the work on B19 virus antibodies there is what I would call rather minor variation and that after analyzing some 1100 plasma manufacturing pools.

The good news though is and that is also a consequence of the rather widespread nature of B19 virus infection, all this antibody is actually pretty potent in that the 11 units that we found at the lowest end actually correlates to 5 log neutralization of virus already and as I said it before the clinical application is probably not very meaningful.

I would like to switch gears to the other aspect, the other kind of virus that I would like to discuss with you and that is West Nile virus that actually until a few years back had not occurred in this country actually and then when it occurred in 1999 only a few cases and those cases limited to the far east of the country actually.

Now, that situation has since rather drastically changed with now a couple of thousand human cases occurring every year and the virus having established endemicity really across the country.

Interestingly though the virus is not evenly spread across the country yet. If you look here and this is

the cumulative annualized incidence per 100,000; so, in other words all of these states had a number of cases that have occurred over the 7 years that you have this virus in this country divided by the number of years that the virus has occurred.

This is the picture that you get. Some of the states particularly here over in the East very low incidence indeed and then here in the Midwest a dramatically higher incidence. This is interesting for the purposes of this meeting insofar as our plasma collection centers are also distributed throughout the states and there may indeed be a difference between an IVIG lot produced from plasma collected only from these three centers for example or collected from for example these nine centers here.

So, the questions that naturally occurred were would the West Nile virus antibody titers in the US plasma be a function of geography or sourcing and then if so would we see a lot-to-lot variation in IVIG lots depending on where the plasma has been sourced from and that finally obviously would all that precipitate that down in maybe a functional difference of our IVIG lots.

So, the investigator has used West Nile virus sensitivity assay that we have actually established quite a while back, a classical TCID 50 assay form, a very convenient to use assay.

Here you can see a dose response established by using a monoclonal antibody nd here are the first samples that we have tested and I would like to acknowledge Susan Stramer from the Red Cross for providing these to us.

These were sera from people convalescent after West Nile virus infection as confirmed by PCR testing of their blood donations by the American Red Cross, and as you can see this is a Vienna plasma sample and there is activity basically and here you can actually see very significant activity. Actually these three specimens went off the scale of the assay. So, they showed complete neutralization of all the virus input into the assay.

Now, that is interesting but what about the IVIG lot now?

This is the picture that we got analyzing a product that is called Kiovig in Europe or gamma gurg(?) liquid here in the US but is produced using the exact same manufacturing process.

Now, here you can see a couple of lots produced from European plasma and their titer is almost as expected, zero and keep in mind this is functional neutralization capacity in vitro and then for the US lots there is a very significant spread of the neutralization titer. This is here in a log scale so that between this lot and this lot here there is roughly a 400-fold difference in neutralization

titer.

This is the same summarized if you will. There is a significant spread but there is a lot more neutralization activity in US plasma than in European plasma.

This is summarizing the same again. Now, the question is where these differences are so significant and there are also such significant differences in the cumulative annualized incidence of West Nile virus in the different US states is it possible for us to predict which IVIG lots would have which titer based on information about where geographically the plasma comes from and what is the incidence of West Nile virus infection in this geography.

So, trying to do this we started out with two lots, one with a very high neutralization titer, one with a very low neutralization titer and you can see that here for this high neutralization titer lot some 10 percent came from a geography that had a very high incidence of West Nile virus infection over the last 7 years. So, we thought, well, the high area here versus virtually no area here corresponds nicely to the high neutralization titer here versus the low neutralization titer here. Well, never repeat a successful experiment and we shouldn't have done probably because if you do that for a number of more lots then unfortunately that correlation of prediction becomes very bad; so this is not a good option.

What you are then left with is well, if prediction is not possible then you need to test lot by lot. When you start to critically depend on the numbers generated by an assay specifically as complex an assay as a neutralization assay then you probably should, well, it would be prudent to make sure that the assay really gives you good results which is why we have validated this assay according to ICH. All the samples that we test are actually analyzed in triplicate and I think in terms of the statistical analytics of that assay this is a pretty robust and reliable assay.

Now, we have an indication of antibody function in vitro but is that really what we are interested in? So, neutralization assay is a functional assay in vitro but the reality is we are interested in protection which is the function in vivo and the question is is this one predictive for this one.

Now, with West Nile virus one can actually address that in that there is an animal model that is very susceptible to West Nile virus infection and has actually for that purpose been used for a number of different flaviviruses.

What we have done here is we have treated these mice 2 hours before challenge with .2 ml of IVIG. That is a dose that roughly corresponds to 100 milligrams per kilogram or the very lower end of the treatment dose that would be

given to humans and after 2 hours we have challenged these mice with a significant dose of West Nile virus and followed their survival for 28 days.

So,this is the result of cumulatively two experiments. Means are given and all experimental groups were 10 animals.

What you can see here is that animals just challenged here actually die off rather quickly so that basically after 2 weeks there is only 10 percent survivors.

That picture is in terms of statistics not changed by treating these animals with IVIG from European plasma. Again, this is not a statistically significant difference, but if these mice are treated with IVIG from US plasma of high titer you can see that basically almost all these animals do survive.

So, this is just summarizing that same thing. US 21 has been the plasma lot that was used for US for the protective treatment and calculating with the significance of the assay you would actually see that this US 21 that we have used has a titer that is equivalent to roughly 28 percent of all the batches that we have tested for that function in vitro.

In other words, these are all the 30 lots that we have tested. This is the one that we have used for protection in vivo and these ones in the yellow box would be

given the variation of the assay statistically equivalent to this one lot.

So, the assumption would be that also these lots would have the same protective capacity in vivo. Well, to not leave it with an assumption we have taken these two lots in addition into the in vivo experimental setup and have seen whether they would be protective or not and as suggested by the statistical analysis we could confirm that also these two lots afforded the same level of protection that we had seen before for the high-titer preparation.

So, in summary there is a functional correlation between the in vitro neutralization, so function in vitro to the function in vivo, that being protection.

We have determined that using an ICH-validated assay. So, we are pretty confident that the data are robust and also I think we have shown that some 20 percent of all the US plasma-derived lots that we have tested to date would have this capacity of protecting in vivo which corresponds to a roughly greater than 1.8 log neutralization of West Nile Virus.

Why might that be important? Over the years in the US here we have seen roughly 10,000 cases of neuroinvasive West Nile virus infection.

From screening the blood supply by PCR there is an estimation that roughly there is 250 times more subclinical

infections that have occurred.

If that is calculated backwards then roughly 1 percent of the United States population has been exposed too West Nile virus just approximately.

Out of this population, however, we have indications that certain populations might be at a very much increased risk of running a rather severe course of disease.

First evidence comes from an outbreak in Israel where it was realized that the non-immunocompromised population had a 13 percent mortality which is actually extremely high, I mean as compared to what we have seen in the US but that immunocompromised patients actually had a threefold higher risk of running a fatal course of infection.

There is more evidence coming out of the data analyzed from Canada where it has been shown that a risk of meningoencephalitis, a neurological complication occurs in roughly 1 percent of those infected whereas in those immunocompromised the risk is roughly 40 times higher.

So, we would argue that prevention is maybe very important for this patient population being either immunocompromised or immunodeficient and therefore at increased risk of a severe outcome of West Nile virus infection and that will not change even if and when a vaccine becomes available.

So, that protection should be afforded, we would argue ideally through the entire year because according to the CDC here you can see that the active season of West Nile virus has been broadening over the years to now basically be active the entire year.

Another potential application of the data that I have shown also jumps to mind and that would obviously be the treatment of West Nile virus infection.

At this point this treatment is limited to only supportive care but there is also in this country an investigation going on at this moment where IVIG source from plasma from Israel where West Nile virus has been endemic for roughly 50 years is investigated for potential usefulness in treating West Nile virus infection, and I would argue that given the data that I have just shared with you there might even be same US plasma-derived IVIG lots that could actually accomplish the same goal.

So, in summary regarding B19 virus, an endemic virus. There is rather minor variation in terms of titers amongst the plasma pools that we have tested. Given the wide prevalence though even the lowest level that we have ever seen corresponds to already a very significant neutralization and given the wide endemicity of the virus therefore all clinical IVIG lots are pretty much equivalent and there is probably not much point in selecting certain

lots for certain applications.

The situation seems to be rather different with West Nile virus where this is an emerging virus and therefore has not evenly spread throughout the donor population as it seems where the variation that we have observed in plasma pools and therefore also in IVIG lots is very significant or in other words it is 400-fold differences between the highest and the lowest titers.

We have generated preclinical animal model data to indicate that the high titer in vitro with the functional assay there does also correspond to protection in vivo and therefore the clinical relevance of that might be higher.

Thank you very much.

(Applause.)

DR. PIERCE: Dr. Pierce. Have you tested other manufacturers' products with your functional assay such as the Israeli Armorgam(?) product?

DR. KREIL: No, we have not done that at this point. I just had a discussion with one of your colleagues before whether that would be something that we could do and we are certainly open to consider that.

PARTICIPANT: (Off microphone.)

DR. KREIL: I would not be able to tell you and you know following some of the discussion particularly of the clinicians in the room in the morning I am not even sure

that we would know because viral diagnosis is not necessarily a very easy thing. I mean given the heightened awareness of West Nile virus in this country I would imagine that maybe this diagnosis would have been made but I don't think that we can be certain, and then I might also add that where there is this enormous difference between titers we don't know whether that person would have received a low-titered lot or a high-titered lot.

PARTICIPANT: What evidence is there in humans that the antibodies play a particular role? So, when you talk about immune compromised people in the Canadian study or the Israeli study what do you mean by immune compromised? Where there examples there of clear antibody deficiency or clear cellular; was it defined and you have got very nice evidence from the mice but what evidence is there in humans that antibodies would really be protective?

DR. KREIL: I mean the evidence in humans is largely anecdotal in nature I would argue. There have been reports particularly out of Israel where people have had established West Nile virus infection. They were treated with IVIG of as in Israel is the case high-titered to West Nile virus and they cleared the infection within only a few days which is a very atypic course of disease progression.

So, I think in humans evidence does exist. The

evidence for the more severe disease course that immunocompromised people would run like after West Nile virus infection comes by and large from people who are immunocompromised for the purpose of having received for example an organ transplant and so that is why I said, "Immunocompromised." They are not immunodeficient people in the sense that we have discussed earlier.

DR.OCHS: This is an excellent example of what you can do to test IVIG and the functional part.

We heard this morning that we really tried to get assays without animals but I think we cannot really do it without animals and you can extrapolate this system that you have by taking these mice, infecting them and then treat them, and you can actually demonstrate how long and in what type or what age of that or date of that disease IVIG is still functional and will still prevent death.

So, you have a fantastic model to test this particular disease, but I think you also showed with the parvovirus story that you can functionally assay the titers, and I would argue that it is important for the clinician to know this.

I have seen several cases of X-linked type IgM who had severe year-long aplastic anemia due to the destruction of precursors of red cells and they respond to IVIG but you would argue that the higher the titer the better it is for

the clinician to select the type of batch you want to give these patients. So, these assays will help the clinicians tremendously in figuring out what too do and when to do it and how much to give and which batch to use.

DR. KREIL: Yes, I really appreciate the nice compliment here but that is something that we are obviously very open to doing and while I, personally believe that regarding B19 virus the differences between the individual lots are not going to be big enough to make much of a difference in a clinical setting. I think that there are other examples and West Nile virus may just be one where it would be important to have this information available because it might well be clinically relevant and quite frankly also I really appreciated some of the discussion this morning because I have an entire list of notes that I am going to carry to my people in the laboratory to see whether we couldn't do an echovirus assay for example, or a varicella virus assay and I think following the same paradigm I think that can absolutely be done.

DR. BAKER: I will take this pause here to set you free. We have a break at this point in the agenda. However, we have been presented with an enormous amount of data so far today and I really want to congratulate all the speakers for both staying on time and being very, very concise and clear in their presentations.

The hard work begins when we get back. We have got a number of questions to deal with. So, gird your loins and let us return at 3 o'clock.

(Brief recess.)

Agenda Item: Panel Discussion

DR. BAKER: Okay, I think we have managed to capture all but the resistant serotypes. So, now the fun begins.

We have proposed three workshop questions which I think will probably invoke a fairly lively discussion. This is free form. So, I am really stuck with the best way to start, but why don't we start with the first question?

So,which antibody specificities would be relevant and feasible to measure in immune globulins with respect to clinical importance, and I think we want to focus on relevant and feasible. Feasible would mean that they were assays that were capable of being run in more than one lab, that could be standardized and compared across labs and of course relevant speaks to clinical relevance.

So, with that I will open it up to the panel.

All right, I will call on Dot Scott because I know she told me that she had ideas.

DR. SCOTT: I think we have heard a lot from the treaters this morning and have seen some good summaries of what kinds of organisms trouble the primary immune deficient

patients and I was struck by the differences among some of the different kinds of primary immune deficiency, but seems that historically and even currently the Strep pneumo and H. influenzae continue to be problematic pathogens and if we were only to think about a different potency test I would vote for considering one of those. I am not making policy but that is my personal opinion. That might be useful. It also seems doable, and so I will leave off with that except to say that this would be in line or analogous to the way that measles potency titers were determined way back when measles was actually a problem.

DR. BAKER: I am looking for audience input here amongst the clinicians here. Could we have a comment on feasibility? You know we know from clinical experience that anti-pneumococcal titers depend upon the laboratory that you choose to send it to.

So, how much work has been done or efforts have been done and who would champion that effort to make sure that the results from different test systems, different methodologies actually yield comparable results?

DR. FRASCH: Looking at the pneumococcus there has been over the past almost 10 years now a lot of effort at standardization of both the antibody quantitation, i.e., measured by ELISA and opsonophagocytic activity, and this has been spearheaded through the World Health Organization

and they have actually designated reference laboratories.

For example, the reference laboratory in the United States is in the laboratory of Dr. Moon Nom at University of Alabama and there is a comparable reference laboratory of Dr. David Goldblatt in London, UK and they have set up the assays such that either lab will give essentially identical results.

While I have got the microphone I think if we are going to figure out what antibody specificities I think we need to first, we need to look for antibody specificities that have actually been shown to be of some protective value and two, we need, if we are going to measure these antibodies, we need to have some idea of what antibody levels are actually correlative protection; so, therefore we know what the antibody levels measured mean and three, getting to the point he asked is we need to use standardized assays that can give comparable results between laboratories because obviously no one laboratory is going to measure the antibody levels in a variety of IVIG products.

Therefore it would be nice if just for the sake of argument if anti-hemophilus assays were being done that they would be done by the same standardized assay at the different companies so that individual physicians and investigators can actually take the antibody and know that they are comparable from laboratory to laboratory and by the

way there is a standardized hemophilus assay.

Again, that assay is, you can get the assay procedure from the same laboratory of Dr. Moon Nom and he has a web site. I would have to think a few seconds to get the right address on that.

DR. SCOTT: I just wanted to see if I could ask Carl another question. In terms of how difficult or easy these are to validate in one's own laboratory could you make some comments?

DR. FRASCH: First of all the hemophilus assay and the pneumococcal ELISA assay you can get a set of what we call calibration sera and these are available from the NIVSC in UK, London and in the case of pneumococcus there is a set of 12 sera that any laboratory can request and these have assigned antibody values and you can therefore determine if your laboratory is within the range specified. In other words you are going to have 12 sera and you obviously can't hit the exact range for all 12 sera but you need to get I think they say 9 of 12. You have to be within the range for 9 of 12 to say that your assay has been calibrated against other labs.

DR. BAKER: Jay?

JAY: I wonder whether it would be a useful approach to go back to the list that Dr. Stiehm provided us and his keynote address was an additional handout and the

last two slides gave us antibody titers as surrogate markers, semifinalists and then the top 12 and I think one way of approaching this is to ask which of these titers would pass the Carl Frasch test that they are of known significance in protection that we know something about a protective titer and there are standardized laboratory assays or assays that could be readily standardized because I think that at least there has already been some antecedent thinking by a knowledge group on this very question, and I would be interested in the opinions of this panel on those agents.

DR. BAKER: As usual Jay cuts right to the point. Thank you.

This is the list you were referring to, I believe.

JAY: Yes. I am not sure that is the right slide. Just go to the last two slides of that same talk. There you go and the antecedent with the runners up. So, we should start this one and then go backward.

DR. SEWARD: I think VZV should be tested and I know that there is a high titer immune globulin but really part of the reason that was redeveloped was because we didn't have it tested in IVIG or that was, I mean they may both be needed but it was a problem when we tried to decide whether or not to keep producing or encouraging a company to keep in the market because the need for high titers going

down as varicella disease goes down, the main use is now going to be in immune deficient people in the future. So, I think it would be beneficial for that particular virus.

DR. JORQUERA: I would like to comment on what would be the procedure that we would follow probably in Europe to introduce a requirement like this via European Pharmacopeia. Group 6B will probably receive or prepare a proposal for the introduction of these as a requirement for the monograph of intravenous immunoglobulin and if discussed and approached in the framework of the group 6B then we will look for an assay for each type of assay.

We will define specifically the assay and this would be the assay once approved that would be employed both by the manufacturers and the various control authorities to check each batch for release.

I don't know if that approach could be of interest. Of course, that would take some time because it would imply also an exploratory study among laboratories from the regulatory authorities and the manufacturers and also would imply probably the collaboration with the World Health Organization to develop if not developed already an international standard for the measurement.

DR.GROSS: Maybe I could comment on that. I have just spoken about normal human immune globulins but of course we have also all the specific immune globulins and

the companies who produce the specific ones are almost the same, produce all of the normal ones and therefore we are in close contact with all these companies that do the assays and all the specific immunoglobulins we test for their potency, for anti-tetanus, for anti-varicella, for anti-HPS. So, we test all of these products for their potency. That is why we try to keep in close contact with all those companies. We try to set up assay sergerasay(?) companies and that is why we really think we have this approach and currently there is a big collaboration study running about anti-tetanus to replace the mouse assay with ELISA assays. So, we try to work closely together with the companies to make assays available to all.

DR. BAKER: If I can capture what I have heard so far certainly the candidates on this slide are considered clinically important. Is there any, in terms of the top 12, are there any ones that the group wisdom would be should be removed or any ones missing?

DR. OCHS: If I may make a comment, they are surrogate markers. I don't think that Dr. Stiehm wanted to say that they are absolutely necessary to be achieved.

For instance who is going to get measles from our primary immune deficiency disease patients or diphtheria? I think they are meant too show that this represents all the antibodies that one should have in gamma globulin. I mean

for a practical physician like me who sees these patients I would like of know if I get a patient who has echo 11 meningoencephalitis, I would like to have a high titer for echo 11 and how do I find this out?

Twenty years ago virology would test it but they have no longer the manpower to do this. CDC doesn't do it either. So, we are stuck and we have to select blindly a lot which we think maybe ha a high titer.

So, there is a difference between surrogate and what really is practical for us and to be practical you have too have a huge number of antibodies, I would say at least 20 or 25 agencies where you would like to have the titers only in specific cases. West Nile is one of them.

DR. SCOTT: I agree it would be wonderful if we knew for a specific patient with a specific pathogen or proneness to that what those titers were.

I think here what we are looking for is what tests would be good for product integrity and function as well as be useful or have something to do with efficacy in the primary immune deficient patient, so really looking more at lot release testing rather than tailoring which would also be terrific but I think the pragmatic question is are we doing the tests that are best if you will now or good enough and they are all surrogates obviously in the sense that they are not being looked at in clinical trials directly for

titer.

DR.GOLDING: From a practical point of view doesn't it make sense too prioritize this and think about what are the commonest infections and I think we all agree that Strep pneumoniae and H. influenzae are the commonest infections that the PID population suffer from and focus on that because you know sure you can put up a list of 10, 20, 30 infectious agents but we know I think from experience that in order to get this to happen in reality you can't go to the industry and say, "Here are 20 infections. Figure out assays for all of these," but what you can do is prioritize and maybe start out with the commonest type of infections.

So, that is one point. I would say that focusing on the strep and the H. influenzae is probably reasonable too start out with but then the next question is what assays and we have been going back and forth about you know if you have a good neutralization assay it is a better assay but what if you don't and it is too highly variable; what do you do? I think there you can try to correlate in clinical trials binding assays to efficacy and I would also say that there is a lot of information that Carl and others and I know Dr. Stiehm knows a lot about. In terms of vaccine trials we know a lot especially about those two organisms you know what kind of titers are protective and can we use that and I know there is always the caveat that while

certainly immunity might play a role in vaccine trials, but you know, I think for some of these infections particularly the two that I am talking about they are mainly antibody dependent infections and antibodies can really play a major role.

So, I don't think we have to worry so much about set of assays. I think we know already what titers should be targeted in a patient in order to get protection.

DR. BAKER: I think to Dot's point here basically if we talked about an incremental improvement in the product and we were going to force rank the pathogens, we were going to pick two, three for an incremental improvement what would they be?

DR. BERGER: Mel Berger, Cleveland. I would listening to Drs. Buckley and Cunningham-Rundles t his morning, I think that it would be important to have not only antibody against the H. flu type B polysaccharide but against a somatic antigen like if it is the D protein then the D protein but because patients that are chronically infected may have the non-typable H. flu we should try to find a protective antibody against that.

I would, also, like to make the point that amongst the criders(?) think we have had the assumption that all of these products have antibodies against VZV such that if a patient on gamma globulin is exposed to chickenpox we

usually say or at least I usually say, "Well, if you are within 2 weeks of your latest IV infusion or 5 days of your latest subcu infusion then you don't need VZIG. You will be protected by the IgG and that may not be true.

So, I think that to whatever extent criders may assumptions like that, like if there is an outbreak of measles in your community you will be protected by your IVIG or you are protected against VZV that there ought to be a minimum standard that suggests that you will be protected if you received this milligrams per kilogram within the half life of IgG.

DR. BAKER: With the lighting here it is hard to see.

Don?

DR.SCHIFF: It is Richard.

DR.BAKER: Yes, it is Richard Schiff.

DR. SCHIFF: You know, there are different things that you have to look for depending again on whether or not you want an antibody for standardization or an antibody for process improvement.

If you are looking for an antibody for standardization you want an antibody that is pretty well represented in the gamma globulin where you can get some consistency.

On the other hand, if you are a physician treating

patients, if the antibodies are always in the protective range then that is not a very important antibody to list on the label. For instance tetanus and diphtheria where the antibodies are consistently several orders of magnitude above protective it doesn't really matter if you look on the label.

On the other hand something like VZIG or B19 or a variety of others that have more variability, those are the ones that you want to make sure are really in a protective range.

So, if H. influenzae is always well in the protective range even though it is relevant it may not be that important to list it.

On the other hand if some of the time it is borderline then you do want to have that listed so that you can get an idea of whether or not those particular lots are going to be protective and then just one other point is that all of these assays are being done on intravenous gamma globulin. Most of the standardizations of assays are being done on antibodies in plasma and so the protective titers that we are getting from trials where the antibodies are measured in plasma may not be exactly the same as when you measure this in sort of an abnormal milieu of gamma globulin.

DR. GOLDING: That is true but there is a

relatively simple way of handling that and that is you take your gamma globulin and you dilute it in antibody deficient plasma and then you have the same matrix. So, I think there is a simple technical way to resolve that.

DR. SCHIFF: Right, it can be done but I don't think that is the way it is standardly done now.

DR. SCOTT: I think to identify titers that might be protective would be a combination of looking at what is actually achieved in patients with licensed immune globulins and also you can do calculations to at least guesstimate about where the serum level is going to be based on what we know about the volume of distribution and the half life. I did want to ask if we can just have the lights all up. We can't see the audience.

Thanks. But I think the other point is that for a lot release test you actually hopefully have lots that are generally going to pass and if they don't pass those lots, the donors or perhaps the manufacturing has a problem or if it is a new product being proposed perhaps there is some problem.

So, the concept of not having all lots pass is one that I would attenuate a little. We don't want lots with antibodies that have lost their integrity or binding ability to get through. We do want lots that are consistent with titers of lots that have proven efficacy in clinical trials

to pass.

So, in terms of a potency test we are talking about one kind of thing. In terms of what works for patients; how to make products better, those are the more, that is also what we are talking about but it does fall into a different category if that makes any sense.

DR. BERGER : Couldn't the kind of data that you have just described as being in the second category be put as a resource someplace voluntarily so that either the FDA or the PPTA could have a web site that physicians could go on where manufacturers could voluntarily report titers so that if we needed to tailor as Hans would say, if we needed to tailor a certain product to a certain patient in a given situation that we could look at a panel of products all of which are approved and all of which have met minimal release criteria but say, "All right, this one has more West Nile. Can I get a bottle for my patient right now whose family has somebody else in their family has West Nile or VZV or whatever it is?" something that is not necessarily on the list and that is not necessarily a specification or a release criterion. The PPTA could do that voluntarily.

DR. SCOTT: I think that is the kind of issue we are struggling with is how to do that within a regulatory framework. In terms of labeling the advertising and promotional people will be attendant to things like this but

that doesn't mean it is out of the question. I think it is an interesting idea and when we had the polio kid with SCID I think Dr. Goldsmith called around and figured out who was doing polio type 1 assays and then what products seemed to happen too have higher titers and what lot of a product and that is how that got to that kid.

So, in practice that could be done because everybody is testing for polio as a lot release although they are not all testing for type 1 which I recall was that type.

So, it could be of real clinical assistance. Then you have to ask yourself what kinds of assays are they doing? Are they validated relevant and so forth?

So, there may be a level of sort of quality control on that kind of information that would be important.

DR. SEWARD: I would just add on the polio case, I mean within a day that lot had been located. It was just tremendously helpful. FDA was just fantastic in helping with that child. It was very, very rapid, that assistance.

DR. GROSS: I would be willing to transfer the suggestion also to our regulatory authorities but I guess you have a problem here. The companies which might set up an assay for a specific immune globulins, they are willing to give it to a web site but still we have the problem of controlling this activity. So, it would mean that the

authority has to set up all his assays and I could imagine that this is quite difficult. This idea is truly fantastic, but to set it in reality it is more a problem.

DR. BERGER: But this could be like what we do now where when we try to assess the strength of the evidence from pooling clinical studies if one has a validated assay which has been approved by the authority or run by the authority that could be quality A and if someone has an untested assay that could be quality D and between there there could be different assays that would be rated in different ways.

So, the more information that is out there , I mean the person you know, it is caveat emptor, the person who is taking the product has to say, "All right, I don't know the validity of the assay, but two of them are using ELISA and this one has a higher ELISA titer and nobody has an opsonic activity titer. So, I will do the best I can." But the quality of evidence could be listed like that or the validity, the state of validation of the assay.

DR. SCOTT: There might be a role for reference labs here and I vote that we send all of our immune globulins to the Paul Ehrlich Institute.

(Laughter.)

DR. BAKER : Charlotte, I know you have been waiting patiently to make a comment.

CHARLOTTE : I guess that is on. Dot, you and I had a conversation a while ago about the pneumococcal titers that you had on your slide and you had it calculated out and this goes back to what Richard was going back to his comment a moment ago, Dr. Schiff. Your amount that was calculated to go into the bloodstream was 2 micrograms per ml of total serum volume. That is the way I calculated it out, too, but somehow that doesn't correlate with what the clinical labs stipulate as being protective and I am having a real problem correlating that calculation with the vaccine literature because commercial laboratories universally throughout this country the big ones, and there are about five big ones, and they all agree that it has got to be someplace closer to a microgram per ml and where they got that number is a tremendously long and complicated story and yours is about one-fifth of that amount.

So, I would love to see something on the label but it goes back to what is in the blood and so what you said about that I think comparing the two and trying to figure out, reconcile those two differences I don't think math will do it.

Dr. Golding, I know that it theoretically would work but it doesn't seem to work at all when I did the math myself in correlating with clinical levels.

DR. FRASCH: I would like to comment on that. The

problem is these low levels you are talking about .2 micrograms. This was from studies in infants which basically have a clean slate before you immunize them. They essentially have no antibody to pneumococcus.

So, you know precisely where all this antibody is coming from but the source of your immune globulin of course is adults.

Adults have a lot of antibodies to the pneumococcus and who knows where they are stimulated and so therefore if you look at antibody concentration versus functional activity you get a beautiful correlation for the most part in infants but the correlation becomes rather poor in adults.

So, therefore, I would say that the protective concentration of .2 micrograms does not hold for looking at your IVIG product. Now, one approach to trying to figure out what protects could be empirical in that we have talked a lot about trough levels but I am not sure too many people have really measured them because in a practical point of view you know that if you give the immunoglobulin once a month you basically protect the individual and in fact that is exactly how the protective level of concentration for anti-hemophilus was determined originally. Dr. John Robbins in his laboratory looked at trough levels and came up with a concentration of greater than or equal to 0.15 micrograms of

antibody. That is how that number was originally determined and then it was later confirmed through vaccine studies but they basically used trough levels too get that antibody concentration.

So, I am not sure that you can, I mean your 1 microgram may be closer to correct from the standpoint of the antibodies in the immune globulin.

PARTICIPANT: Can I just follow up on that because I had the same question, Charlotte and it was my understanding that whether it is .1 or .2 of pneumococcal antibodies was protection against bacteremia or sepsis and that the higher levels of 1.0 or 1.3 were what was needed in order to control tissue infection. So, there was a difference in quote, protective titers depending on the type of infection that you were really addressing, and I wanted to make one other comment. You asked about what other pathogens you might throw up on the slide. We haven't heard anything about the other influenza and this is a common question that I get from patients, influenza A and B, you know, patients ask me all the time, "Am I protected against influenza?: and I have always assumed there is enough cross-reacting antibodies in IVIG from the donors that they are protected and in fact the observation, at least my observation is these patients actually do very well with regard to influenza in a family setting where maybe other

family members get influenza and they do not, but with all the you know potential emerging new pathogens related to influenza this may be a concern and maybe that is something that we should address in this antibody panel although it takes 9 months of make this product. So, it may not reflect current serotypes.

DR. SEWARD: I wanted to comment that there is no correlative protection known for VZV and there is no gold standard test that is widely available either. The FAMA(?) test that is considered the gold standard is basically done at Columbia University and hardly anywhere else. Merck for the clinical trials developed a special glycoprotein ELISA test. CDC does have that test available but a comparative study has never been done and they are dependent on that antigen being provided to them by Merck and so there is no commercially available test or widely used test. Neutralizing antibody test isn't widely available right now either

DR. SCOTT: Just to mention,. we sent CDC some IGIV samples from our repository and they did in fact test those on the GP ELISA for anti-varicella antibodies. So, the GP ELISA is designed to provide an epitope that is considered protective against varicella and we actually presented that data at the ACIP at some meeting when we were considering what to do about the impending VZIG shortage. We found it

very similar to what I showed you with the HiB assays that we did and the pneumococcal that there was clustering for products and most of them were, however, within a certain range. How protective that range is I am not sure but if you compared it to VZIG there was not always a very large-fold difference actually because as has been pointed out some IGIVs happen to have kind of on the higher side titers either because the donors have all been naturally infected; many of us have had chickenpox or vaccinated. They still weren't as high as VZIG I should point out but they were up there. You could probably give a dose of 400 mgs per kg for most IGIVs and be okay. That said you don't know for any particular lot that you have on hand what that titer is.

So, we, FDA, certainly can't make, don't make recommendations like that across the board. The CDC recommendations are I believe if you don't have VZIG that you could use IGIV in a susceptible person who could get disseminated varicella and has been exposed.

DR. STIEHM: When I developed this list of course some of these are very, these antibody titers are very constant like diphtheria, tetanus, hepatitis B, measles but the ones that really showed the marked variability from lot to lot were hemophilus, Strep pneumococci(?) varicella and CMV which is also a surrogate for Epstein-Barr virus. So, if you are going to try to identify those antibodies that would

be most useful to measure in gamma globulin I think that hemophilus, several strains of Strep pneumoniae, varicella zoster and CMV are the ones that vary and so those are the critical ones. Parvovirus is present in all of them and I don't think that is a very useful marker for strength of gamma globulin.

DR. BAKER: Jay?

JAY: I think that the discussion is confounding a couple of very, very different ideas. One idea is to try to improve the products by standardizing minimum levels of certain antibody potencies. I think that is what people have in mind when they are talking about Strep for example. We know it is clinically important. We know it is variable in the products. We think it ought to be there. Should there be a standard? That is product improvement. That is an entirely different question than what is a good consistency test for products. You want to be able to weed out bad lots and in that context which is really the lot release issue you are looking for antibodies that you expect to be common and relatively stable in their representation in the plasma pool and that comes in two ways. It comes from infections that are themselves highly common like parvovirus, B19 or where this is universal vaccination so that we expect most donors to have this immunity and then I think there is a third category which is antibody specificities that are very

important in particular cases but where we would not necessarily expect all products or would necessarily want to require that all products meet that standard, and I think what has been put on the table is could we find ways to let the companies communicate what is true about a particular product lot and I think that that is where you get to VCV and CMV but I am finding it difficult to follow this discussion because I think that people are answering different questions in their remarks and partly it is because we haven't sharpened you know one question at a time. It is all important but I think it is answering different parts of the issue.

DR. GOLDING: I think that is very helpful and I think that what I have heard, I mean when Dr. Stiehm just said, "Well, hemophilus, strep, CMV, VZIG, VZ are highly variable," I would say, "Yes, maybe the answer using what Dr. Epstein just said is for IGIV for the general product we really to fix the hemophilus and the Strep pneumoniae. When it comes to other organisms such as CMV and VZ maybe those should be in the realm of hyperimmune gamma globulin. Maybe that is the way to think about this that most people with primary immune deficiencies are going to face hemophilus and strep infections and we should focus on that because that is their main problem and the IGIV needs to take care of the -- and for a lot of other infections, not all of them but a lot

of the other infections maybe the answer is hyperimmune globulin.

DR. GROSS: Exactly what I want to say. The manufacturers are free to claim specificity for one antibody but in this case it would be the specific immune globulin and then you have to test it anyway for specificity.

DR. BAKER: Yes?

PARTICIPANT: So, I have been very impressed with the variability amongst the different preparations much more so than I had imagined and I guess what I wonder given the variability within different lots and the marginal titers of some of the important antibodies in a multivariate analysis are there certain antibodies that would be more predictive of protection against the others? Is there one particular titer that might be useful given the data that I have seen presented by industry today that might be predictive of an overall higher quality immunoglobulin?

DR. BAKER : I would say probably not.

PARTICIPANT: But you know I would like to come back and capture what Jay said at the beginning. If we put in one category those antibody specificities that we intend to use for product release and I would argue right now that actually we do a pretty good job of releasing IVIG products, that clearly they are very efficacious in this patient population. So, whatever we are doing now works. So, with

the exception of wanting to address perhaps the measles titer maybe we are doing what we should be doing now. I would just throw that out.

The second category is those ones that okay, what would be do for product improvement, what specifies, what pathogens would we be looking for product improvement and I think this really addresses this issue where if we were to identify some pathogens they have got to be clinically relevant. Obviously they have got to lead to an improved product and there have got to be assays that we can meaningfully relate to the clinical.

Then there is a third category that I would call for information only. These are antibody specificities which either are highly variable or that we really don't have a lot of information with regard to the clinical relevance and the relationship between the specific assay and the clinical relevance. Those might be specificities that manufacturers could for example post on a web site as was suggested with appropriate caveats. You know, we measured it. Here is how we measured it. Here is what we have got, buyer beware.

So, if we took a look at those three categories, first off do those categories make sense? Does that capture what we are talking about here?

I need a show of hands or a vote here.

PARTICIPANT: I would argue that the first category

is by and large what IVIG is used for today. It is used to provide patients who do not make their own IgG with the protection that average individuals have so that in some ways what you are really talking about is pooled lots of 1000 or more. So, that represents some reasonable segment of the general population and then the question becomes for release criteria compared to the antibody titers in the pre-processed product how much of the antibodies that you are looking at have you lost. Obviously if you are losing 50 percent or 100 percent of the activity you don't want that lot. In practice we are probably losing only a very, very small fraction in which case we probably can choose whichever of Dr. Stiehm's surrogate markers we want. The ones that are common it is essentially a statement that they are widely distributed amongst your 1000 individuals. The ones that are uncommon and therefore variable are likely to be ones in which large portions of your pool are probably negative or near negative and a few individuals are positive and therefore the number of those individuals is going to give you a dramatically different titer.

MR. FRAZIER: Let me jump in if I can, Doug Frazier, CBER, Division of Hematology. I review BLA supplements for these things. I was going to suggest we take the easiest one first and Jay actually beat me to it, largely, if we want to see just lot-to-lot consistency of

the product. Here is something that shows that it was appropriately made. You haven't beaten up the antibodies. They retain functionality. You would want as he said some pathogen specificity that is common to the donor population widely endemic or everyone is vaccinated for. Then you would want a stable antigen so there is no drift. You want something hopefully to be adapted to a binding assay with appropriate validation, you know. Then you have got consistency. The other things are more problematic and that is my input.

DR. MEZENDICETI(?): Mezendiceti from France. For the third category you gave us about the specificity on lot-to-lot products. In our experience we sometimes had the calls from doctors asking for a specific lot, high titer in lot. We have seen earlier this morning that the testing for each product is somehow specific, too, because we have excipients in these products and they can interfere with results.

So, I think the best way is to ask the producer to give you the product that you need for this kind of high titer and in general consideration I can say that we have only for the moment one product which is specific for all the diseases and the rules are done now like that. I don't know if we can, we have to manage or to commercialize the specific product with specific titers for all these

pathogens or not.

DR. BAKER: As to specifications for multiple pathogens we would not be releasing many. So, that is why I said that I think we will have to have a category 3 that is an FYI for information only essentially and the other two category 1 and 2 I think we have possibilities for being more prescriptive about the titers or at least more standardized.

DR. SCOTT: I want to go back to question 1 which is which antibody specificities would be relevant and feasible to measure in immune globulins with respect to clinical importance and we have talked about some of the bacterial pathogens perhaps relative to diphtheria, for example, some of the ones we have talked about might be more desirable as a connector really to the clinical outcomes but we haven't really talked about viral pathogens and measurements of those and I just wanted to ask the audience and especially the treaters because we heard some about this this morning if there are some of the viral pathogens listed here or some others that might actually be relevant and feasible to measure with respect just to the clinical importance and then the lot-to-lot variation question comes later.

PARTICIPANT: I was going to say that now that Resbegam(?) is not going to be available we really don't

have a preparation that has high titers of anti-respiratory viral antibodies and you know in particular parainfluenza influenza 3, adenovirus or RSV.

So, preparations like that would be highly desirable for people who are prone to have viral infections and I don't know if there are any plans for development of such a product in the future or for testing currently available products for these antibody titers and of course EBV and CMV would be equally important.

DR.SCOTT: I think it is worth looking into all three of those. From my point of view I can't answer. I really don't know if there are any plans to develop another Resbegam or for testing of current products.

We have a lot of manufacturers here and I don't know if any of them just happen to be testing for RSV specificity.

PARTICIPANT: At least for RSV you have got Synages(?) you know you can use but we don't have any Synages for adenovirus which is a very severe pathogen in people who have T cell defects and the same thing is true for EBV. CMV we have Cytogam(?) and that seems to be very effective.

DR. GOLDING: So, these infections are occurring; you are not talking about the PID population. You are talking about say transplant populations or young infants

that are premature in case of --

PARTICIPANT: The ones that I am dealing with are people who are genetically deficient in T cells and so they have no resistance at all to any of these respiratory viral pathogens and if there were antibody preparations that were high titer they would benefit immensely from those.

DR. GOLDING: The one solution there may be that they need hyperimmunes rather than trying to cull out you know from the IGIV lots.

PARTICIPANT: The problem is I think we really don't know because no testing is done.

DR.BERGER: I think that most, at least most children's hospitals have a viral respiratory antigen panel. They don't necessarily do viral cultures on children admitted for respiratory infections but certainly if I have a primary immune deficiency patient in the community I would like to have confidence that the IgG product I am giving that patient has protective antibody titers against the five most common causes of respiratory infection, admission to my hospital which I think is adenovirus, RSV, influenza and parainfluenza but I think the CDC probably has that data. So, I would say the most common, if you look at the most common causes of respiratory infection admissions in children those would be a very good set of antibody titers to feel confident that are in the product.

DR. OCHS: I mentioned before the enteroviruses and those are the real problem patients if they pick up echo or coxsackie virus and have XLA and I have seen the development of echo in two patients who were on regular IVIG infusions and we did not know the titers, but documented they had their 400 milligrams per kilo per month and developed echo and in both cases these were patients who had years before the same type of echo infection.

So, I think echo or these enteroviruses, they may not be eliminated and they may be in these patients and if they get for a while a lot that has low antibody then these echoviruses cannot -- one of the two died and so I think to know the echo titers is important for those of us who are in the trenches and I must say the one who survived we are alternating because we don't know the titers. So, we take two different brands of gamma globulin which she alternates hoping that one of the two will have adequate antibody titers but you can see for us we are just using a black box and don't really know what we are giving these patients and so if I would have a wish I would say that every lot is being tested in a central laboratory with the same confirmed testing procedures and we can compare the results and they are available for those of us who need it. It doesn't have to be on the slip that comes with the product but it should be as Dr. Berger suggested; it should be somewhere, maybe on

a web site or at the FDA or someplace where we have it easy to find out which lot is for this particular disease in category 3 is available.

DR. BAKER: Don?

MR. JACKMAN: Sorry, I was lost in thought there for a moment. Dennis Jackman with CSL Behring. I think we all understand that people are trying to come up with measures here that would be valuable and I mentioned valuable especially because the more we add additional variables and that gets back to the point of prioritization, the more we add those and try to get that into a general IVIG the less likely that it is going to be able to be manufactured over time consistently. So, I think there has to be a balance here between value and feasibility and I think it is great to have this discussion but then we have to go through the logistics of this and see how this can possibly be done. So, that is just something I think it is worth mentioning again.

DR. SCOTT: I did want to comment on the lot-to-lot variation because many times when we have done different tests on these five lots of immune globulin we have from each manufacturer and I agree it is a small number relatively speaking, we haven't found so much lot-to-lot variation at least within that time frame of 2000 to 2003 for the Strep pneumo, the H. influenza, the varicella zoster

and I think even measles.

So, with respect to that I think that if any testing were changed at all that that would be an important prerequisite before actually approving any test changes would be to understand for a given validated test just how much variation there is within a product. I wouldn't go across the board and say that there is a lot of variation or not at this point until we have identified perhaps the kinds of tests that would be most desirable.

DR. BAKER: I would like to capture that thought that Dot just had and you know that famous quote from the Institute of Medicine about letting the perfect become the enemy of the good. If we were talking about a next step suppose we just suggested, I think we have got consensus on consideration or on product categories. Suppose we said, "What would be the smallest next step we could take on category 2 that would give us meaningful information?" and I think Dot just outlined a potential approach. We take a couple of clinically relevant pathogens that we think we have got some reasonably decent assays in and just start collecting the data. At least we would advance something with respect to our knowledge here. Would that be a reasonable next step around the category 2? We could call them candidate product improvement pathogens, I don't know, something like that.

Does the group have any enthusiasm for that?

Well, it is not overwhelming, but Juan?

DR.JORQUERA: I think it is worth trying definitely if it is relevant for the efficacy of the product. My only question here is that I think that we should begin by defining very specifically the assay because otherwise we will never get comparable results or really we will not be doing a worse exercise. We need to have a common system for testing.

DR. BAKER : You know I couldn't agree more. Either it is going to be a central lab or it is going to be a group of labs that we have cross referenced. That would be the only way to make meaningful progress.

DR. SCOTT: Let me ask Carl if he thinks that Moon Nam or NIBSC would be interested in looking at just some blinded panels of immune globulins in their validated tests?

DR. FRASCH: I think one of the pathogens that is probably mentioned most often is the pneumococcus and I think in that case there has been a considerable amount of work over a period of at least 10 years to get both an opsonic functional test validated and the ELISA antibody quantitation and the assay that has been most quantitated, I mean calibrated between labs is the ELISA. I think there is no doubt that there is a good standardized assay for pneumococcal ELISA and there are sets of sera that allow a

laboratory that is already familiar with doing ELISAs in general could adopt and clearly the two WHO reference laboratories would be willing to, one or the other would be willing to run assays on a reasonable number of samples and then those samples could of course be rerun in the individual company's laboratory or national authority's laboratory for comparison, but I think if one wants an assay that has a lot of work been done on standardization from laboratory to laboratory it would be the pneumococcus.

DR. SCOTT: I am sure we would also be interested in the functional assay that could also be done.

DR. FRASCH: I can give you the web site that has all the protocols and that is www.vaccine.uab.edu.

DR. SCOTT: We have worked a little bit with Moon Nam.

DR. FRASCH: That is Moon Nam's laboratory and you will find all the protocols for both hemophilus and pneumococcus and the source of all reagents

DR. GOLDING: May I ask a question? You know what was brought up by some of the speakers, Dr. Buckley and others and Dr. Ochs that there are viruses out there that are important for the PID patients. I don't know the exact frequency. I assume it is relatively low compared to Strep pneumoniae and Hemophilus influenzae and what I am hearing from industry is that we have to have something that is

feasible and if we have a whole long list it is not going to be possible.

Is there another possibility here in terms of having, talking about a central lab; what are we talking about; are we talking about the CDC or the NIH? I mean is there something that is feasible that is done as a service for treatment of patients and that the central lab takes certain lots and in a certain number of lots get the testing, gets the information and then has that information available for treatment? Is that something that could work?

DR. BAKER: This would be what I was calling category 3, the for information only. Manufacturers could submit a subset or some number of their lots, some normal production and the central lab perform a menu of tests and provide the information.

DR. SCOTT: That seems to have a lot of utility because then the same test would be getting done and it would presumably be validated for those products and I think it is an interesting idea.

I wanted to get back to the other potential use of a central lab and that would be in testing for candidate specificities because it is really likely to be unwieldy, I think for all the different manufacturers even to work off the same protocol and develop something where we are really looking at a candidate for lot-to-lot consistency and

something that is testable and we would just like to look at our products first and see what is there.

That might also be another use of a central lab.

DR. JORQUERA: I wanted to further comment to the issue of the testing by the manufacturers. I don't think it is impossible that we test for 20. I think it is impossible that we will do it in a short framework of time.

What I mean is that if we prioritize I think pneumococcus would be probably the first one to look for, Hemophilus influenzae and once we have solved that we could continue on that path and for me it is more important to have a common system of testing for all the people that are involved and I mean manufacturers and lot releasers that really are the thing. So, looking for a standard about 3 is an option but that could be as he said maybe a solution or maybe something for a third level of category of testing but I don't think that the manufacturers are close to incorporating further specificities. The other thing is what we did with 20 simultaneously and we prioritize; we can have more testing later.

DR. KREIL: About this concept with the central laboratory quite frankly I see that as a complication more than a facilitation of getting equivalent results because I mean as far as I can see it would be much easier to just establish one standard and then require for every lab to

rightly reproduce that standard before test results from that laboratory are accepted.

The beauty in that concept would be that as Peter Lerch has shown there are actually depending on the matrix that you are setting your specificity in requirements to validate the test for the specific matrix you are interested in. So, that I think should be incumbent upon the manufacturers and then they need to just come up with the right results for one generally agreed-upon standard which I think would be easier than just to have one central laboratory.

Also, I think that would make it easier coming back to the Paul Ehrlich comment. I don't think that the authorities would have to necessarily reproduce the assays at their facility for every product.

I think as long as there is one agreed-upon standard the manufacturers could still do the assay and could verify the results of their assay by reproducing the value of the standard.

PARTICIPANT: Assuming that the assays that have been used today in today's data presentations are accurate we have seen a lot of lot-to-lot variation and even greater manufacturer-to-manufacturer variation. I presume that the manufacturers believe that this is a representation of biology and not of manufacturing.

If that statement is true that this is actually a biological phenomenon is that biological phenomenon important in terms of how these products are used in the immunodeficient patients?

DR. BAKER: Probably the short answer is yes or maybe, I don't know. Certainly I think all manufacturers would concur there is measurable lot-to-lot variation. How significant that is would depend on the pathogen and the assay probably.

It certainly has been at least my experience that specific antibodies, RSV comes to mind the titers and the neutralizing titers can be very much driven by a relatively small number of donors in your pool and so you can see quite large fluctuations in neutralizing activity.

PARTICIPANT: Right. So, that is an argument that is biology but is some of it also manufacturing?

DR. JORQUERA: The data I presented is a comparison of the same product obtained with the same manufacturing process coming from US source plasma versus Spanish recovered plasma. As you could see from my data in some cases you got better or higher titers for some pathogens and in other cases it was different.

I think at least inside the manufacturer it is a matter of biology. I find it difficult also to believe that different manufacturing processes could deplete one

specificity more than other ones. I find that difficult but I cannot say for sure of course.

DR. GOLDING: May I just butt in there? We have seen manufacturing methods where certain immune globulins were removed during the manufacturing and some of the immune globulins such as IgG 3 being much more susceptible to proteolysis. So, I think the reason why the FDA and the idea of the consistency issue is related to that is that you could imagine that a certain manufacturing system could damage the molecules. On the other hand if you look at a particular manufacturer that has made hundreds or thousands of lots of IGIV and you are not seeing major differences, now and again if something went wrong with the manufacturing we would use that as -- that is used as a safeguard against something that happened during the manufacturing, the wrong temperature, the wrong pH, the wrong enzyme concentrations that were added that could affect the product and looking at the actual functional assays is a very good way, in vitro way of testing the antibodies and the quality of the antibodies.

DR. GROSS: Just to add one thing more manufacturing is important because what we have seen is that consistency of the products becomes much more or even much better after they have introduced batch release. So, there is some variability due to the manufacturing process.

PARTICIPANT: Getting back to the category 3 type of infectious agent where the very intriguing idea has been put forth to have a web site where manufacturers could voluntarily put up information about titers of specific lots against specific agents I just wonder if there is any, you know that sounds great from the practice of medicine point of view and I am wondering whether there is a down side to that in terms of that tending to inhibit new hyperimmune products coming to light, coming to market because a manufacturer might think, well, why should I develop this hyperimmune product because people can already identify certain lots of my competitors' products and just use those in the practice of medicine, you know, off label for specific use? So, in the case of West Nile virus for example I think we would like to have evidence-based medicine to know that a high titer product against West Nile virus is clinically helpful and if we have information with respect to titers I was wondering whether that or in certain other diseases certain products will, applications will not be made and the more important ramification of that is that the companies may not invest in research that answers in some cases important clinical questions that we would like to have the answer to.

DR. BAKER: I won't speak for all manufacturers but I will speak all manufacturers. You know as manufacturers we

spend a great deal of effort trying to understand what the customer wants. If we had on a web site a list of specificities and we found out that the demand or the interest for a specific specificity was high, what that would certainly drive my company and I expect most companies to do would be to produce a product that had that specific characteristic.

So, I actually think that it would probably drive us to produce products with elevated titers of specificities of interest. That is my own personal perspective but I really suspect in a free market economy like we have that is what would happen.

We would try to differentiate our products to have those characteristics most desired by the clinical community.

DR. OCHS: I wanted to remind you that our chairman this morning said, "Don't listen to the manufacturers," but I think you are quite right here but the previous discussion where we were sort of trying to drift away from a central laboratory I think there we don't have to listen to the manufacturer. I think logic makes it much easier for us consumers and for the patients to have a central laboratory and to sort of dictate what kind of tests we want and then there are done in a proper way with the same conditions and they are made public with an element of the company that

makes the product.

So, yes, we have to listen to you but also we don't have to listen.

DR. BAKER : That is fine. One caveat I want to put on the central lab and this is a matter of practicality. I think you know that inventories of immune globulins are very low and in fact when I look at the time from when we release a product to its use in the community we are typically now talking about weeks. In some cases it is longer but generally speaking we run relatively low amounts in the distribution chain.

So, if you think about a central lab doing testing presumptively we would not want to delay release while the lab was testing. So, a sample goes to the central lab. Lot is released for distribution. The test results, the turnaround would have to be very rapid or by the time the community got the information the lot would be exhausted. So, there are practical considerations but I wouldn't rule out a concept of a central lab.

DR. MELLQUIST: Can I add to that? Jenny Mellquist, FDA. I like the concept of actually having a standard personally better than a central laboratory. Nobody has really brought up the logistics and the funding of a central laboratory, who is going to do it and the turnaround time I think could potentially be very long whereas if the product

stayed within the hands of the manufacturer I believe that the manufacturers actually are interested in what antibodies to these agents are in their products and if as a group we can decide which one or two or three of these we are going to test for as long as we have a standard to compare everyone could potentially just test their own product and then come together and share.

DR. BAKER: Richard?

RICHARD: I think there are really two categories here. We keep subdividing everything but there are two categories. I think things that are common pathogens, H. flu, pneumococcus, parainfluenza, adenovirus, ones that we might want tested on every lot and from every manufacturer it would make sense then to have this on a web site in the package insert, however we want to distribute it.

For others a more boutique question such as Hans brings up, it doesn't make sense to test every lot for adenovirus, I mean for enterovirus 9 or 11 because you don't really know which one is of issue for a particular patient.

The big problem is that you don't have a laboratory to do the test for you if you need that testing done. To have a central laboratory to be available for individual testing to make these tests available or even we could even have a network so that we could identify a laboratory that could do the testing would solve the

problem.

There is a cost to every test and if you do 20 or 30 more tests on every lot it will increase the cost of the product. The common ones it makes sense to do it because it is of use for everybody but we need to be able to provide laboratories for these more rare conditions and it could either be done by a central laboratory or identifying laboratory in the network so that if he calls and says, "I need echo 9 tested," you can say, "Okay, we can send three lots to this laboratory for echo 9 and we will set lots aside for you for that patient." I mean this is all possible. We have done that in the past but right now there is no laboratory for a lot of these tests.

So, we don't have to have every manufacturer do every test.

DR. OCHS: May I just agree totally with Richard. I think what I was mentioning was these tertiary type of tests. The release of a product should follow what the FDA requires and that the individual manufacturer is set up for that. That is not the problem. I think the problem is these what you call boutique titers which occasionally come up like this patient with polio and we need to know how do we handle this. When I had these patients with echo 11 I asked CDC. They didn't do it. I asked my own viral laboratory. They didn't do the testing. I was stuck and so if either we

know where this could be done or if it is being done on certain lots and the data is available somewhere on the web site I think everybody would be much more content with the possibilities to treat appropriately the patients.

DR. BAKER: You know I think I was reflecting on the fact that this was the first time I had ever heard the words "Hans" and boutique used in the same sentence but anyway you know I don't think it probably doesn't need to be an either/or solution here and I liked the comment that I heard there about if we had say acknowledged reference laboratories for this testing. I am a believer in the free market obviously and I think for the category 3, the pathogens that we are looking at as in essence for information only I don't see why we couldn't have a combination of reference labs, specialty labs and manufacturers' labs if they were acknowledged and had submitted some appropriate validation data to remove obvious biases but let us have it all out there and again we recognize that this is going to be a little bit of buyer beware here. These are not assays that have been demonstrated in well-controlled, double-blinded clinical trials to have relevance, but I think they are better than nothing.

DR. SCOTT: I just wanted to mention that unfortunately Dr. Sullivan couldn't come but he is involved

in various kinds of multiplex assays for finding specificities and it may be that this kind of idea would become more feasible if there were a way to test a lot of specificities on one chip or whatever it is they use. It would be quick. It wouldn't be too difficult. They would be binding assays. That is the down side but I think now we are talking about the less common specificities. We are not talking about lot release and from a regulatory framework I think one of the questions becomes how are we involved or not involved and that is something that we would have to figure out.

DR. BAKER : You know I would like to take the wisdom of the group here. According to the original agenda we were supposed to do a summary of the action items and as you know I am action oriented and would like to get some action items here. What I was going to suggest provided nobody leaves the room that perhaps Mike and Dot and I could have a little sidebar here and consolidate what we saw as action items and then feed them back to the group for up or down.

Does anyone have any enthusiasm for that proposal?

DR. SCOTT: Jay, did you want to make a comment?

DR. EPSTEIN: I just wanted to endorse what you said and what Dr. Pierce said. You know labeling even, information even if provided on a web site is still

labeling. We have to start with that understanding and then the question is are we dealing with validated or not validated information and I don't think we should trivialize the questions of whether posting if you will investigational or non-validated or non-standardized potencies for specificities undermines the role of specific immune globulins. It is true that it may give you a reflection of demand and it may cause you to develop specific immune globulins but after all specific immune globulins are likely to remain more expensive and there will still be a market incentive.

If there is a choice between a specific immune globulin like VZIG and a commercial lot that happens to have a higher varicella zoster titer the market may choose the cheaper product even if it is less effective and there will be no efficacy data for products that have simply been if you will potency tested by non-standardized means and I think that is a very significant issue. I think there is also a conceptual issue which is what is the threshold? When do you need a specific immune globulin as opposed to a garden variety IGIV and I think that we need to have more discussion around the clinical factors that drive it.

For example are there well-defined risk factors? You will after-the-fact treatment be sufficient or do you need it as part of routine prophylaxis and I think that

plays into the equation as well because for things that you can't really treat in an emergent fashion you really want to know that the immune globulin works routinely and then there is another issue which is can you make it routinely and I think this is what Dennis Jackman was getting at.

One of the thresholds for making a specific immune globulin is that it is not feasible to have that potency in a routine product. You have to do something special to make it happen and it is never going to be part of routine production and I think that distinguishes it quite significantly from this idea that we were having in category 1 which is enhancing a routine potency.

So, for example, for H. flu or Strep pneumo the preponderance of lots probably have a fairly consistent titer. All you are really trying to do with a standard is eliminate outliers. That is quite different than the situation with VZV where you really don't have a preponderance of standard lots with inadequate titer or are not likely to.

So, I just think that there are these two other variables that come into play which is that the clinical relevance of hyperimmune globulin versus routine monthly prophylactic product and then the feasibility to manufacture a product that has that potency routinely which is not a given. So, I just see these as again different questions and

the products as different animals but I appreciate that there is overlap and I am not dismissing the idea that you know additional information may play a role, but just to support Dot Scott's point there is a very strong regulatory question here which has to do with unvalidated claims.

DR. BAKER: You know to Jay's point change is going to be painful here. If we keep on doing what we are doing we will keep on getting what we are getting and so I think the challenge to us as a group is is there a way; can we navigate the regulatory hurdles and legitimate regulatory issues and yet still provide an improved therapy for our patients and practitioners?

So, a simple job.

(Brief recess.)

Agenda Item: Summary and action items with audience discussion

DR. BAKER: Okay, I am ready to resume, and I am very much driven by the need to have many or all of you on the shuttle that is going to depart at five-fifteen.

Getting consensus was a challenge, coming up with a proposal but I think we have come up with a viable first step and Mike or Dot if I misspeak you can kick me under the table but we have a proposal and this is actionable that between the stakeholders, between the PPTA, the IDF, the FDA and any other stakeholder that wishes to weigh in on this

that we perform a survey of the existing products in a central laboratory to determine titers to what we would classify in the pathogens of special interest and we may still need to refine that list, but these were the ones that have been identified as clinically relevant and broadly present or likely to be broadly present in the population.

The intent of this is twofold, one to gather information on the existing products we have on the marketplace and secondly to come up with a potential better and more clinically relevant at this point release standard for our category 1s.

So, Dot have I captured that?

Okay, we have got one step. It is actionable. I think it is within both the economic and the ability of our collective will to do this.

So, congratulations. That is not an easy thing.

No. 2, and this is where I am going to leave this one to Dot. There was a secondary proposal.

DR. SCOTT: I think you are all aware that we can't commit to advisory committee meetings and things like that but I think what we have heard today certainly allows us to consider the category 3 and what the possible approaches or frameworks might be to get the kind of information out that the clinicians want about if you will, I don't want to call them the boutique pathogens but at least the ones that are

less common and for which there may be a great deal more lot-to-lot variation and for which immune globulin has not been shown in clinical trials to be effective and there are a lot of hurdles in doing that for things that are relatively rare or for patients that are relatively rare, but we do understand the need and the wish out there to find out more about the specificities in order to be able to help individual patients and classes of patients and we will be talking about this internally and hopefully we will be able to discuss any path forward within our regulations.

DR. BAKER: So, congratulations, everybody. This was a very productive workshop I believe.

DR. EPSTEIN: Discussion?

DR. BAKER: Not if you are going to complicate it.

DR. EPSTEIN: I am just wondering what other people may think and you know is the working group going to be formed? For example, you talked about a cooperation to look at category 1 agents and specificity testing and common standards for the laboratory and where the reagent is going to come from and is it going to be central lab or you know, in other words is there an effective mechanism to move that concept forward?

I, personally, feel that that is a great concept. Maybe you want to see a show of hands but then there is the issue of how do you bring it forward. Is there a volunteer?

For example, has PPTA offered to work on it?

DR. BAKER: I don't know if Mary is still here. What do you think, Mary?

MARY: I think it is a viable option, yes and I think that with the cooperation of member companies we surely could work on this.

DR. BAKER: Let me ask the question in a more provocative manner. Most of the, I think probably all of the member companies are represented here. Is there anybody that wants to opt out?

DR. SCOTT: I am sure that we would be enthused to assist PPTA and the manufacturers in terms of identifying labs asking for Dr. Frasch and others' assistance and also finding out more about a WHO report that is coming out very shortly concerning validation of opsonophagocytosis for Strep pneumo.

DR. BAKER: If there is no further commentary I pronounce it over and we will -- oh, a question.

PARTICIPANT: Thank you. I still have to wonder because for the first thing you were talking about, the first action is there not the first need to identify really which is clinically relevant in terms of what are the infections that still occur with the products considered as efficacious and what is the prevalence of these infections? So, in a way what is really the need for that? It is the

whole question in a way that I put. Is there really a need for or maybe I should formulate it differently. Are the immunoglobulins on the market not efficacious enough to prevent a number of infections that are clinically relevant and what can be done on the products as a whole not on lot-by-lot but as a whole to achieve this efficacious level?

DR. SCOTT: I think the answers about trough level titers and the clinical efficacy would have to be answered in some other way but for the category 1 what we are looking for if there is any change to be made is testing for relevant pathogens, antibody specificities and with the assumption that the immune globulins that have been proven in clinical trials to be effective in prevention of infections actually have what we would normally consider very good titers because they have been proven effective.

So, we are not really talking about in category 1 improving products. We are talking about finding out what is there, setting a rational standard the way it was done for measles and using that both to monitor lots for the integrity and the characteristics of all individual lots the way we do with the measles, polio and diphtheria in order to identify outliers that may have had problems in manufacture or new products that may not have what is really a bench mark level of these.

So, I don't know if that answers your question and

I think that we heard this morning that at least two of the pathogens specificities for which we can test that are common in these patients and were substantially helped once the immune globulins existed and were used are Strep pneumo and H. flu.

I don't think the idea is to figure out a titer that really eradicates these infections if it is possible. That would be nice but that is not really the purpose of looking at a candidate or potential new lot release test.

I will say a different last word. Thank you, everybody for your attention, your assistance and for making this a very useful workshop I think for everybody.

(Applause.)

(Thereupon, at 5:15 p.m., the meeting was adjourned.)