

UNITED STATES FOOD AND DRUG ADMINISTRATION  
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS  
DISEASES

IMMUNE GLOBULIN POTENCY IN THE 21<sup>st</sup> CENTURY

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PARTICIPANTS:

**Welcoming Remarks:**

PETER MARKS  
Food and Drug Administration

JOHN BOYLE  
Immune Deficiency Foundation

MARK BALLOW  
Immune Deficiency Foundation

MARY GUSTAFSON  
Plasma Protein Therapeutics Association

STACY FERGUSON  
National Institute of Allergy and Infectious  
Diseases

**Introduction to the Workshop:**

DOROTHY SCOTT  
Food and Drug Administration

**SESSION I: Measles Antibody Levels in U.S.  
Licensed Immune Globulin Products:**

**Session Chairs:**

MARK BALLOW  
University of South Florida

DOMINIKA MISZLELA  
Plasma Protein Therapeutics Association

**A. Summary of Measles Lot Release Testing  
History, Rationale, and the Current Release  
Specification:**

DOROTHY SCOTT  
Food and Drug Administration

PARTICIPANTS (CONT'D):

**B. Measles Epidemiology -- To Include Overall Risk of Measles in the U.S. and Globally, Reported Infections in PI Patients, and Impact of Herd Immunity on Risk to PI Patients:**

MANISHA PATEL  
Centers for Disease Control

**C. Passive Immune Therapy for Measles -- Protective Levels and Pharmacokinetics of Measles Antibodies After IG Infusion; Pathogenesis of Measles in Primary Immune Deficient Patients:**

MARK PAPANIA  
Centers for Disease Control

**D. Measles Antibodies in Donor Plasma; Longitudinal Data and Forecast:**

TOBY SIMON  
CSL Behring

**E. Measles Antibody Trough Levels After IG Treatment; Theoretical Values Assuming Lower Measles Antibody Specifications:**

PETER VANDEBERG  
Grifols

**F. Use of MMR Vaccine to Increase Measles Antibodies in Plasma Donors:**

THOMAS KREIL  
Shire

**SESSION II. Polio Lot Release Specification for Potency of IG Products Proposed Session:**

**Session Chairs:**

ROBIN LEVIS

Food and Drug Administration  
PARTICIPANTS (CONT'D):

THOMAS KREIL  
Shire

**Polio Lot Release Specification -- Origins and Rationale:**

DOROTHY SCOTT  
Food and Drug Administration

**Polio Antibody Tests in the Context of Polio Eradication**

**A. Progress of Polio Eradication Efforts and Containment Requirements Post-Eradication:**

STEVE OBERSTE  
Centers for Disease Control

**B. Polio Disease, Passive Immune Therapy for Prevention or Treatment of Polio, and Incidence of Polio Infection in Primary Immune Deficient Patients:**

MANISHA PATEL  
Centers for Disease Control

**C. Polio Virus Shedding in Immune Deficient Patients and Incidence of Polio in Primary Immune Deficient Patients:**

MARK McKINLAY  
Task Force for Global Health

**D. Development of Hyperattenuated Poliovirus Strains and Validation of Their Use in Antibody Assays Under Reduced Containment:**

ANDREW MACADAM  
NIBSC



PARTICIPANTS (CONT'D):

**Other Participants:**

ANTHONY ADSON

LYNN ALBIZO

MEGHNA ALIMCHANDANI

STAN AMMONS

RACHAEL ANATOL

SUSETTEE AUDET

MICHEL BAUR

JUDY BEELER

MEL BERGER

ROGER BRINSER

NANNETTE CAGUNGUN

IRENE CARROLL

TARA CAULDER

LARISA CERVENAKOVA

KYUNG-IL CHA

SEIIN (EILEEN) CHOI

DANIELLE CRAIG

LUCY DEMARIO

LU DENG

ADERONKE DENLOYE

PARTICIPANTS (CONT'D):

SHALINI DESAI

AMINE DJEFFAL

UROS DJEKIC

NANCY ELLER

GABRIELA ESPINOZA

MARIA FARCET

ALBERT FARRUGIA

MAHMOOF FARSHID

STACY FERGUSON

LAUREN FREESE

NICHELE GIBBS

BASIL GOLDING

PAMELA GOVAN

MICHALE GRAY

RHONDA GRIFFIN

LINDA GRIFFITH

KENAN GU

JOUD HAJJAR

YONG HE

ESTHER HENDRICKSON

MARTIN HOULE



PARTICIPANTS (CONT'D):

STEVE HUANG

KIMBERLY JONES

MICHAEL KENNEDY

ALEXEY KHALENKOV

BO KYUNG KIM

YEOWON KIM

MARY CLARE KIMBER

ADINA KNIGHT

MIRJAM KUHNE

MAJID LAASSRI

FIANA LEVITIN

WILLIAM LEWIS

HEATHER LILLEY

MARTIN MACPHEE

PAUL MAGLIONE

NICHOLAS (NICK) MANETTO

EWA MARSZAL

ALISON MAWLE

SITA MODALI

JAMES MOND

KARA MORAN

PARTICIPANTS (CONT'D):

ELISA MORETTI

MEGAN MORSHEIMER

MOON NAHM

APURVA PARIKH

WOJIN PARK

FRANCESCO PIERANTONI

DOMINIQUE PIFAT

GRIGORI PRIKHODKO

JIAHUA QIAN

MARC RAMBY

BARBARA RANGETINER

JENNIFER REED

IRIS RENNER

SHERRI REVELL

JUERGEN ROEMISCH

JANIE RUSSELL

ANDREA SANCHEZ

CORRY SAWATZKY

RICHARD SCOTLAND

CHRIS SHAMBLEAU

WILLIAM SHEARER

PARTICIPANTS (CONT'D):

SANG MIN SHIN

OLGA SIMAKOVA

RICARDO SORENSEN

MOLLY SPENCE

KELLY STONE

EVI STRUBLE

KATHRYN TAYLOR

RUTH TURNER

MARIA VIRATA-THEIMER

YONGGANG WANG

TARA WATERMAN

CELIA WITTEN

HAO XUE

HAILING YAN

JUNSOO YUN

ANNAIS ZARATE

CLARK ZERVOS

PEI ZHANG

LILIN ZHONG

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P R O C E E D I N G S

(8:02 a.m.)

DR. SCOTT: Good morning. I think it's time for everyone to take a seat and we'll get started. First, a couple of housekeeping announcements. Remember to bring your badges back tomorrow. They're only issuing one badge per person so they would really like to have you with a badge back. If you lose it I'm sure there's a backup plan though. The speakers will be timed. There'll be a light it's a stoplight right up here. So don't be surprised if you're on the green and it moves to the yellow. Just try to wrap it up. We have a bit of a tight schedule in the morning. And lunch will be served. I'll let you know where that is after the end of the session.

I think we'll get started with the first set of slides. Yes. So, first I'll ask Dr. Whitten to come up. We have opening remarks from all of our sponsors. And I do want to say welcome to everybody. I think it's clearly a very important topic to all of us here to figure out what to do with respect to our potency assays both

the current ones and the potential for future different potency assays. And this is Dr. Whitten. She is the Deputy Director of CBER. Dr. Marks sends his apologies, but he wasn't able to make it here this morning. Thank you.

DR. WHEATEN: I'd like to welcome everyone to this workshop and I'll be brief. I want to thank our planning partners, the Immunodeficiency Foundation, PPTA and NIH. This meeting is aptly named Immune Globulin Potency in the 21st Century because indeed the landscape has changed over the last several decades both in terms of - because of our own success with public health measures and infectious disease control, so I think this meeting is going to be an important meeting in discussing the impact of immuno, immuno globulin products of some of these issues, such as declining measles antibodies and polio eradication and the risk of immuno globulin shortage and some of the challenges with potency testing. I am going to turn it over to some of the other sponsors to give a few welcoming remarks as well. Thank you.

JOHN BOYLE: Good morning, all. My

name is John Boyle. I am the President/CEO of the Immune Deficiency Foundation and we are so thankful to be here today and for all of you here to be as well. We are especially grateful to all of who have made this day possible. Especially the Food and Drug Administration and Sever the Plasma Protein Therapeutics Association, PPTA, the National Institute of Allergy and Infectious Diseases and of course all of you who are participating today.

This workshop is tremendously important to people who are living with primary immunodeficiency disease who especially rely on immuno globulin therapy. As most of you I would assume know, primary immuno deficiency diseases or PID are a group of 300 rare and chronic disorders in which part of the body's immune system is either missing or functioning improperly. One of the most important functions of the normal immune system is to protect us against infections. Patients with PI have an increase vulnerability to infections, which can be recurrent, usually severe or that won't clear up. People with PI face frequent health problems

and often develop serious illnesses. Now, IDF is the national non-profit organization dedicated to improving the diagnosis, treatment and quality of life of people with PI through advocacy, education and research.

There are approximately 250,000 people who are diagnosed with PI in the US according to estimates and thousands more go undetected. IDF provides accurate and timely information for patients and families and offers vital resources for our community including educational publications, online resources and in person regional programming. Through outreach, research and public policy initiatives we work to help improve the lives of people with PI including ensuring the safety of IG therapy and its availability which is, of course, why we are here today.

Now, there is a particular reason I am up here in addition to my official role with IDF. In 1978, when I was six months old I was diagnosed with a form of PI, X-linked agammaglobulinemia. And I received IG therapy ever since from inter muscular in the bad old days to IV to subcu, I've

experienced it all.

Now XLA a common variable immunodeficiency among other types of PI are characterized by lack of and/or impaired antibody function. And for these disorders mine and with the population that we represent IG therapy is lifesaving and lifelong.

Now IDF has conducted surveys with the patient community for more than 20 years to collect data on PI as well as to the use of IG therapy. In fact according to our surveys more than 70 percent of our patients rely on IG therapy to temporarily replace the antibodies that they don't produce.

Our community is not the only population who relies on IG therapy, but we are the only community who depends on it for antibody replacement. The antibody make up of IG must be at a productive level for people with PI. We've had a long history of involvement with the FDA and others here to ensure sufficient antibody production through IG. As you know, people with B cell and T cell immuno deficiencies are enabled to develop protective immunity following



vaccination. As such, IG must have protective levels for acute and serious infections including, but of course not limited pneumococcus and homophiles influenza B.

Because of the decline in titers in some productive antibodies there are critical questions that need to be addressed. First are the current IG product providing and that will in the future, provide sufficient protective antibody levels for people with PI for measles. These titers will not only make IG products less effective, but the reduction in herd immunity may also lead to more outbreaks and less ability to control the spread of disease. Another important question is, what other serious and acute infections including pneumococcus and homophiles influenza b should we be studying?

In short, we are concerned for our community and we have these questions. How low can you go with titers to protect patients such as those that are on IG therapy who have PI? If there is no protection for measles or not enough protection, what then? What do we do? And, in general, how are we going to best protect patients

with PI who rely on antibody replacement? And then finally, what are the communication pathways to ensure that our patients are notified and protected if there is an outbreak or some other problem?

These are the questions that need to be answered to protect PI. And we see this important, important workshop as a way to further address these issues and we really are looking forward to the future studies and discussions that we will all have together.

In short, we appreciate this opportunity to discuss this matter that is of critical importance to those who are receiving the antibody replacement from IG and wanted to state the obvious that IDF will continue to fight for the highest quality IG, the most effective antibody replacement for the patients who rely on this lifesaving treatment. For all of your time here today and for all that we will do together in the future, thank you.

DR. SCOTT: Ms. Gustafson will speak for the Plasma Protein Therapeutics Association.

MS. GUSTAFSON: Thank you and I want to

welcome everyone as well from the PPTA and our PPTA member companies. Special thanks to Dr. Scott who has organized this. And we have worked with Dr. Scott on co-sponsoring several other workshops over the years and we find these workshops to be extremely helpful. It brings together the regulators, our industry, academics at clinicians and of course when John spoke our patient population. And at the end of the day those are the people that we really need to serve. I would have a special thanks to our PPTA member companies who have worked behind the scenes and also the steering company, Larissa Chervinikova from our staff has been instrumental in planning. And Thomas Crile from Shire was also on the steering committee.

And also, to our member company speakers who have agreed to speak today to present in a very transparent and I hope, helpful way to discuss the issues that we have today and work towards common solutions. Thank you al.

DR. SCOTT: And we have Stacy Ferguson, to represent NIAID, who we have to thank for this beautiful room and setting and also for the work

that they do on the NIH side with respect to supporting studies on primary immune deficiency and related diseases.

STACY FERGUSON: Good morning and welcome. I am speaking on behalf of Dan Rotrosen, our Division Director in the division of Allergy and Immunology Transplantation. He was unable to make it to this meeting unfortunately, so he asked me to fill in for him.

Our division has a strong interest in a lot of the issues that are being discussed and my branch the basic immunology branch we promote and fund basic and applied research that is relevant to IV/IG and the efficacy of those products. It is definitely upstream. We do have programs for discovering development of novel (inaudible) to amplify and promote responses - more durable responses to vaccines. We have large portfolios in both basic t-cell and b-cell immunology. T-cell memory is clearly relevant.

Definitely, I have the basic b-cell immunology portfolio and definitely one area that is really expanding quickly is the study of

(inaudible) plasma cells. The cells that are creating the antibody, hopefully throughout the life of the individual. We are finding there are - it has been difficult because just finding the cells are pretty rare cells, finding them and phenotyping them is difficult. But we do have a bunch of researchers who are noticing there are sub populations of these plasma cells. Some last for a few years. Some appear to last for the life of the organism or the human or mouse actually. There are a lot of parallels.

So finally, another area that we are expanding is we recently had a council concept cleared for solicited research to understand what contributes to curable immunity. Of course, this is important both for people who are vaccinated, but also as donors for IVIG products that would increase the likelihood of giving us sort of a steady pool of high quality plasma products. And so, with that, I will stop.

DR. SCOTT: I can gratifyingly report that we are still on time in this meeting and I'm going to try not to make us too late. If I could have the first talk for Scott, please?

So just very briefly I want to help set the stage for this workshop by giving an overview on how it came about and how we needed to address the topics we are addressing in the three sessions. This is a disclaimer. I am speaking four times. I am only going to say it once, but this counts for the entire duration of the session. The sessions.

My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate the FDA.

So the goals of the workshop are three-fold and they are addressed in three sessions. Addressing the declining measles antibody titers in IG products and the significance of that for patients and also for the products and their availability.

To examine options in the second session for polio antibody testing in the setting of polio eradication and new restrictions on the use of polio virus. And the last session, which is tomorrow, will be to discuss potential new potency assay specificities that reflect antibody activity to pathogens of concern for

immune deficiency patients who receive IG products. It is all about potency. I will say a few things about potency and show you where the underpinning the regulatory underpinning of potency how it is defined.

So the International Conference on Harmonization document ICHQ2B defines potency in products as the quantitative measure of the biological activity. Very nice short definition. We will come to the FDA definition in a minute. And potency should be measured by a valid biological assay. There are three essentially kinds of assays. Animal based biological assays, cell culture based biologic assays and biochemical assays that measure biological activities, such as enzymatic reaction rates or biological responses induced by immunological interactions in other words, vaccines.

Our definition is a little bit longer, but I would mention that we do it here to the ICH guidelines. The definition in biologic products is the word potency is interpreted to mean the specific ability or capacity of the product as

indicated by appropriate laboratory tests or adequately controlled clinical data obtained through the administration of the product and the manner intended to effect a given result. This is a very old definition that has withstood the test of time. And you can see it is very broad.

To enforce there are also requirements in the 211 Section of 21 Code of Federal Regulations. We are going to get into the details a bit now that lab controls need to include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to ensure that drug products conform to appropriate standards of identify, strength as potency, quality and purity. So manufacturers have to institute these laboratory controls as part of good manufacturing processes and according to the regulations. We have to have specifications for all of our products.

And here is one of the more interesting aspects of this: What if a potency test fails? A licensed potency test for release of the product. Well, drug products failing to meet the



established standards of specifications in any other relevant quality control criteria shall be rejected. In other words throw away the lot. This can be an expensive and product consuming way to meet your specifications and only distribute products that are within your current licensed potency. This presents a problem when we come to the measles topic which is that our lots are in danger of failing the specification. We will come to that more obviously, in the more specific session.

Immune globulins are tested to ensure that their biological activity and potency. The important characteristics of potency specifications for immune globulin products are they provide assurance of the functionality of antibodies. So the tests need to measure antibody function not just binding. They provide evidence of lot to lot consistency in manufacturing and the specificity is relevant to the indication. And in this case, we are talking about the primary immune deficiency indication.

These are the potency assays for US IG products. There are three specifications all

firms test for all three. One is for measles antibodies by an in vitro neutralization or a human agglutination test. And I've written the specifications here and you can read these later. One is for the ability to prevent the affects of diphtheria toxin. Essentially, it is like a diphtheria anti-toxin assay. These are by animal bio assay or in vitro neutralization. And the third specificity is for polio. I apologize for the typo. It should be polio type1, type 2 and type 3. We will send out corrected slides to you after the workshop. And these are the specifications. Now, in fact, almost all firms test for polio type 1 and a few for polio type 2 but that is going by the wayside very shortly and none for polio type 3. If you have questions if we have time we can have a few questions after I speak. And I have just put some details about how these are done. There are Sever standards available for all of these.

Here is a history of potency testing. In 1943 the first immune globulin was licensed. In those days people actually tested the safety of immune globulins by injecting them into some

of the staff or even themselves to see if it was safe enough. But there weren't really standard potency tests.

In 1953 the Department of Health Education and Welfare published minimum requirements for immune serum globulin which means the IM form of immune globulin which was actually made from plasma. The ability of the method to recover specific antibodies should be demonstrated by titrations for several antibodies by which they are recognized methods of titration. In other words at that time any manufacturer could select which antibodies to look at. But also, several lots of the material shall be shown by clinical trials to be effective in the prophylaxis of measles. The early uses of the immune globulins were not to treat primary immune deficiency that came up a little bit later but to - for post exposure prevention of measles and hepatitis A virus.

In 1961 the first measles antibody standard was promulgated by I believe it was the Bureau of Biological Standards for measuring anti-measles antibodies in the immune serum

globulin. And not until 1965 around 1965, 1968 did the Code of Federal Regulation Requirements come about for potency testing of immune globulin products to look for antibodies against measles, diphtheria and polio. That was quite some years ago. I think it's 42 years ago and we have had those specifications ever since. They translated over into the intravenous immune globulins and subcutaneous immune globulins. Actually, it is 52 years.

So the first session co-chaired by Dr. Ballou and Dr. Mishtella is about the decline of measles anti-body titers in US licensed immune globulin products. At the end of these presentations we will hear about the potential impact for primary immune deficiency patients if the lot release specification for measles antibodies is lowered.

We also will discuss the impact on immune globulin supply of not lowering the current specification. We'll hear about predicted protected levels of measles antibodies in primary immune deficient patients and we will see some data related to that as well. And we

will talk about options for measles post exposure prophylaxis for PI patients if the current measles specification is lowered.

So subsumed in all of this is a possibility that decreasing the specification will diminish the protection for primary immune deficient patients and that really is the rub because it seems that plasma donor titers are getting lower and lower now that most plasma donors have been vaccinated and have not had actual infection.

The second session is about polio lot release testing in the setting of polio eradication. Co-chaired by Dr. Crile and Robin Levis. And that will cover the progress of polio eradication efforts. I think you will find the talks really quite fascinating. The anticipated containment requirements for polio virus and whether or not these seem to be infeasible or burdensome of the manufacturers who now use polio antibody testing as a lot release specification. You need live polio virus to do this -this test.

We'll hear about live polio virus in immune deficient patients and the potential

protective value of polio antibodies and we will talk about and we will hear talk about a potential replacement test method for polio neutralizing antibodies.

So the challenges to two of the three existing potency assays prompted us to consider and revisit the relevance and feasibility for the future. And the third session is devoted to the future of immunoglobulin potency testing. First we'll hear about bacterial and viral infections in PI patients. What are the problems today and what kind of antibody potencies are important. We will also hear about anti viral and anti bacterial antibodies in the IG products. We'll hear a lot about measuring pneumococcal antibodies in IG products using bio assays and other methods.

And we like to at the end of that session to have the goal of identifying assays and tests that might be considered for further studies for potential new potency assays.

After the workshop we will publish the transcripts. We hope to prepare a supplement for publication with participation of the speakers and FDA along with stakeholders, most of whom are

here, will continue discussions about the measles antibody specification about which we have to do something, I believe. Polio virus antibody testing and the evaluation of new candidate antibody tests for IG product lot release.

The steering committee has been terrific and they put together this agenda. It would not have been properly done without them and I thank you very much. I want to thank the workshop support group from the FDA the PPTA, the Immune Deficiency Foundation and from NIAID. There are actually many other people that aren't listed here also that provided a great deal of support to get the logistics and other aspects of the workshop in place.

I want to announce there will be a lunch and I will tell you where that is at the end of this session. And I just want to welcome all of you, the audience. You are very important to us and we are depending on you to have a lively discussion and to bring up points that we haven't considered or to advocate or not advocate for certain lines of investigation. So please, participate. The audience has opportunities to

speaking during the panel sessions. It will just be informal. You can raise your hand. You will have a mic or a mic will be brought to you, but we very much look forward to your assistance as we plow through these difficult issues. And I thank you for your attention. If there are any questions we have a minute before I talk about the next thing.

Okay, we're onto Session One. This is going to be a very quick introduction. Just a little background on the measles antibodies in US licensed immune globulin products. The specifications and the problems that we're confronting.

So measles antibody titers are potency tests for a lot release of all what we call non specific immune globulins licensed in the US. In 1944 there was a demonstration that measles effectively prophylaxes. I'm sorry, that immune globulin intramuscularly effectively prophylaxes against measles and that was published by Stokes in 1953 as I just mentioned. We had the minimum requirements for an immune serum globulin, which at that time included proof



that they are effective in prophylaxis of measles. And we developed the first standards in 1961. So for 45 years everything went great, right? But then around 2006 we began to reports from manufactures that their measles antibody titers were decreasing the products and that they had been decreasing over time and they were close to missing specifications. And, in fact, in those times some lots did fail lot release testing in this period.

There were occasional failures, but there were a lot of close calls as well. So, in 2007 10 years ago we had a workshop on this issue and we developed as a result of the workshop a strategy to support the lowering of the measles antibody specification from what it was .6 times the CBER standard to .48 times the CBER standard.

Now, one of the speakers at that first workshop predicted that this would work really great for the next 10 years, but that eventually as the plasma donors with high titers who have actually had measles aged out of the donor population that we would be getting plasma ultimately only from US donors that had been

vaccinated. And the vaccine gives lower, less long lasting antibody titers than actually having had measles.

At that workshop we discussed the evidence that the protective level of antibodies against clinical measles in normal individuals was about 120 mili IUs per mil. That sterilizing immunity is probably much higher than that. And we also recognized then as is the case now that the protective level for measles antibodies in primarily immune deficient patients is not known. There haven't been any studies, there certainly haven't been many cases to look at. The protective level is likely to vary depending on the specifics of the type of immune deficiency people have, but we still needed a number. And what we proposed was that trough titers of antibodies that is right before the next infusion of antibodies in PI patients should reach 240 MIUs per mil double the protective level against clinical measles in normal people. So, we proposed this specification and it was based partly on modeling of pharmacokinetics of immune globulin and the

goal was to demonstrate at this specification.48 times the CBER standard. The 400mg per kg of immune globulin would provide serum trough levels of a least 240 mili IUs per mil in the patient.

So there was a - tactics or a strategy to actually accomplish this through regulatory submissions. So the regulatory pathway was that manufacturers could voluntarily propose to change the measles specification of their product from.6 to to.48 times the CEBR standard, which is adjusted for IG concentration, but that is a technical detail. They needed to agree to report measles in PI patient that was a 15 day report to FDA. They agreed to making a labeling change that reflects the potential need for dosing alterations for a PI patient with potential exposure to measles. They needed to provide trough level data for measles antibody from prior clinical trials and PI subjects where the infusion dose and IG antibody titer of the product that was given were known. Or submit a post marketing commitment to do essentially the same thing in the context of upcoming ongoing or completed trials that had retention samples. Or

they could do a stand alone trial to look at trough titers and the measles titers needed to be measured by a functional assay.

So the data that we saw as a result of these submissions affirm that trough levels greater than 240 MIUs per mil should be achieved in patient's receiving IG IV or intravenous or subcutaneous immune globulin at a minimum measles antibody potency of .48 times the CBER standard. Obviously people are not making lots or exactly .48 times CBER standard so there is a way of modeling we call it proportional shrinking analysis where you can take the actual data and adjust that ratio to say if the product had a .48 titer than what would the trough level be? It is just a ratio.

Since then, we are not aware of measles infections of PI patients who received IG on a regular basis, but I will point out that exposures now in the US are uncommon given the size of the population aren't that many outbreaks. There was one death in an immune suppressed patient related to the Disneyland outbreak and measles was only diagnosed post

mortem. There was no rash. And I think the CDC if we are interested can fill us in more on what the nature of the immune suppression was.

I already mentioned the last point. So the questions for discussion here that you can be thinking about while you hear the presentations are what is the potential impact on patients of decreasing the lot release specification for anti measles antibodies in IG products? And what is the possible impact on IG supply of maintaining the current measles specification? What level of measles antibody is sufficient for post exposure protection of immune deficient patients? We can discuss that if there is additional data that we don't know about we would be very glad to hear of it. And this is a long question, so it is broken down into bullets, but it is to give you an idea of the kinds of solutions that have been proposed in the past and presently related to what are we going to do if we have to lower the release specification to allow products to be released over the coming years? What other options would provide protection against measles infection in immuno compromised people exposed to

measles or potentially exposed?

So these options could include the use of intravenous immune globulin post exposure. The labeling of IG product lots with high measles antibody titers that is to put a titer on the label. The development of specific measles immune globulin preparations from high titer donors. Those donors do exist. The labeling of the immune globulin product lots for primary immune deficient patients indicating that they have a measles antibody level that is sufficient at the .48 or higher. Or the development of a (inaudible) antibody, which would be nice, I think for everybody in terms of post exposure prophylaxis. But that would be a longer term solution should it ever come about.

So we will be hearing about measles epidemiology from Dr. Patel of the CDC. Post exposure prophylaxis and some pharmacokinetic modeling from Mark Papannea also from CDC. The measles antibody titers and donor plasma and the trends in those titers over time from Dr. Simon. The measles antibody trough levels after immune globulin treatment from Dr. Vandenberg of

GRFLS. And use of the MMR vaccine to increase measles antibodies in plasma donors.

So, I want to welcome our co-chairs and our speakers. I think there is space for our speakers to come here to sit. It is up to you, but the cochair I think it would be nice if you can come up to the table.

DOMINICA MAHESHTALA: Good morning, everyone. My name is Dominica Maheshtala and I represent the PPTA. Thank you all for being here and thank you very much for Dr. Scott for giving me the opportunity to co-chair the session.

The first talk is going to be by Dr. Patel. Dr. Patel will speak about the measles epidemiology, risk of measles in the US and globally, infections in PI patients and impact of herd immunity. Dr. Patel, is a medical epidemiologist with the US CDC and is at the moment an epidemiology team lead in the Division of Viral Diseases where she heads several viral programs including measles, polio, rubella, varicella, zoster and CMV. Dr. Patel?

DR. PATEL: Okay, good morning. I'd like to thank the organizers for inviting me to

participate in this workshop. I'll be giving an overview of the epidemiology measles in the US during the post elimination era and providing you with some unpublished data.

So, just as a reminder measles is one of the most highly contagious vaccine preventable diseases. It's an acute respiratory illness. Incubation period averages 8 to 12 days and the symptoms include fever, malaise, cough, coryza, inner conjunctivitis and a macular popular rash that spreads from the head down. And certainly, there are modified presentations of measles for example, in our previously vaccinated persons as well as immuno compromised hosts.

The infectious period is four days before until four days after the rash onset and MMR vaccine the first dose is recommended between 12 to 15 months of age, the second dose between four to six years of age and for adults that are low risk it is one dose that is recommended. And for high risk adult students, healthcare personnel and travelers two doses is recommended.

So there has been substantial progress globally with the reduction of measles. The



incidence has actually decreased by 87 percent since 2000. This graph looks at the annual number of measles deaths in millions. The upper gray solid line is the estimated number of deaths without vaccination. The lower solid blue line is the estimated number of deaths with vaccination and the dotted lines are the competence and errors around those estimates.

And then the gray shaded area are the number of deaths that have been prevented by vaccination and that has been 20.4 million deaths prevented, which is actually quite extraordinary. It is also important to note that the region of the Americas is the first and only region that has verified elimination and that actually just happened last year in 2016. And so, even though there has been a lot of progress globally there is still a lot more work that needs to be done.

Since the measles vaccination program was introduced in 1963 there has been a substantial reduction in the number of measles cases. The occurrence of outbreaks in the late 1980s led to the two dose recommendation in 1989.

And it was really a combination of factors including the school based program the implementation of the vaccine for children's program which increased access to MMR vaccine. And a concerted efforts with other countries in the region to reduce measles through vaccination programs that ultimately led to elimination being declared in the US in 2000.

So it is important to note that elimination which includes which is interruption of year round transmission does not imply zero incidence. The epidemiology of measles during elimination is characterized by importations from endemic areas as well as limited spread among non immune persons. The US has been able to maintain elimination because of the high vaccination coverage greater than 90 percent for two doses of MMR as well as a strong public health response to each case, which of course, is quite resource intensive.

So this graph shows the number of reported measles assays shown by the blue bars using the left axis. Your let axis yea. The incidence which is shown in the yellow line using

the right axis. As you can see there is year to year variability in the number and incidence of measles. There is no cyclical pattern which would be consistent with elimination. And 2014 was one of our peak years that was primarily by a large outbreak in an under immunized Amish community in Minnesota. You also recall that there was the Disneyland outbreak and that started towards the end of 2015 - 2014 and into 2015. This led to spread to eight different states in addition to California as well as exportations into Canada and Mexico. The other thing that you can't really see here is that there is actually then a significant increase in the trend and incidence since 2000. I am going to come back to that in a couple of slides.

Measles really has been reported pretty much anywhere in the US. The incidence is highest where there is one dense population. Usually those are more likely on the coasts where there are major ports of entry and also where there are pockets of susceptible person in these densely populated areas.

This table is looking at the number of

incidents and vaccination status of measles cases by age group from 2001 to June 2017. All of the data that I am going to present will be within that time period. The first thing you will see is that infants, 6 to 11 months of age are at highest risk in the US. This is due to them being too young to be vaccinated, but also because of waning maternal antibody. The second highest incidence group are the 12 to 15 month olds and these infants are actually recommended to get vaccines. It is important the sort of highlights the importance of getting these infants vaccinated closer to 12 months of age and not waiting until they are 15 months of age. And then if you sort of look down at our third column you will see that incidence decreased by age. I also just want to point out that it has been really challenging to document vaccination status in adults. For adults that are 30 plus almost half of them we cannot confirm vaccination status and this is really a critical piece of information that you want to ascertain really in any measles case, but certainly in an elimination setting. The reported measles cases among high risk people 36 cases were in infants

less than six months of age. Seven cases were in pregnant women and only seven cases were among immuno compromised persons. This is among 2,215 cases during that entire time period.

This would include your solid organ and bone marrow transplant patients, your primary immuno deficiency patients as well as those with rheumatologic conditions on immuno modulators. Considering how highly contagious measles is and the highly contagious measles is as well as the limited spread that we are seeing it really is a testament to how highly successful our vaccination program is.

This slide is looking at the number of measles outbreaks which is defined as three or more cases, same time period. There have been 117 outbreaks reported in those 17 -

years. Again, you will see there is variability in the number of outbreaks reported year to year with 2014 being again a peak year similar to a number of incidence. There were actually 23 outbreaks reported that year. All of them were linked to an ongoing outbreak in the Philippines including Disneyland as well as the

large outbreak among the Amish.

Here is the we are looking at the distribution of outbreak sizes. The number of chains looking at the blue bars and using the left axis and the proportion of each of those listed chain sizes at the bottom here among all chain sizes by the yellow line.

The main point I want to make here is that 70 percent of all of the cases are just single cases so those 117 just so I can orient you a little bit more the 117 outbreaks which are three or more that would be distributed within these other chain sizes here and then we have our single and two size chain cases and again, 70 percent of them are limited to just single cases. This really supports how high population immunity is limiting spread as well as the size of these outbreaks in the US.

I mentioned earlier that we had been seeing an increasing trend in our incidence and this is partly due to increasing global travel patterns. But that are importing into the US, but then these importations are spreading into our pockets of susceptible hosts. This slide

just goes through some of the figures that we have in terms of importation. 26 percent of cases are directly imported from outside the US, so they get measles outside and then they develop symptoms in the US. 39 percent are acquired measles in the US, but they have been epidemiologically linked to an imported case. 16 percent are import virus only so these cases acquired measles in the US, but there is no known source or travel outside of the US. The genotype, however, is consistent with acquisition outside of the US. And then 13 percent are import virus linked. Again, acquired in the US, but now linked to a case with the genotype. These are the case patients that we don't have a genotype on, we don't have a source on we don't have a travel history on. But they are known to be linked to this category up here. And then 6 percent we just don't know where they got measles.

If we look at measles importations by WHO region there is really basically wherever there is endemic disease they can import into the US. One, there is not any single region that is importing disproportionately higher than another

region. And secondly, you can see that there is variability sort of year to year which region we are getting cases from.

This question we get a lot - who is bringing measles into the United States? What we are finding is that it is US residents traveling abroad and not foreign visitors that are responsible for 62 percent of direct importations. And this is really important as we counsel our providers in raising an increased awareness because I don't think we are doing a good enough job in providing guidance to our patients to remind them of their travel recommendations when they do to abroad.

This is looking at the global distribution of measles genotypes. This is just for 2016. And what you can see is that it is over here B3 and D8 are the main genotypes that are imported into the US in 2016. But if you look at the rest of the world B3 and D8 are pretty much everywhere as well. It has really been hard to determine which genotype that we are getting cases from, which countries that we are importing cases from.



I just want a couple of slides on sort of prevalence data. These are both studies are done through the National Health and Nutrition Examination Surveys, which estimate measles prevalence using US population estimates. The first study you may all be familiar with was done SERA collected from 1999 to 2004 through (inaudible) and the overall sort of prevalence was 95.9 percent. And whether you looked at this by either birth cohort or by race or ethnicity there was some variability. But in general, the sort of prevalence remained high.

And then the second study was in 2009 to 10 where an overall SERA prevalence was 92 percent. The third line here was the measles prevalence rates. And again, whether you looked at it by different race or ethnicity or by different birth cohorts it still remained relatively high. I think it is important to note especially for this conference that there has been a decrease within those 10 years. So we have been sort of talking internally. I think we may be due for another SERA prevalent survey.

And then, just the last section on

control and prevention. Certainly isolation of cases while they are infectious up to four days post rash onset is critical in limiting measles spread, quarantine and actively monitoring exposed individuals that do not have presumptive immunity is also important. Post exposure prophylaxis which would include MMR within 72 hours of exposure or immuno globulin within six days of exposure - and health departments often get really overwhelmed when they even just get a single case of measles. And so we do try to provide support in helping them prioritize who should be getting help, your infants, your immuno compromised hosts as well as your pregnant women that do not have evidence of immunity.

The next speaker, Mark, is going to be talking at a lot more length about immuno globulin peps I will just briefly summarize that for measles pep we are really just thinking IGIM and IGIV and this is given for IGIM for infants less than

months and for infants that are 6 to 11 months they can actually also - not also, but get instead vaccine. For others it is really

optional. We try to reserve these to high risk settings. There are obviously volume limitations so IGIM really shouldn't be given or would provide only sub optimal protection if you weight more than 30 kilos. And then IGIV for either the severely immuno compromised persons or pregnant women is recommended.

Some considerations after receipt of immuno globulin. One is that if you are a healthcare worker you should not be returning to the healthcare setting. Again, immuno globulin is given to protect the host that received it. It is not used to prevent transmission.

There are certain other settings where you may want to consider limiting returning back to that setting and those factors you want to consider are the immune status of the population you would be re-entering into. The intensity of the contact that you will be having and whether there are high risk persons such as immuno compromised hosts in those settings.

If you do get pep you may need to get MMR vaccine depending on your situation or your clinical status. But that should be no earlier

than six months after IGIM and no earlier than eight months after IGIV. Immuno globulin can prolong the incubation period of measles and so it is important to monitor for signs and symptoms for at least 28 days. Our health department often forget they are thinking 21 days, so it is important to remind them that you need to monitor for at least

days after immunoglobulin. In summary, the global incidence of measles has decreased substantially since 2000. The number of incidence of measles remains low in the US, but infants continue to be at highest risk. High population immunity is a major factor in decreasing risk of transmission particularly high risk person such as immuno compromised hosts and there is a rapid public health response to each case. Measles serum prevalence is still high, but has decreased from the early 2000s to the late 2000s.

And just this is my last slide, just to have some - think about some of the challenges we still have with measles control. One is that there is still heterogeneity in coverage so

outbreaks tend to reveal sub populations of accumulating n aging susceptibility. There is also diversity of susceptible groups. We often think of you know the community like the Amish which do not vaccinate or the vaccine hesitancy groups in California, but there are actually other groups too. Last year there was an outbreak in Tennessee and there was concern it would be spread into part of the city that was more of the inner city population because some of these kids even though there is a school mandate they still fall through the cracks. An access issue.

As long as there is measles elsewhere in the country there will be measles in the US. I mentioned this about the importance of travel recommendations. I can't over emphasize because this is really how we are getting measles into the US> We want to protect our PIPD patients we want to do better job of recommending travel vaccination as healthy people go abroad.

Measles is resource intensive for any of you that work in public health It diverse resources, creates mission fatigue and so providing support to our health departments are

working extraordinary lengths to limit transmission and maintaining elimination in the US is really important. The early diagnosis of initial cases is also critical so keeping measles in your differential diagnosis of fibril rash illnesses. Ascertaining travel and vaccination history and then obtaining the proper specimens for testing early in the case either in the case certainly early in the outbreak.

I'd like to acknowledge the measles team at CDC and I can't say enough about our state health departments that keep us in elimination. Thanks very much.

DR. SCOTT: Thank you very much, Dr. Patel, for very interesting talk. We have three more minutes, so if there are any questions from the audience, Dr. Goulding, please.

DR. GOULDING: Yes, so that is obviously very interesting and related to what we're talking about today, but I'm wondering if we should also besides being worried about the PID population we should also start worrying about the general population, the healthy people? And the reasons I'm saying that or asking that to you

is the titers are decreasing. We know that. The titers may not - may reach a point where they may not be sufficient to provide immune globulin. But if the titers are decreasing in the immune globulin it means the titers are decreasing in the population.

I'm also concerned about the waning of antibody titers with age. So what you explained is that the first vaccines were given in the 60s so people today they have got those vaccines are reaching the age of 60 and my question is do you have data with all the people? And the other thing that you indicated was the fact that the virus is being brought to this country by travelers. Well were those travelers vaccinated? Did they have infections? What were their titers? And the fact that they are going overseas and picking up the virus if they were vaccinated then I'd be additionally worried that the vaccination is starting to wane in those people maybe all the travelers.

I will finish off by asking you if there are any plans to boost in all the people if there are antibody titers waning should we be thinking

about giving them another vaccine? All of this, of course, would help the development of donors that have higher titers for immune globulin.

DR. PATEL: No those are all really relevant points you brought up. I think there is a couple of things that we need to do. One, aside from the titers decreasing not just from the SERA prevalence surveys, but like you mentioned immunoglobulin products I think it might be time to do another SERA prevalence study to better understand what the titers are in the US population and different age groups. I also mention that incidence has been increasing which is concerning. And it is hard to tell exactly why again I mention direct importations what we are not really saying are that many cases in adults. And if you remember the incidence in our adult population is actually quite low. That doesn't mean that we shouldn't be thinking ahead and thinking about what should be done, but I think initially we need to do some further evaluations to determine if an additional dose is needed.

The ACIP just recommended two weeks ago a third dose for mumps outbreak control. That's



for mumps specifically because we do have waning titers. We know that these are fully vaccinated people. The direct importations we are seeing most of the cases in adults are the ones like I mentioned they are either unvaccinated or we don't know what their vaccination status is. Again, importance of really able to ascertain all of the different data elements before we would go on to do another recommendation for a vaccine dose. I appreciate - all of the comments really helpful though.

DR. SCOTT: Thank you very much. I am afraid we are out of time, so those who wanted to ask questions keep them for the end of the session. Thank you very much.

SPEAKER: We may have an opportunity to ask questions during the Q&A. I'm going to introduce the next speaker. Mark Prapannea with the CDC the title of his presentation is Passive Immuno Therapy for Measles, protect levels and pharmacokinetics of measles antibodies after immuno globulin infusion. Pathogenesis of measles in primary immune deficient patients.

MARK PAPANIA: Thank you. Good morning,

all. So, I work on the global - the global measles elimination team, so don't specifically work in Dr. Patel's group that works more on the domestic side. But I'm delighted to be here. I appreciate the opportunity to talk to you and the invitation from the organizers.

I think one of the kind of a specifically relevant point to the last question is that cellular and mucosal immunity are both effective in protection against measles and this is demonstrated has been long demonstrated by the fact that measles can be prevented by passive antibody administration. But also that children with primary agammaglobulinemia do not tend to have more severe measles in persons with normal immunity. This indicates that there is more than antibody that is really relevant in protection against measles and I think that when we look at - when we look at these SERA prevalence studies we are typically, the studies that Dr. Patel were mentioning were not looking at - first of all, they're not looking at titers. You are more looking at the percent of the population that has ELISA documented antibody and not the titers.

But also being SERA negative doesn't mean that you're not necessarily immune. So, there is some proportion of the population that don't have documented antibody by these tests, but still may be immune.

Historically, the evolution of use of immune globulin in measles prevention back in 1926 people started using convalescent blood products, whole blood, serum or plasma from patients who had recuperated from measles. And Zinger showed that this tended to decrease the measles attack rate. And this was widely used in the 1920s and 1930s as the method of preventing measles in people that were exposed to measles.

In the 1940s Janeway found that IGM given within six days of measles exposure significantly reduced the attack rate and IGM at that time replaced all the other blood products for post exposure prophylaxis. Dr. Scott gave a very -- an excellent review of the adaptation of the regulations for use of IGM. So I won't go into that.

The current products in the immune globulin. I know we are focusing mostly on IGIV

here, but immune globulins are blood products that provide antibodies for the short term prevention of some infectious diseases including measles and they're prepared from plasma pools derived from thousands of donors and you know, make a specific distinction between pre exposure prophylaxis against measles and other disease that is provided to persons with immuno deficiency frequent administration of immune globulin that is given IV or subcutaneously in post exposure prophylaxis, which is specifically had been given mostly with IGIM but more recently we have been using IGIV as recommended by the ACIP as persons who have been exposed to measles and are at risk for severe disease and complications.

So, IGIV has been available since 1981. There are products currently licensed. The major indication is

prevention of common infectious diseases in more than 50,000 patients with primary immuno deficiency disorders, but there are many off label uses. The recommended dose range is from 200 to 800 mg per kg and typically given every three to four weeks. Some IGIV

labels recommend post exposure prophylaxis in patients with primary humoral immunodeficiency at a dose of 400mg per kg but that is not consistent across all of the products. And just a note about the cost in 2007 there was a study on the cots and the average cost of their products was \$55 per gram. Or a 400mg dose for a 10kg child that would be \$220 per dose and for a 70kg adult it would be over \$1500 per dose.

Immune globulin given subcutaneously has been available since 2006. There are four products currently licensed. And the major indication again is for primary immuno deficiency the benefit is that the subcutaneous administration avoids the need for veinous access. The subcutaneous administration does require a pump and advanced training. Recommended dosages range from 100 to 200mg per kg given weekly by subcutaneous infusion at 15mls per hour with separate sites for volumes more than 15mls. For subcu multiple consecutive weekly doses are needed to establish a steady state protective antibody levels.

The current ACIP MMR recommendations

for post exposure prophylaxis and these - I will go into some of the slight changes that were given - were made in 2013 revision based on the declining titers in IG products. First of all, as Dr. Patel had mentioned the preferred post exposure prophylaxis for vaccine eligible persons with measles mumps rubella vaccine given within 72 hours of exposure for anyone over 12 months of age. The other recommendation is that a high risk patient should receive IG within six days of post exposure. Infants, that are less than 12 months of age should receive IGIM given at a dose of .5mg per kg body weight and this is - this was a new recommendation in the most recent ACIP recommendations because the - one of the components of declining antibody titers in the population as Dr. Patel had mentioned was infants are more susceptible. The prior recommendation didn't recommend IGIM for patients less than six months of age. But this recommendation changed so that all infants that have been exposed to measles should receive IGIM.

The second recommendation for high risk patients is for pregnant women without evidence

of measles immunity should receive IGIV and 400mg per kg and also severely immunocompromised person should receive IGIV at 400mg per kg. Prior to this change in the recommendations all of the past exposure prophylaxis was recommended to be given as IGIM and we realize that the doses that were being - the titers that were being achieved were not sufficient for people over 30kg so this was - this change was made for pregnant women and severely immuno compromised to receive IGIV.

The ACIP states that the post exposure prophylaxis is not necessary for patients that are already on pre-exposure IGIV of at least 400mg per kg given within three weeks before exposure or at least 200mg per kg of IGSC for two consecutive weeks before exposure. That should be sufficient to prevent measles infection. You would just continue with that dosing and not need to give an additional dose on top of that.

As Dr. Patel also mentioned the maximum of the IGIM can be given to other persons that don't have evidence of measles immunity, but should be prioritizing those with intense prolonged exposure. And we need to recognize

that people that weight over 30kg are going to receive less than a recommended dose and have lower titers recommended.

I will go through some there aren't a lot of studies. Probably more data in industry than there are published studies in terms of the - effectiveness of post exposure prophylaxis, but there are a handful of studies out there. There was a study in 1990 in a neonatal ICU in Ohio and 21 infants had post exposure titers that were - 21 infants had titers tested after exposure. They were given pep with gamostan at .25 mg per kg and a second blood sample was taken. Of the 15 infants that were initially SERA negative only two were SERA positive at 48 hours and two with initial equivocal titers became SERA positive. In terms of ELISA testing there wasn't evidence of much impact of the delivery of post exposure prophylaxis with IGIM. None of the patients developed measles. I think the exposure was pretty limited.

During the 1989 to 1991 measles resurgence in California there was a retrospective attack secondary attack rate study



of unvaccinated household contacts who were less than one month of age to 22 years of age. The attack rate was

percent in children who did not receive IGIM and 60 percent in children who did receive IGIM within six days post exposure. The effectiveness was only 8 percent. However, the doses were not recorded, so we don't really know what dose was given. This was all with IGIM.

In a study in Japan (inaudible) looked at - this is really one of the stronger studies because they were able to look at the not only do they have control of the doses, but they looked at the lot titers. So there were 33 unvaccinated infants that were given IGIM at .33 mg per kg within five days of exposure and they tested neutralizing antibody concentrations in the IGIM lots. The attack rates were 57 percent among infants given IGIM from lots with 16 international units per ml. 1.6 or 17 percent among those given IGIM with 11 international units basically gave them a dose of 11 international units per kg and the attack rate was zero among those given with 40 or 45 international

units per ml. Definitely dose reduction there.

So overall, the protected children received a mean dose of 11 international units per kg and those for whom pep failed received a dose of 5.7 international units per kg.

In the New South Wales measles outbreak there is 157 cases. They looked at 553 exposed patients who were in the same room as the confirmed and they were given .2mg per kg of IGIM. Estimated concentration was 32 international units per kg and the attack rate was 4.5 percent without post exposure prophylaxis and .8 so overall a protective efficacy of 76 percent. Within six days when the pep was given within six days the effectiveness was 100 percent.

So as Dr. Scott mentioned earlier, the FDA requires that all US licensed IGs contain measles antibody titers and she mentioned that the titer for IGIV has - is now .8 of the referenced standard. As I understand it the titer for the minimum standard is .6 of the reference standard for IGIM.

As we are all aware the plasma from donor populations is with predominantly vaccine

induced immunity shields lower antibody concentrations and this has made it difficult to obtain the required titers for IGIV on IGSC lots. However, as has been noted before you can give much higher volumes of IG by IV and subcutaneous compared to IM. There is this limitation of 15 mls given IGIM and given IGIF IM.

As Dr. Scott mentioned in 2007 the requirement was lowered for IGIV and she went through some of the calculations to provide - to go over the at a minimum label recommended dose of 200mg per kg that would provide measles antibody titer of 120, which is considered protective for 28 to 30 days. She mentioned that basically, the suggestion was that so the dose should be 400mg per kg to achieve a titer of double the protective titer 240 international units per ml. The IGIM minimum titer was not changed. When all of these studies were done we decided it would be worthwhile to repeat the pharmacokinetics calculations for the IGIM at the currently recommended doses because these calculations we had been using the standard requirement and I don't - -we went back and

couldn't find that those calculations had ever been done.

And so the e looked at the - we looked at the US minimum antibody dose for various products and the original ACIP recommendations added a dose of .25 mg per ml per kg for normal patients who didn't have immuno compromised and then .5 for those who were at higher risk. You can see that these would give doses in the antibody dose for 70kg person would be very low. 5.4 international units per kg for 70mg and it doesn't really depend - it is kind of the same regardless of the - because you are working with the 15ml maximum dose you end up with the same lower dose.

With IGIV with the current minimums you would be getting 12 international units per kg and that increased if you are giving 100mg per kg you would be giving 12 international units per kg at 200 would be 24 international units per kg. At 400 it would be 48. Using the same pharmacokinetic calculations we came up with the trough titers if you are giving - and this is for a 30kg - this is for somebody that weighted 30kg

even with the - even with that small sized person the trough titers for IGIM at .25mls per kg would be 32 and only the peak titer was above the protective level. For the .5mg per kg dose at equilibrium you would still be above protected, but the trough titer was still low and you were able to get much higher titers with IGIV and especially this I kind of the calculation that Dr. Scott had mentioned your trough titer at 400mg per kg would be 250 or two times the protective level even at 200mg per kg she had a trough titer of 120.

This is just a graph showing the effect of the basically, this is the 3kg cut off which would give you the 15 ml maximum dose. After that the titers for IGIM after IGI post exposure prophylaxis drop of significantly and are only above this protective titer at peak for most weights.

Those specific issues for consideration you know, basically some of the things that Dr. Scot mentioned, decrease in the minimum lot release titers could be offset by increasing the dose volume. IGIM is - would not be useful I mean if there were any decrease in IGIM

titers it would not be useful outside of infancy and infant dose volumes would probably need to be increased. That would be advisable in any case. The IGIV doses of 400mg could still potentially give protective trough titers at 28 days meaning titers above 120 if we weren't insisting on getting titers up to 240. And also the titers maybe more stable with IGSC due to the dose frequency you don't have the big trough differences.

We have been mostly working with modeled and estimated antibody titers for peak equilibrium trough and it would be very helpful to see these validated clinically. Hopefully, we will be seeing some of those doses. Of course, we need to consider the economic implications of the changes if we are going to basically if we release the - if we reduce the minimum titer and that causes an increase in the volume required and the prices based on volume you could have a significant impact on the cost of the delivery of these. I wanted to thank Judy Baylor and Suzette Odette and CEBR viral products help us prepare this for ACIP back in 2012 and so did Dr. Scott

so thanks so much.

We have 32 seconds for questions. Maybe we can sneak one fast one in or we can wait until we have the Q&A period later. Is it fast? Okay.

JIMMY MOND: Is it possible that as the antibody titers wane that t-cell immunity in these individuals are increased in view of the fact that there are so many more vaccines and more came out in the last 15 years possibly their chronic exposure to antigens may enhance their t-cell immunity. Some non specific, some specific. Might be interesting to see if those have low antibody titers maybe they have very high t-cell immunity to measles.

SPEAKER: That's a good question. I have no idea.

SPEAKER: Can I get a 10 second? I am concerned about this idea that cell mediated immunity might be great in some patients with immune deficiency. The margin that Dr. Scott spoke about was doubling of 120 to 240 for immune deficient patients. I would like other immunologists especially treaters to comment on the fact that I thin many people with immune

deficiency that require immune globulin also have t-cell deficiencies particularly those with common variable. I am not sure that we can allow - get away from the margin of safety that Dr. Scott was talking.

SPEAKER: It sounds like a comment, and I agree with.

DR. SCOTT: We can discuss that again in the Q&A.

DOMINICA MAHESHTALA: With this, I would like to introduce the next speaker, Dr. Toby Simon. Dr. Toby Simon is the Senior Medical Director for plasma product development and CSL plasma at CSL Behring. And I think his CV is quite considerable including writing more than 100 original and review articles and book chapters on principals of transfusion medicine. And Dr. Simon will speak about measles antibodies in donor plasma, longitudinal data and forecast. Dr. Simon?

DR. SIMON: Good morning. Obviously we're very concerned about these titers and so I'll give you some of our most recent data and compare it to the prior data. I think we've



reviewed these important years and so I'll proceed through.

And we've also talked about the fact that antibody titers that are elicited by vaccination decline over time as do those elicited by natural infection and may become undetectable. And vaccine induced antibody titers are typically lower than those induced by natural infection, and of course, that's what brings us to this issue that we deal with.

Of a screening assay that we have used, one is the ELISA method, which is not the one we use for product release. But we'll see some of our data with that initially and then with the neutralization antibody. And so we use an internal calibrator reporting range and so this gives you a little data on that particular assay.

We also, back in 2007, impaired the enzyme amino assay and the viral neutralization assay, which is done for release by testing many pools based on statistical analysis. The viral neutralization or functional assay was calibrated against the third WHO standard 21 IU/mL anti-measles activity. And at that time we

tested five aliquots in each mini-pool.

So this is our 2007 data that was presented at the prior workshop. And what you can see if you look at the birth year, those born before 1967 had fairly good IU/mL of around four and then this dropped off fairly rapidly. In our younger donors, particularly, had sort of flat line at much lower level of around -- a little bit above 1 IU/mL.

And we compared this with the enzyme amino assay with both the mean and the same values retesting the mini- pool. And the EI is a much less sensitive, so it gives lower levels because many of the donors will have absent activity with the enzyme amino assay but still measured by the more sensitive neutralization assay. But basically the two assays follow the same pattern.

So based on our snapshot, which at that time was over 4,000 donors and 3 snapshots in 2006 and 2007, and we had specific birth years for the enzyme amino assay. So again focusing on these key years of 1963 when the vaccine was licensed, and then by 1967 we have sufficient penetrants in the population so that all the donors donated

after that have a pretty consistent mean lower level.

And so this was the problem that we addressed back there, back at that time. So now we have done two additional donors snapshots, so here's the original 2007 data, 2011, and then 2017 data that was done about -- collections from about 2 months ago. So this is the age group, not the birthdate. So you can see now that it's only the donors above the age of 50 that have an elevated level. And otherwise our forecast has come true that all the donors age 50 and below are at a relatively low level. And it's fairly consistent except the suggestion of a little bit of increase in our youngest donors, which would be possibly due to being had the vaccination more recently. And with less waning of the titer or this may be -- this is still within the standard deviation so there may in fact be no real difference.

So back in 2007 we had -- it was sort of, donors that were 40 and over that had good levels and then those declined about 40 years later. And now 10 years later we only have this

group that's about age 50 and over. And in our snapshot that's 24 percent of the more than 1,000 donors that we looked at from 24 different donor centers in 2011.

And if we look at our overall marketing data, about percent of our donors are age 45 and above. So less than a

quarter of the donors now will be in this age group with probably natural immunity that's increased over what we see in the vaccine induced immunity.

The EIA results, of course, are lower because of the decreased sensitivity of the assay, but pretty much tell the same story. So our forecast has come true so to speak and this, again, is taking the birth year so we're using the EIA data and the same critical birthdates. Nineteen sixty-seven, after that birthdate donors fluctuated somewhat, but are at a lower level. Between 67 and 63, when the vaccine was licensed, we have a somewhat higher level. And then those born before 1963 with no vaccine licensed, we have this higher level of immunity.

So for our higher activity in the

product, we're really dependent on this diminishing group of older donors. And so one would predict that sometime in the next 5 to 10 years our pattern will really be this one all the way but this will be the entire group of donors that will have providing plasma for Immune Globulin products.

So in summary in the snapshot, 24 percent of the donors were ages 50 or older, current overall marketing data indicates that about 28 percent of donors are 55 or older and though we don't have data from all the companies we think this is pretty representative in the United States. And keep in mind that our source plasma donors are constituting more than

percent of the total plasma available for pools. So the recovered plasma donors that might be at a slightly higher level with older donors and less decline with frequent donation are a very small part of the pool available for the product.

So our current data, I would suggest on donors age to 49 represents the forecast for the levels for measles

antibody titers in the near future and one would guess in the next 5 to 10 years, that's the level that we'll see. So in the next decade measles antibody titers will reach a steady state at a new lower level.

So of course the concern is what is the level and the product and how does that effect protection of the patients? And before I get into that I'll just acknowledge those who helped with the snapshot: Mirjam Kühne was in charge of the neutralization assay's I think performed for all three snapshots at CSL Behring in Bern and she is here at the conference if we have some specific questions about that assay. Peter Fitzgerald was in charge of sorting the samples and EIA assays at our laboratory in Knoxville, Tennessee. Keith Bycholski assisted with the design of the 2017 snapshot and the data analysis and John Knolls and Connie Farr in charge of our laboratory in Knoxville provided the support and oversight.

And I'll just briefly show you information that was presented for the most part in 2007. This was an analysis of anti-measles antibody in primary immunodeficiency patients in

a clinical trial that was conducted. And this analysis was done by Othmar Zenker, who is no longer with our company so I've taken his report and will present some of the data for you.

And to recapitulate that serum titer of 0.12 IU/mL has been associated with protection against measles disease in healthy vaccinated individuals. But for the purposes of this study he assumed that primary immunodeficiency patients might need a higher level and it was suggest it might be 0.24 IU/mL or double the other levels shown.

And he studies 18 subjects who were chosen arbitrarily; they were receiving subcutaneous immune globulin. So he selected steady state and used both the ELISA and Measles Neutralization Tests and the samples weren't started until there was at least 12 weeks of treatment to get to a steady state. He had the lot potency values to calculate the measles specific doses and then he calculated the hypothetical serum antibody concentrations. If you lowered the expectable limit and this is the shrinking analysis that Dr. Scott referred to.

And the characteristics of the patients are shown here. Most of them have common variable immunodeficiency. There was one ex-related deficiency and most of them were female in this study and they offered a wide range of age's but mostly adult -- in the adult category. Mostly white Americans with about 76 kilogram weight. And he looked at their troth levels as well, which are somewhat variable.

And the manufacturing lots that were administered to these patients had the potency shown here. So this was the days of the higher potencies and the lots so they varied from .6 to 1.4 times the U.S. reference standard. And these were the data that was actually shown for the patience so he's drawn this minimum protective level. And with the lots shown this is the dose that was given and the titer that they achieved and it was somewhat variable but even at the lowest specific dose, all the patients were well protected using this assumption of protection.

And then he did the shrinking analysis to the 0.48, which was selected by the FDA at that time as the new lot release limit. And you can



see once again the patients are fairly well protected above this minimum level. And then he carried this out to the 0.3 that we would presumably be considering now with the lowering levels in the donors. And while some of the ones -- the patients who got the lower specific doses are getting somewhat close to this line, the patients still seem to be protected at this lower level of dose.

So he concluded that variations of individual dosing as well as variability of kinetics among subjects requires the higher minimum allotment potency in order to safely maintain immunodeficiency subjects above protected levels. But with a minimum lot potency of 0.3 times the CBER Standard, this variability would still allow the vast majority of subjects to stay above the desired protected level with a dose of 100 mg/kg weekly subcutaneously.

So I thought I would just make a few additional points. One is that at least we do not make a clinical claim for protection against measles with the product. And the measles antibody level, keeping in mind that that is a lot

release specification and not an indicator of clinical efficacy.

But we of course are concerned about our patients and their well-being and their protection and therefore we support the public health efforts that we've heard about to achieve the universal vaccination, which we think is ultimately the most important protection. And I think it's worthwhile for those people or those parents who are withholding a vaccination for their children for various reasons, to make sure that they know that they're putting immune suppressed patients at risk for measles, as well as other diseases by not vaccinating their children. And this is just the way in which we did the calculation, which we can discuss if need be. Unfortunately the statistician who did this is now retired and Dr. Zenker's not with us so I can just present what he did in 2007 for your consideration. Thank you.

DR. BALLOW: So I have a question; I have a comment. I guess I should say who I am. Mark Ballow, USF for the transcription. I noticed that the troth level, this is a subcu

study.

DR. SIMON: Yes.

DR. BALLOW: And the troth level was very high. It was about 1200 --

DR. SIMON: He's really using where they hit a steady state --

DR. BALLOW: They maintained a steady state --

DR. SIMON: Yes.

DR. BALLOW: After so many weeks so about 1200 milligrams per deciliter. Obviously it reaches that high because there's an adjustment factor that's used and giving subcu. So I'm not sure how much of that is real world, you know, and in my realm as a clinical immunologist I don't often achieve that kind of serum level unless on purpose. I increase the dose of either IV or subcu Immune Globulin Replacement Therapy whom most of the, either steady state or troth depending on whether it's IV or subcu, is somewhere around 750, 800 maybe 850. So even though protection was achieved, I want to just point out the audience that that 1200 milligrams per deciliter is very high.

DR. MISZTELA: Another question, yes. Maybe it was a comment, Dr. Simon. Can you comment on this?

DR. SIMON: Well, I mean the study was done back in 2009 so I think that was the way he constructed it. So he took data from a clinical trial that was used for Hizentra for the licensure so the subjects who were in the PK part of the study and then continued on the efficacy part of the study.

DR. BALLOW: I know, but I'm just saying because we're all worried about the waning measles antibody titers in the product. Is that even though those results are encouraging the levels of serum troth levels achieved is not what we generally see out there in the real world.

DR. SHEARER: Can I make a comment, please? My name is Shearer from Baylor College of Medicine. Every clinical immunologist who deals with transplantation is faced with the question of when to restore to children to the vaccine program including my continuator virus.

To a person there's never (inaudible) of opinion willing to go head and harm the

patience, which theoretically we could. Most people say, my gosh and by golly it looks like your immune system is restored and lets go ahead. That may be well and good but there's going to be a day when cellular immunology seems more important so I think in these viral infections. So I guess my comment is really directed to who will we have a definitive statement about the role of cellular immunology in such patience that I just quoted. Thank you.

DR. MISZTELA: Thank you for this comment. Any other questions or comments from the audience? Yes, please. Identify yourself.

DR. SORENSON: Ricardo Sorenson, New Orleans. This is for Dr. Ballow to and for anybody. I have never heard about anybody getting any dose of gamma globulin of the modern time 400 milligrams or above developing measles. And nobody has reported and some lists where everybody who makes a funny observation about something sends it there. Anybody knows any patient that got measles while on gamma globulin because that makes this whole discussion about what the exact level is that you need to achieve

a little less relevant, I mean.

DR. SIMON: Yes, you know, I know this was discussed back in 2007 as it is today. And I think from the communities point of view, and we'll hear more about it, I know one of the concerns is they want their patients to be able to travel. So there concerned when the patient's travel to these areas where there isn't a universal vaccination. So I think that's one and of course they're also concerned about the exposure that may occur here in the U.S. when there's an outbreak.

DR. BALLOW: So Ricardo, so the some of the data presented back in 2007 at the previous workshop showed that a dose of this is IV now 400 milligrams per kilo, was able to achieve at least a protective level of 240, right Don? From what I remember.

But that's back in 2007 when we had, you know, donors that had natural measles that had obviously contributed to the donor pool, higher levels of antibody-measles in it, but now we're getting towards, what you're saying, is a steady stain level much lower because those 50 year olds

and above are going to disappear from the donor pool. So the question is, going forward, you know, what is the appropriate dose? Is it still 400 milligrams per kilo? Or do we have to modify that and perhaps consider a higher dose?

DR. SCOTT: Well, we can talk about it more in the discussion section but basically all of the products currently still maintain that .48 times CBER standard. Which was what was calculated for 400 mgs per kg to reach at 240 MIU per mil troth level for IVIG.

One other point, about has anyone seen a case of measles in a primary immune deficient patients? I know that an immunosuppressed patient was reported before but Dr. Patel showed us that at least one primary immune deficient patient got measles in one of the outbreaks. And perhaps we can get more information about that patient, if it is available, in the discussion. We're not aware of any reports but that doesn't mean there aren't any cases out there.

DR. MISZTELA: Thank you very much.  
Dr. Simon.

DR. SIMON: Let me introduce the

speaker. Peter Vandenberg who is R and D Project Director at Grifols in North Carolina. His extensive experience in the plasma protein industry and the title of his talk is measles antibody trough levels after immune globulin treatment theoretical values assuming lower measles specifications. Kind of related to our recent discussion.

DR. SCOTT: Just to say that we will endeavor to have a copy of this presentation available tomorrow. I'm sorry we didn't get a chance to copy.

DR. VANDEBERG: I would like to thank the organizers for the opportunity to present this study. I'm going to present some results from a fairly recent clinical study where we measured measles titers in the patients and then do some of the shrinking analysis.

Just some very simple mathematical modeling based on those results. What if we change the levels, you know, what could the levels be? This study was an open label, single sequence crossover study to evaluate the PK safety and tolerability of subcu in pediatric



subjects with PID.

It is published. It was published in 2016 in the Journal of Clinical Immunology. And the study was a fittage for multi-center study in pediatrics, ages 2 to 16 with PID and it involved both IV and subcu infusions so we got to evaluate both of them; both types of infusion.

The dosage and the protocol listed 200 to 600mg per kg per infusion of the SC and the 1.37 factor was used for the subcu dosing. We have the results from the 10 subjects, which completed both phases and for which antibodies were measured at troth levels. In the actual doses used in the study were 300 to 600mg per kg.

Just to look at a little bit of the IGG data from the study, you see the typical profiles for the IV and the SQ at the -- sorry, subcutaneous administration the PK profiles. And the samples for the measles analysis were taken at the end of a treatment cycle before the next treatment was taken, so these would be the lowest levels that would be seen by the subjects. These are the actual results from the study.

I think I failed the mention from an

earlier slide, the testing done was a measles neutralization assay using the vero cell neutralization. The standard was the CBER standard but IU/mL per ml were calculated based on results based on a crossover study with the third international standard for measles antibodies. These results are listed in just arbitrary order. Probably the order the samples came into the lab. And there's no -- don't think there's a trend or anything; again these are just arbitrary results.

And you see both the IV results and the subcu results. The line drawn here, it is at the .12 IU/mL as you heard from comments and from earlier speakers maybe .24 IU/mL or 240 IU/mL is more appropriate in this population. Just for a yardstick to measure the results, I've calculated them all versus the .12 IU/mL level.

For the actual results we see that the IV patients had an average -- about a 11-fold increase above that .12 IU/mL level and the subcu results were, of course, a little bit higher as you would expect from the PK profile.

So in taking these results, I did a

little bit of the shrinking analysis. Just very simple linear modeling taking the first slide -- I looked at two cases, the first slide is what is the worst case now, the lowest dose, the lowest potency, what does that mean?

And the second case would be a future case. So this first case assumes the lowest dose.48 times the CBER reference. And then I looked at the actual dosing of the subjects and assumed a 300 mg per kg lowest dose. Now I know 200 mg per kg is mentioned by some but actually in the package inserts, the prescribing information for many of the products 300 mgs per kg is the lowest dose listed, and hence I used the 300 mg per kg.

So the results, if I shrink everything down were still 3.9 fold or 4.8 fold above the.12 IU/mL level. If you go to the.24 level then it's simply divide those numbers in half and they're about 2 or about 2 and a half above that level.

So the next case is what if we reduced the required potency down to.3 times the CBER reference. Again we saw from Dr. Simon how the levels in plasma donors are decreasing. This may

be something that needs to be done and just a simple linear adjustment of the results. And this case it shows the 400 mg per kg dose as mentioned earlier that was in updated CDC asap recommendation for persons receiving IGIV therapy that the administration of at least 400 mg per kg within 3 weeks before exposure should be sufficient to prevent measles infection.

So I selected these two factors as the lowest dose and as can be see, this would result in levels of .39 or .48 IU/mL which would still be 3.2 or 4 fold above the 1.2 level or about 1.6 and 2 fold above the 240 level on average.

So just to summarize the results, we saw in our actual study and these 2 cases the results observing the actual study were greater than 11-fold above this minimum protective level. And using these 2 cases and even going to down the .3 times the CBER reference, we would still see levels that would be above the minimum protective letters. And this is really my summary. This is a fairly small study but the results are what they are. I would like to just acknowledge the labs for doing the testing and the clinical group for

doing the study and thank you.

DR. SIMON: Yes, please identify yourself again for the transcription.

DR. MOND: I can do this all the time. ADMA Biologics, Jimmy Mond is my name. When you talk about the minimal protective level, does that assume a certain viral inoculum so that if one goes to a country where there's no immunity and the viral inoculum could be potentially high, that minimal protective level might change or be different?

DR. VANDEBERG: Yeah, that question is certainly beyond me. I mean that's more for the, I think the treaters and the CDC. Certainly I could see there'd be a heterogeneity in what would be required.

DR. PAPANIA: I can answer that to some degree but also I have a comment. So the minimal protective level is just kind of a standard that was originally derived from a --

SPEAKER: Can you say who you are, sir?

DR. PAPANIA: Mark Papania, CDC, sorry. A study in college students when that outbreak occurred after a blood drive at the

college. So they were able to go back into the -- get the blood specimens and measure titers before the outbreak occurred and they found this titer of 120 was protected from clinical disease.

We don't really have -- it was a small study and it's held true for, you know, it's been kind of our standard for 20 years and seems to be worthwhile but it doesn't really -- we haven't tested it in situations and certainly don't have a (inaudible) burdens.

So that's kind of the background of that titer. It's held true in mostly in primate studies is also seems to work very that titer; I've got anything wrong, Paul Rota can correct me.

But my comment was that the ACIP doesn't make recommendations for pre-exposure prophylaxis. They did recommend 400 milligrams per kilogram of IGIV for post exposure prophylaxis, but you used the ACIP recommendation there at, you know, basically what the recommendation was saying if a patient has received 400 milligrams per kilogram then they wouldn't need an additional dose.

It's not to say that -- I think it would

be very worthwhile to repeat that calculation with the minimum possible dose as you did for the earlier standard. If it's possible that patients are going to be getting 300 milligrams per kilogram, it'd be worth repeating the reduced dose CBER reference with that minimum dose to make sure that they -- they would obviously be more than two fold above the standard, but I think that would still be a worthwhile calculation.

DR. VANDEBERG: Yeah, thanks for the comment. I think the bullet item I have there is if it's not verbatim it's pretty close to what is in the recommendations, which basically what you said. I will note that at least in the Gamonex package insert we have adopted similar language to that and that's perhaps something that more of the manufacturers would be going to in the future.

DR. BALLOW: Any other questions? Just one comment and Mark Ballow for the transcription. So those are encouraging results. Is that, you know, given that those 400 mg per kilo and, you know, decreasing the potency down to .3 it looks like we can achieve at least a two fold level above the .24. So that's

encouraging. It may help us make decisions going forward. We may have some disagreement --

DR. MOND: One more point to that is it is encouraging but I think we should keep in mind that the protective level assumes that everything else in the immune system of that primary immune deficient patient is normal. If the encasels, the macrophages, the neutrophils, and T-cells are not normal then being two fold above or three fold above may not suffice.

DR. BALLOW: Yes, I agree. Can you use the microphone, please?

DR. HOULE: Martin Houle, Health Canada. My question is, so the data you are presenting is average and when we were looking at the actual troth levels and steady state levels and the graphs you presented, some of the patients had lower values. So did you calculate what it was for those worst-case patients as well?

DR. VANDEBERG: Yeah, I certainly did. I didn't present it here; I tried to add the standard deviation. But you know, you make a very good point that there's heterogeneity in the data. Every patient is not average.



DR. MISZTELA: (off mic)

DR. SORENSON: Yeah. Thank you. I was thinking about the immunization schedule and to why kids do not get the measles vaccine until 12 months because they are protected with what is low paternal antibodies that remain. And actually they are still sufficient to kill the vaccine virus. So it would be interesting to see how low an 11-month-old kid goes, you know.

And the immunization has been postponed for two reasons: because there is no measles before that unless there is immune deficiency and because the antibodies, the little amount of maternal antibodies still remaining, is sufficient to prevent a response to a live vaccine. So you know, it looks like from my point of view that you need really, a very small amount of antibodies to be protected in a normal person.

DR. MISZTELA: I think the correct thing to point out, in a normal, in a healthy individual. What happens in PID patients I guess has to be (inaudible). Yeah, you never know. Thank you very much. Thank you Dr. Vandenberg.

Then I invite the next speaker to come

to the podium. The next speaker is Dr. Thomas Kreil. He's the Senior Director for Global Passage and Safety at Shire and also Associate Professor of Virology at the University of Vienna. And in his role he also serves on the PPTA, Passage and Safety Steering Committee as the Chairman. Dr. Kreil.

And I forgot his presentation is going to be on one of the topics we mentioned about the use of the MLR vaccine to increase measles antibody titers in plasma donors.

DR. KREIL: All right, good morning everybody. Thanks to Misztela for the nice introduction and I really appreciate the opportunity to contribute to the discussion of this really important subject.

What I would like to discuss here is specifically the potential application of the MMR vaccine to increase measles antibody titers in plasma donors. And I hope already the title is not going to raise two high expectations.

So to refocus our discussion, this is really where all this discussion started, and that is when, in 2006, authors from the FDA wrote

out what, I think, was a seminal paper at the time. And what they showed was how over time different IVIG's that they've analyzed here and wide from sourced plasma. So this is very young donors and, here in shaded, from recovered plasma so they are donors typically from elevated age. So you would have more people who have gone through measles infection in those.

But generally speaking, the measles antibody titers in IG products did go down. Now a decrease -- we always want more, a decrease is something that carries a negative connotation, but in some ways also, I think, it is important to keep in mind that this is a reflection of a very successful public health intervention that has happened in this country. And that is, as we have heard, a greater 90 percent, I think, in measles incidents over the last 15 or 18 years or so. That's a very important thing because this also improves herd immunity and thus serves to, I think, reduce some of the dangers associated with the virus.

And this, I think, it is feared to project into the future is not going to get worse

either. In that measles eradication is one of the declared goals of the World Health Organization. Just accessed a few days ago, they still claim that by 2020 there will be eliminate measles in 5 of the 6 WHO regions. Now, whether that is too ambitious of a goal or not, I cannot tell. Looking at what they've done with polio, that we are going to discuss later, they have done a great job there. And I think it is fair to then extrapolate into the future, that it shouldn't get worse than what we have now.

And also in this country, the around 100 or so cases a year, I mean, this is less than 1 per million inhabitants so I think it's a fairly rare (inaudible) and I think these are important to keep in mind when discussing the subject.

Anyway, after that paper has come out there was all this illegitimate concern about the IVIG products and would they still do their job. And that was discussed first in a workshop actually quite similar to this, almost precisely 10 years ago, I think, it was April of 2007, and then followed up by a BPAC of 2007. And I've taken verbatim from the transcripts some of these

quotes. So consideration was given that the current lot release specification might include a significant reduction of the IGIV supply and that many of the lots at the time were getting close to the recommended minimum measles antibody titers. That is for release. I think it is fair to state that probably somewhat less visible issues with stability of IVIG lots would probably be worse at the time and continue to be at this stage.

And there were two strategies given conservation to during that workshop and within CBER that might address this potential concern around the supply. The first one was the obvious, to lower the recommended measles antibody titer for lot release. That obviously could only happen if you could better ascertain that the products would still be effective in doing what their supposed to do, and that is protect the recipients. An alternative approach that was considered was the revaccination of plasma donors so that ultimately the plasma supply could be brought up in antibody content.

I shall say also that during that

workshop there was a review of all the scientific evidence at the time and it didn't result in a very positive view in that it was held to be rather unlikely that the revaccination could result in higher and, more importantly, durable increases in the antibody levels. And that was based on studies that had shown that the increase after revaccination of the measles antibody titer was only about two fold. And that increase was transient in nature so that within about half a year, those that had received the vaccination were back to base line level.

So in summary, again, the likelihood was held to be low, well the likelihood is nothing to base decisions on, that's why it's important to have the data. And that is what our colleagues in the BioLife Organization, who do the plasma sourcing for Shire, that is why they have done this study and that is to take this into the actual setting of plasma collection.

So plasma donors, there are just a bit more than 100 of them, male, and I'll come back to that in a second, who have been regular plasma donors before and fully qualified according to

the PPT donor qualification requirements. Did receive an MMR boost and then samples were collected, obviously, before that vaccination and then at different time points after the vaccination to investigate how effective that boosting might be in terms of increasing the measles antibody concentration in the plasma supply for vaccination.

Before we go to the results, I shall say that there were a number of limitations to that study that are important to keep in mind. Firstly there were only around 25 percent of the donors that could be included in that study. The first and major part of it is a limitation that you can actually not administer the live vaccine to females of potentially childbearing age because you cannot exclude that they would get pregnant at that stage. And so the females had to be excluded so you're left with half your donors already.

And then, of those half of the donors despite a fairly substantial incentive that was offered to study participants, only roughly 50 percent accepted to be partaking in that study.

So why is that necessary? After receiving a live vaccine you need to be deferred for 28 days per FDA as well as AMA regulations. So that's where people are losing opportunity of 8 donations roughly. So 4 weeks times 2 donations per week and they need to be compensated for that, that's one thing. More importantly, so for the plasma supply you're losing that donor for these 8 donations and plasma already is something that we could use more of.

And then the vaccination frequency, you could not do that, you know, repeatedly on and on and on because there is a label copy restriction that actually allows that one revaccination. So there is, shall we say, a number of limitations around the inclusion of people into that study.

So then the plasma samples were sent to actually my lab where they were analyzed by standard neutralization assay. Not going to be labor this just for the sake of completeness really. It's a live virus assay that is used there so it's a proper, functional read up that is used with a sale based readout after an incubation period that is long enough for the



sales to develop a cytopathic effect that can be easily read. So these assays are fully validated according to ICHQ2.

So this is a combination of the data that Dr. Simon just shared with you and data that we have collected ourselves. So this here, is the 2007 CSL Donor Snapshot Study where the age is plotted against the titers of plasma collected from these respective donors. There is an addition here and that is the relatively young on average donors that we have included into the revaccination study. I think it is interesting to note that after here, where there is now a routine second dose of vaccination, the titer in these young donors, they were less than 27 years of age, is actually fairly low.

The good news maybe that it seems that the titer is going to stay stable there; so maybe we've reached that plateau and the decline is just a reflection of initially the first dose of the vaccine and then later the application of a second dose of the vaccine. So maybe this is a stable level that we're going to see here.

But vaccinating these young people

against measles virus resulted in somewhat expected, but still disappointing results. And that, here you see the titers on the zero and here you see the increase at roughly a month after vaccination, so there is a statistically significant increase. But that increase is only around two fold, that is fully consistent with the scientific evidence that had been available earlier, now confirmed here in the specific setting of the plasma collection environment with the specific donors that are involved there.

And then for a certain subset of the donors, if you go back after this increase at around 5 months or 6 months, half year, and what you see is that they almost came down to baseline level so there is a little bit that is left but it's miniscule. Again fully consistent, I think, with the deliberations 10 years ago by CBER first and then the BPAC, but it's somewhat disappointing.

Now there's a few more things that we can read out of the study with respect to the vaccine performance, I think it is going to be very surprising. That is that the vaccine virus

titer increases are indirectly proportional to baseline titers. Now this is a live replicating vaccine, the higher your titer initially, the more difficult for the vaccine virus to be attached and therefore the lower increase.

So you have these very high titer people over here, they have virtually no increase. And then there are a few people here who actually have quite significant increases, maybe that would have been an individual who has not been vaccinated before, could be. And this is another thing, the vaccine in itself, is applicable, I think, in terms of use to people of all ages, so in other words there is not a significantly statically correlation of the age of vaccine recipient to the fold increase of antibody response. So that vaccine certainly could be used for people of advanced age. Coming back to Dr. Golding earlier request could be considered revaccinating who have gone through a vaccination a long time back. That seems feasible.

So in summary the BioLife Study has shown that what we knew 10 years back did hold up in the plasma donor community and that is that

vaccination increases the measles titer by less than or equal two fold and that increase is transient to returns to baseline pretty much 6 months later. Now that combined with the fact that of that donor community only 25 percent of the people, through the limitations that I've discussed with you, can be accessed makes it very unlikely that this is going to be the intervention we are looking for.

I will also make mention of the fact that there is a very recent study that has been larger, while not in the plasma donor community but still a very important thing to keep in mind, that study tried to address the question of potentially waning antibody immunity and also potential failures of the two dose vaccine. And so they've investigated in some 600 plus individuals whether a third dose of vaccine would provide for a benefit, "would be worth the effort." And in that study results have been obtained, they're actually quite similar to the study that we have performed and that is there is an increase. Yes, it was limited again around to two fold and it declined to mere baseline levels

just one year later. They did say that of the 3.6 percent that a study initiation had very low or negative baselines. They could bring them up and so that would be a benefit, but they felt equally that they didn't provide compelling data to support a routine third dose of MMR vaccine.

Then I would like to summarize, that data that we have reviewed some 10 years back in the first workshop of this nature are fully consistent with two more recently conducted studies and I think in summary, one can see that therefore the revaccination of plasma donors will not be a sustainable option to increase the measles antibody titers in IVIG. Thank you very much.

DR. MISZTELA: Thank you very much, Dr. Kreil. Questions from the audience? Dr. Golding?

DR. GOLDING: Basil Golding, FDA CBER. So from a theoretical point of view or maybe somebody studied it, I mean, you saying and you provide a lot of evidence that a third boost doesn't give much of a boost in the first place and it wanes after a short period of time. I

would suggest that the likely explanation is that these people have preexisting immunity, both cell mediated and they have some antibody. And this is a live virus, so they clear the virus so quickly it doesn't have a chance to replicate so you're not getting much of a boost to the immune system.

So my question is, in these studies did they look at that, did they try to look at viral shedding or any marker that would indicate that the virus was removed so quickly that it cannot replicate, it cannot induce an immune response?

DR. KREIL: I do not recall that level of detail in that publication. What I will say though, and maybe I'll go back this one slide.

So this actually illustrates the relation of the baseline titer and the vaccine response. And what you see is that even the titer's around 1 and 100, which is not low, there is still a 2 to 4 fold increase.

So I think to completely quench the vaccine initially it would take a very high titer. So I think it's just that you cannot propel the antibody response much beyond what we see. And so that's why this limited increase that we see

and it's not a sustainable thing either. So there seems to be a robust baseline that cannot be propelled much further than that. But again it would probably take more of a study there.

DR. MISZTELA: Yes, please next question. Please identify yourself.

DR. LEVIS: Hi, yes. Robin Levis at the FDA. And kind of a follow up question to that, are there any other antigens that could potentially, maybe give a higher initial response on this secondary immunization that have been tested rather than the traditional MMR component?

DR. KREIL: Well, I mean, obviously --

DR. LEVIS: That's kind of -- my question was similar to Dov's but just in terms of looking at different potential antigens as a solution.

DR. KREIL: I'm afraid I have not much of an answer. I mean, our job has not been basic research into vaccinology but we were using a commercially available product to see whether it would be usable for addressing (inaudible) so I'm afraid I don't have the answer there.

DR. MOND: Did you look at the antibody response to the other components in the vaccine?

DR. KREIL: We did not.

DR. MISZTELA: Any other questions or comments for Dr. Kreil? If not, thank you very much for this very clear presentation. Very interesting data. We are on time for our break, yes. Our 30-minute break so I would like to thank Dr. Kreil for his excellent presentation and we now have a 30-minute break so I would ask you to come back at 5 minutes to

for the panel discussion. Thank you.

(Whereupon, at 10:25 a.m. a recess was taken.)

DR. MISZTELA: Thank you. May I ask you to take your seats, please? May I also ask the speakers from the first session to come to the podium and take their seats for more questions?

MR. BALLOU: So while everyone has a chance to think about the first three questions that are not yet projected on the screen, but they're on the computer. Do we have the projectionist? There we go.



Let me just make a couple comments.

The first comment is to the CDC. Their recommendation is to use intramuscular for infants at .5 milligrams per kilo, so if you have a 10 kilo baby that's like 5 mL. That hurts. So I would suggest maybe there's some consideration to thinking about using subcu immunoglobulin. We do this all the time by push actually, not with a pump, but by push. We do this all the time in babies with severe Combined Immunodeficiency Disease where we need to give them smaller amounts, maybe a little more frequently, but we just give them a subcu push. And it doesn't hurt as much as IM. IM is -- have you ever had IM? It hurts. Okay.

There was another comment or question about cell mediated immunity and maybe Dr. Blaese may want to comment on this as well. But yes, particularly patients with Common Variable Immunodeficiency are very variable as the name suggests, as the diagnosis suggests. And some of them do have compromised or cell mediated immunity that is less than optimal, less than the normal range.

We do phytohemagglutinin and PHA responses and specific antigen lymphocyte proliferative responses in all our patients with immune deficiency but in particular CVID patients and yes, some are decreased. Unfortunately we don't have the tools to be able to measure what their cell-mediated immune responses to vaccines.

I'm only aware of a few studies actually in patients with CVID. One is with Zoster and the other is with influenza vaccine, which shows diminished responses. So that may be a caveat when we consider, perhaps, what the appropriate protective antibody levels should be in these patients as we think about changing, you know, the requirements for measles prophylaxis. So that may come in to play. We just don't know. We just don't have, obviously, have the data to address what the roll or the effect of immune cell mediated immunity might play.

In patients with severe combined immunodeficiency, those are picked up by newborn screening now, so very early on, within weeks or days or months, those babies go to bone marrow

transplant. So obviously that's a cure for them. So that target patient population, which is actually the largest with regard to primary immune deficiency and immunoglobulin replacement is patients with common immune deficiency. We just don't have enough data with regard to their CMI response to vaccine unless somebody else in the audience can address that. Mike, I don't know if you have any additional data or information?

SPEAKER: (inaudible) make antibodies to some things and yet you will have a negative cellular response for instance skin testing with tetanus toxoid is a very effective way of immunizing people and a lot of the --

DR. BALLOW: Okay. I guess we can address question one --

DR. MISZTELA: Actually, I have a question because it came up during the discussion to Dr. Patel. It was mentioned that despite the recent measles outbreaks, there has only been one immune-compromised patient who has died from measles. And whether you can shed some more light on the case itself because I think it has

been of interest to the audience. Before embark on the general questions.

DR. PATEL: Sure. So that case was in a woman -- that was a case in Washington. It was related to an outbreak that was occurring in the state of Washington. She had dermatomyositis, so this patient was probably taking immunomodulators and subsequently died from giant cell pneumonia; so not a PID patient.

Now, I'm just waiting to hear back from my team to see if we can characterize -- I mentioned in my talk that there were those seven cases of measles since 2000, who had some sort of immunodeficiency including PID. I don't have information on that right now. I can see if they can get back to me and if not I can let Dr. Scott know and share that with you all later.

DR. MISZTELA: Thank you very much. Okay then, let's start with the first question, which is what is the potential impact on patients of decreasing the lot release specifications for anti-measles antibodies in IG product? Maybe for the first instance, I open this to our speakers and then to the audience.

DR. SIMON: Well, I think based on the data that we've seen that's been shown plus has been mentioned that the rarity of measles case and the patients I still think while I know it is a concern to the patient community and to their physicians that we can feel secure that if we reduce it to this next lowest level 0.3 that there still should be minimal impact. So I would put that out there as a hypothesis at any rate for discussion.

DR. VANDEBERG: Yeah, I would hope that the levels that we have, will be protective even going down to .3. Certainly the other factors are the rarity, and if we keep the immunization levels up. But based on the little bit of data that we have it does look like .3 will still be protective.

DR. PAPINA: I think the risk of measles in anybody in the U.S. right now is extremely low in any case. I mean, the risk has been, except for 2014, the risk has been below 1 case per million population per year, so that's very small and the numbers of cases that we've seen in PID patients is, you know, we're just

barely finding any.

I think it would be very useful to hear from -- because I know a lot of people here from Europe, to hear what's being done in Europe. I know that we have European countries that have larger outbreaks, you know. I know a lot more about measles right now in countries in Africa where they're not going to be using immunoglobulin products and we're focusing largely on vaccination. And ultimately the goal is eradication, which is the best protection for everybody as was mentioned, but we don't actually have a global goal for eradication. Each of the regions is working towards elimination and we're behind schedule pretty broadly. But you know it'd be good to hear, is there information on the risk of measles in patients with Primary Immunodeficiency because we're not really seeing it here.

DR. MISZTELA: I can perhaps answer this. So in Europe we do have large outbreaks and actually certain countries have resulted in actually making vaccination mandatory. For any daycare center, school entry, vaccination is

mandatory for the patients.

And that was one of the issues we were discussing in the regulatory differences, that in Europe we do not have potency release specifications. And at least to my knowledge, I would have to concur with patient representatives there, that have not been any documented or high increase in infections of patients with primary immunodeficiency with measles. So I think countries still maintain a good level of immunity. As Dr. Simon and many others have concluded, this is the only way to protect people.

DR. PAPINA: Are the titer profiles in the plasma in Europe are significantly different?

DR. MISZTELA: We don't have actually measured --

DR. PAPINA: They're not even measured?

DR. MISZTELA: Yeah.

DR. GOLDING: This is Dr. Golding, FDA. So I'm hearing, you know, a few people say that it might be reasonable to go down to lower level, to the .3 level, but I think what we have

to think about is in combination with what dose. So we've heard doses ranging from 200 to 800 milligrams per kilogram, we've heard 300 milligrams per kilogram, the .3 is predicated on a dose of at least 400 milligrams per kilograms.

I'd like the panel to -- the second question related to that, and Dr. Ballow or other treaters could answer that, you know, there've been papers in the literature saying that many patients with PID do much better with actually higher doses, higher than 400, 600, 800, even a 1,000 milligrams per kilogram so -- not a 1,000 -- so where are we in that spectrum?

Are most patients already receiving higher doses? We need to take that into account in our discussion, I mean the implication from the FDA is to change labels so the minimum dose is not 200 or not 300 or maybe higher, so maybe you could comment on that?

MR. BALLOW: A committee of the American Academy of Allergy and Immunology convened several years ago to write some recommendations or practiced guidelines. That was just published in that March issue of the



Journal of Allergy and Clinical Immunology.

And from that committee the recommendation is a starting dose of 400 to 600 milligrams per kilo. Clearly patients who have chronic lung disease require higher doses, so in general I tell colleagues to start at 400 and then determine if that's an adequate dose based on clinical progress, but certainly if they have underlying inflammatory disease or chronic lung disease they should start at a higher dose.

So with package inserts saying at 200, I'm disturbed by that. I think we need to revisit that because everyone that prescribes Immune Globulin Replacement Therapy may not have the experience or have read the more recent literature and practiced guidelines that would steer them to a more suitable dose.

DR. SCOTT: Dorothy Scott, FDA. I just wanted to point out that actually I don't believe there is a package insert anymore that states that dose range of 200. That was changed because of the measles issue. But there may be a 300, so I'll have to check.

DR. SORENSON: I want to get back to

an issue that's probably going to not make me very popular, but we consider primary immune deficiency experiments of nature that can teach us a lot. So one of the speakers mentioned that a I gamma globule anemic, that's the most severe form of antibody deficiency that doesn't get measles. But the measles cases that are described in the literature occur in severe combined immune deficiency patients that do not have cellular immunity.

So what I hear is that you are spending a lot of time defining under which level patients may no longer be protected, but may be we are focusing on the wrong side of immunity. May be cellular immunity may be more important. I know that I'm probably not right about that but I --

SPEAKER: (inaudible)

DR. SORENSON: If I gamma globule anemic, I think you said it, yes you had a slide, it was surprising to me actually. A gamma globule anemic have the worst forms of antibodies suppose not to have a gamma globulin, a gamma globulin anemic, they don't get measles. So what's this?

DR. PAPINA: Just to clarify what I said was that patients with A gamma globulin anemia don't have worse cases of measles than patients with normal immunity so that cellular immunity kicks in and they don't tend that have worse outcomes. Patients with SKIDS do have a much higher risk of more severe complications and death. It's not like they don't get infected, it's just that they're able to manage the infection. And these are old historical studies since we haven't seen measles in these patients in a while.

DR. BALLOW: Any other discussion about question number one? Identify, please. They're transcribing, so identify yourself. Now, did you have a comment?

DR. BERGER: Mel Berger, CSL. In 2013, Charlotte Cunningham Rundles published data on more than 3,000 patients receiving gamma globulin for ICD associated with immune deficiency and in the patients that were getting IV, the monthly dose was 568 milligrams per kilogram per month. So that's 4 year ago, 5 years ago, in something like 2,000 patients on IVIG.

Patients getting subcu were actually on 483 --

SPEAKER: (inaudible)

DR. BERGER: So the patients IV were getting 568 milligrams per kilogram per month and the patients on subcu were getting 409 milligrams per kilogram per month.

DR. BALLOW: And do you have the paper in front of you? What was the troth or steady state in IG levels?

DR. BERGER: I don't think it tells that.

DR. PAPINA: Could I ask a question on that? So those sound like average values and I think it would be important to know what the minimums were because I think the concern is, if we lower the minimum release titer, what's the lowest dose? What's the worst-case scenario? It sounds like that you're quoting is average titers given to patients through ICD --

DR. BERGER: Average doses.

DR. PAPINA: Average doses. So was there a range associated in that paper?

DR. BERGER: Yeah, of course. But I mean it doesn't really -- first of all it doesn't

have any data on titers. These were just insurance claims database. Another point, maybe I'll ask Tom while I still have the microphone, the slide you showed of the vaccine response -

SPEAKER: (inaudible)

DR. BERGER: It's on. So it's Mel Berger from CSL again. So the slide you showed of the range of the effect immunizing donors, over on the extreme left is the pre-immunization titers. And there's a range there, the range of values is like 80 fold or more than 80 fold. And so I wonder how many donors with titers how much higher than the mean do you need to think about to make a hyper immune? I don't know if you could answer it or Toby can answer it but you know if there's an 80 or 100 fold range of measles titers in the donors that are walking around, is there enough to consider a hyper immune?

DR. KREIL: Well, intellectually I think it's a very interesting thought. But before I think you can call anything hyper immune then you would have to correlate the number that you're measuring with clinical efficacy. In times where we don't see measles from happening

I'm not sure how you would ever come by this data. It would probably have to be a trial during an outbreak in the Philippines. It would be quite, I think, convoluted statement.

DR. BALLOW: Yes. Identify yourself again, please?

DR. MOND: Jimmy Mond from ADMA Biologics. It's a general question not related to measles but it appears as the years move on and people get immunized with vaccines, their natural immunity wanes. Doesn't apply to measles, but everything, influenza, pneumococcus, or mumps, rubella, so the question we're asking now for measles I guess applies to anything in which there's currently a vaccine. Vaccine's basically will immunize the donor pool but at the same time they'll minimize the natural immunity the patient had to the organism. Is that correct? This is not a specific discussion for measles but one really that you relate to any pathogen to which there is a vaccine.

DR. KREIL: So, the one other example that I'm going to actually show about tomorrow is Hepatitis E virus where we see exactly the same

thing. Once you start vaccinating you're actually driving down the titers and the plasma supply. That's exactly what we see happening.

That said there are other viral agents that actually enter the community and for a notable example, West Nile virus. Where we've actually seen the nations here convert, if you will, to West Nile virus. So I think there's more of a fluctuation of different titers that we see and for those that we vaccinate we're driving them down, yes.

DR. MOND: So this becomes a general problem?

DR. KREIL: For those where we vaccinate it is probably something that is more widely applicable.

DR. MISZTELA: Okay if there are no further questions, we move to question number two. Which is, what is the possible impact on IG supply of maintaining the current measles specification? So first -- oh sorry, Toby.

DR. SIMON: Yeah, I can start on that because we did make an attempt to present some of the data from the companies on the titers on the

products but it was difficult to put into a consistent presentation.

In general though, from falling titers in the products in the number of lots that fail sort of mirrors what we're seeing in the donor snapshot data. So obviously the reason that we're hear is that several of us have approached FDA through our industry organization to sound, sort of, an alarm bell that if the current measles specification is maintained that there could be serious disruption of supplies. To that we would have lots that would fail and not be able to be used, be released on the United States and there could be, we would anticipate that there would be a significant impact on supply.

DR. KREIL: I would actually like to follow up with that statement. I mean, supply it's almost a matter of a global supply situation. We need to be clear that there is already not enough plasma around to provide treatment for everybody and therefore I think if nothing else than it would be a shame for the wrong reasons to reject the release of the lot. I mean, it's a raw material that is not easy to come by. It's an



ethical donation that I think we need to make best use of and to form a specification that we all know how meaningful it really is. To reject a lot from the market is something that I think we need to think hard about.

DR. MISZTELA: Yes, please go ahead.

DR. MOND: Does it make sense maybe for the FDA, that we could keep dropping what the measles titers needs to be but maybe FDA ought to just drop the requirement for measles titer at all if the donor pool is what the donor pool is? For measles and everything else and the best you can do is collect from multiple donors, and hope for the best I would say. Unless the idea is to find somebody to enhance the titer, which you can't do through vaccination but you could do from selected from hyper immune donors.

DR. SCOTT: Dorothy Scott, FDA. And there are a lot of other people at FDA who might want to chime in, but my personal opinion is that we are still concerned about the potential for measles in primary immune deficient patients and we think -- well I think, it is my personal opinion, this is my disclaimer again -- that it's

better to get control of the titers than to just let them go. Because we might get lots that are very low, how do we even know what to recommend for people for post exposure prophylaxis?

At least we'll have a floor, we'll always have a floor for that titer so that we know, for example that you can give any immune globulin and you'll get not less than this amount of measles antibodies in post exposure cases. Because what we're talking about is the potential that we might allow the titers to go down mainly because we're all forced to in order to avoid rejecting large number of lots in the future.

And I have to tell you, we've seen plenty of lots that are close to the line at release and we know from some of the modeling that we've seen that it is possible for the occasional primary immune deficient patient in the scale down to .3 to fall under that 240 IU/mL. So that's based on modeling and a calculation, but it comes from real data from the clinic. It's seldom but it happens.

I think just to let the problem go and fly off in the breeze would be potentially harmful

to people with primary immune deficiency. This is my opinion. I think it would be nice to hear from the Primary Immune Deficiency Foundation and from others at FDA.

DR. BOYLE: Hi, this is John Boyle from IDF. Trying to think of the best way in which to respond. Dr. Mond, it's all worth looking at, of course, but this process in order to ensure that safety, and again this is an unknown, in somewhat to point hypothetical.

We grappled with this within the plasma world with prions and all the other issues of what are some of the areas that could potentially impact our population on a reasonably large scale if we had that perfect storm. Of course the hemophilia community experienced this, you know, back in the 1980's with a different scenario.

But to just tie in something, Dr. Golding was mentioning earlier and others followed up on. You know one of the challenges that we see, and that the practitioners here who are in this room and listening I'm sure that they see it to a point, but they are also more or less at the top of their game and exceptional

clinicians.

A great deal of the folks that end up contacting IDF or seeking resources out there, we would argue based on some of the survey data and, of course, a lot of the anecdotal that they are under treated. And so these discussions, you know, of well if we lower it to .3, which to me seems given everything that's being discussed reasonable, but it is somewhat dependent on that dosing level that's being discussed. And those dosing levels can be lower than you know what the recommendations should be.

So there are a few other factors that are at play here to ensure that we are protected and, sorry guys, the main concern here is that we are protected. If we have to judiciously continue to alter the levels, the PI community would ultimately be in favor of that, I speak primarily for myself, you know, with that but something that we can discuss. But going to the more extreme is something that we would like to avoid at this point in time, I think.

DR. BLAESE: Mike Blaese, IDF. I think there's a couple of points that we have to

consider and part of it is we've been avoiding trying to consider one of them. And that is that the population of patients that are receiving immunoglobulin, the PI population, represents less than half of all the uses of immunoglobulin and the other people besides the PI's are not using immunoglobulin for antibody specificity. They're using it for immune-modulatory specifically with neurologic disease. And possibly one solution to this dilemma is to take the products that don't meet the measles, or what other antibodies specificity we have, and direct that towards the patients that don't need antibody replacement.

I think that would be one potential solution as we get closer and closer to the problem we're having of to disqualify various lots. Now the manufacturers will have their own particular point of view on that but that's one of the issues.

Another issue that I think is important is dose, as we've talked about earlier. What is the appropriate dose and the starting dose? I have to go back to a paper that was published by

Jordan Orange about 5 or 6 years ago now, addressing the instances of pneumonia as it is related to troth values as it relates to patients with PI.

And they were all patients that were done in phase 3 clinical trials, so they had accurate measurements of the instances of pneumonia and they had troth values. And as I recall for every 100 milligrams per kilogram increase in the dose in immunoglobulin, you saw about 121 milligram per deciliter increase in troth level.

The really interesting data was that for every 100 milligrams increase in troth level, you saw a 27 percent decrease in the instances of pneumonia in those treated patients. And as we went from 500-milligram troth level to 1,000 milligram per deciliter troth level the instance in pneumonia actually fell 4-fold.

So patients that may be doing reasonably well with immunoglobulin, frankly these patients have -- you know, the median time for detecting and appropriately diagnosing a patient with CVID is 9 years. So half of our

patients are sitting there chewing up their lungs or their sinuses or what have you for 9 or more years before they're diagnosed and put on immunoglobulin.

And so starting those patients at 400 is very unlikely to be the optimal therapy for those individuals. And I think we have to think more seriously about treating them until they get better, not just so they're sort of getting better. I think we've got to push it and that's another challenge for the supply.

DR. MISZTELA: Thank you very much for this comment; certainly something to think. Any other comments from the audience?

DR. SHEARER: I'd like to follow up on that comment by Mike, please. Clinicians in the field don't come to conferences. We're increasingly frustrated by the inexact science of gamma globulin therapy. When it goes from diagnosis and testing to the actual application to their patients.

The (inaudible) of some of this confusion is that there's good reason to think that you can just treat the patient until the

infection ceased. Perhaps not completely, but if there's a dramatic reduction in the number of infections per year using certain sending doses, go for it. So you know a lot of these considerations sort of fall by the way side when it comes to real human issues.

DR. MISZTELA: Thank you. Another question or comment?

DR. SORENSON: It's actually a comment to what Dr. Blaese said. That paper by Jordan Orange is much quoted, but you have to see that basically patients between zero and one pneumonia in the reduction, but very significant increases in cost and dose were actually minimal. They were statistically important, but in real life they were almost nothing.

And at the same time, Vincent Bonagura published another paper showing that for each patient, if the aim is preventing pneumonia like in Jordan Orange's paper, there is an individual level. Some needed to be at the 1,00 troth -- at the 1,000 milligrams troth level and if they fell below that then they were developing pneumonia. Others did fine with a much lower level.



So no matter how important it is for you to regulate the quality and potency of everything in the gamma globulin, in real life there is still the individual management of each patient that needs a dose adjusted to the patients needs. So that's the other side of the same coin.

And you know, here in this country we don't worry about increasing costs, but yes if we keep increasing the dose to provide a higher protection level insurance companies get less and less inclined to authorize gamma globulin treatment. I know that the mission of this meeting is different, it's not to discuss these clinical issues but you cannot avoid also considering them; that no matter how well you define every single antibody concentration and every lot of gamma globulin, that will not completely solve the management of individual patients.

DR. BALLOW: We've kind of gotten off the topic a little bit. So I know you have a question, but let me rephrase this question number two.

If we decrease the standard to .3 of the

FDA standard, are we going to lose lots because we can't achieve that level of protective antibody against measles? It appeared to me on one of the slides that was shown of donors that we're kind of reaching a steady state; measles antibody level where most of those donors have been immunized and not have natural measles.

So if that holds up and we use the 0.3 as our cutoff are we still concerned about losing lots of gamma globulin? Crunch the numbers gentleman, what do you think?

DR. SIMON: Well our best data indicates in the next several years that we're probably going to be okay with that level, but certainly as we look out further, I think that is an issue. Which I think is why the workshop has, sort of, brought up, you know, other questions for what we do for the long-term future. I wonder if anybody from other companies has a view on that particular question.

DR. KREIL: So the one thing I will say is we realize the current situation is too close. The other thing that we see in your donor snapshot study as well as the baseline for our

vaccination study, is that we may be at a point where the young donor population has gone through two vaccinations anyway.

So that may indicate to us that that is the plateau that going forward we are going to have. Now young donors are over represented significantly in our donor pool for source plasma, so they are probably a large part of our reality. And so I think for right now, we need to see to fix the situation that is eventually going to result in lots not being usable. But I think going forward we are going to be in a stable situation that if we do the right step now, there may not be a need to revisit the topic again.

DR. BALLOW: Well since you agreed with my hypothesis, is that right?

DR. KREIL: (inaudible) right, yes.

DR. VANDEBERG: Yes, I think lowering the limit to .3 would buy us more time. And is it enough, will we reach that plateau? I think, I mean, you've got data that suggests that maybe it won't be enough, but on the other hand we would be seeing that over the next few years.

DR. SIMON: Yeah, I think to clarify.

It should be enough in the next -- for at least the next 5 plus years. I'm not positive about beyond that but hopefully it would be.

DR. MISZTELA: If there are no other questions or comments -- or one more? Yes, please go ahead.

DR. HAJJAR: This is Joud Hajjar from Baylor College of Medicine. It almost seems to me that lowering the titers are going to be inevitable because the nature of the donors and the loss of pools. So as a clinical immunologist, something that we usually do for our patients is to try to prevent them from infections that are not inevitably protected by immunoglobulin's, is to look at the household like influenza vaccine. We make sure that all the household is vaccinated.

So is it something that we should consider for measles in this cohort that we have to start evaluating the immune status of the household? And whether we should vaccinate the ones who are not vaccinated?

And obviously some of our adult patients are healthy; they travel. Who have COVID

or a gamma globulin anemia should we increase the dosing for specific patients who have increased risk of measles? Rather than saying we have to maintain a higher level for everybody given the (inaudible) that Dr. Patel has presented earlier like target the higher risk patients?

DR. PATEL: Thanks for that comment. Certainly we want to make sure that there's cohorting that does occur around our most vulnerable patients. Not just immune deficient patients but also babies.

We strongly encourage that these healthy individuals that around these vulnerable patients do follow the ACIP recommendations, but again it's -- I think this was mentioned earlier, that it really comes down to the clinician increasing awareness. It's challenging, we've tried to do cohorting, for instance with pertussis vaccination around babies because those infants tend to have severe complications. And it's still often difficult to do. It's not just the immediate family. It's also including grandparents, including other friends that are frequently traveling, and so, that to me, is a

major educational point, but I very much agree with you.

DR. MISZTELA: Thank you. Question number three, what levels of measles antibody is sufficient for post exposure protection of immune deficient patients? I think in follow up to all this discussion, quite a valid question. Panel, please?

DR. PAPANIA: I don't think we know that. We have limited information on what level of antibody is sufficient for preventing disease in the normal population but we don't have, you know -- we don't know that and it's unlikely to know it. And I think, kind of, taking this margin of error, let's say that it's twice as a reasonably approach because I don't think we're likely to be able to get that answer. And I think it's also -- it's not going to be -- it wouldn't be one answer. I think the levels of antibodies sufficient to protect a patient that has -- one immunodeficiency is going to be completely different from another so I think we have to accept that we're not going to know that information.

We have kind of a baseline that we can work with and we can think of a margin of error but I guess one -- in the study that was mentioned earlier, the Chen study, that looked specifically at healthy college students who were exposed to measles and had donated blood before they were exposed. That gave us this unique opportunity to look at titers and what the outcome of exposure was based on preexisting titers.

One thing that you can look at in that data that could give us, you know, kind of an idea of how we should be thinking. The titer of 1 to 120 was basically the titer that protected almost anybody. Above that didn't get measles disease. But the students that had a titer between 1 to 120 and 1 to 1,000 many of them had evidence of infection and that titer increased. And so the titer of 1 to 120 is protected against disease. Titers over that, you need to get a much higher titer to have a sterilizing -- you're not going to get infected by exposure. And so certainly in somebody that has a primary immunodeficiency, you want to be in that higher range. But I think that we don't know that answer to that and it's a very

difficult thing to study and it's difficult to answer for all the different patient populations.

DR. MISZTELA: Any other comments or questions? Dr. Scott, please.

DR. SCOTT: Actually, I'll let Dr. Golding talk first; I just wanted to mention that technically we could go to lunch as early as 11:30. But if we can get question 4 in the next 10 minutes and then maybe discuss more at lunch and even later, I think that would be helpful. Because this is a very good discussion and I don't want to cut it short.

When we do leave for lunch if you line up by the exit door here, you will be ushered into the room with the food. And they say there's no such thing as a free lunch. And then you'll be asked to just -- you can't come back here with your food but you can sit anywhere else, in the cafeteria across the way or any of the other lounges and so forth to eat. But I'll let Dov say something.

DR. GOLDING: So I just wanted to clarify. I mean I just heard your remarks that we can't be sure about it and we don't have



evidence for the immune deficient population. But as a reasonable working hypothesis, are we willing as a consensus at this workshop to say that the 240 IU/mL is a reasonable target? And if that's the consensus then we're all talking the same language. But I assume there is a consensus. If people don't agree with that we should hear it.

DR. PAPINA: My personal opinion is that that's a reasonable target but I think it would -- I'm not an immunologist, you have a lot of clinical immunologists here that I would give more weight to their opinions. I'm an epidemiologist, so I just look at patterns, I don't know --

DR. MASZTELA: Yes, please?

DR. DJEKIC: Djekic, Shire. Out of curiosity, that estimate that was based on the study, do you by any chance know how it was derived at? So the doubling, that it is a reasonable estimate?

DR. PAPINA: How the 1 to 120 was derived at? I mean it was done -- the study -- they used plaque reduction

neutralization in the study.

Basically there was a college outbreak; again, there was a blood drive in the college before the outbreak. And so they looked at titers of the kids that had donated blood and took the pigtail specimens, looked at the titers using plaque reduction neutralization, and then looked at their outcomes. Whether or not they got clinical measles. And they did a follow up blood test to look at their titers boosted.

So that was basically the methodology of this study. I'm not sure if that's what you're asking.

DR. DJEKIC: And then the, I guess the protective levels in immune deficient patients, so then that level was doubled if I understood correctly?

DR. MASZTELA: The reason is it an arbitrary doubling or is there any data to support it? I think that's what you mean, right?

DR. DJEKIC: Right.

DR. PAPINA: That's a good question for Dr. Scott.

DR. SCOTT: Dorothy Scott. It was

arbitrary. So we felt that 120 might not be enough and we arbitrarily doubled it. We don't have good data for that; we just thought more was probably better.

So you could argue with this, but it seemed reasonable to have -- and we do this in other situations all the time, sort of a -- maybe you could call it room for error or maybe you could call it a margin of efficacy. But we felt that there should be some buffer there. That we really shouldn't aim for that limit in people that didn't even necessarily prevent infection, though it did prevent disease.

DR. PAPINA: So one of the things that's important to understand is that these titers are not that precise. When you're doing a plaque reduction neutralization test, your margins of error are pretty wide. So somebody that has a measured titer of 240 might actually have a titer down close to 1 to 120. That's an important thing to consider. And I'll also say that when we presented the information to the Advisory Committee on Immunization Practices, they considered this arbitrary value reasonable.

That's why it was included in the ACIP recommendations.

DR. GOLDING: Just one more quick comment. The reason for dabbling is that healthy individuals have both a cell mediated and antibody response so if you think that 120 is the lowest titer that's going to protect you from disease, there also have cell mediated immunity so you'd want to have at least some increase over that to take into account that fact that many of our immune deficient patients don't have; good or normal cell mediating.

DR. BALLOW: Let's go to the next question, but I want to make one comment. I think it's still open whether, you know, when we're going to reach this "steady state" measles antibody levels in the donor population. So I think it's important to get more data, obtain more data on the donor population going forward over the next 2 years, 3 years, 5 years. In order to determine if that's truly the case that we're kind of at a "steady state" level based on individuals receiving the measles vaccine and not natural measles.

Three? So all of you had a chance to read this question. So if we decrease the lot release specification as discussed, are there other options that we might provide or suggest to protect against measles in an immune-compromised individual, whether it's primary or secondary?

These are the choices or suggestions that Dot had put on the slide. I think we've heard that by immunizing the donor population, that's probably not feasible and may not be productive. Agreed?

Development of monoclonal antibodies, a long-range plan and again, may not fit into what we're doing here. Identifying lots that have higher antibody levels to measles and to push those aside and to use specifically in recipients either primary or secondary immune deficiency who have had exposure. Is that possible?

DR. SIMON: From the point of view, I think, of the manufacturer that's not really very feasibly because we have a product that's in short supply and demand and we would be holding it for a very unexpected event through many years. So I think that there have been other attempts at doing

this for other specific entities and it generally does not work out. It just isn't very practical.

DR. BALLOW: Especially for such a, I would say, uncommon event of measles exposure in this population. So I think we're left with one other possibility, which is the easiest and that is to recommend an extra dose upon exposure. Just recommend an extra dose of immunoglobulin, whether IV or subcu. Is that achievable? I think so. Is that advisable from the CDC perspective? Does that sound like a reasonable suggestion?

DR. PAPINA: I guess you'd have to state it more specifically. Basically the current recommendation is if it's been more than three weeks since your last IVIG dose, you should go ahead and get another one.

So it's almost embedded in the ACIP recommendations that at some point IVIG you probably don't have a projected titer and you should go ahead and get another dose. You want to shorten that interval if your titer is lower? Can you provide some information on -- you know -- I think that the -- can you provide some

information on what's the target troth level that you're trying to set that time interval at? And if you're exposed to measles, should you get a post exposure dose if it's only been two weeks since your last IVIG?

I think that most of the data that was presented and calculated on the lower dose was focusing on off titers in subcu. Which don't get very low so if you're getting subcu IG weekly, there's probably not any reason to -- how would you change that post exposure? So I think for subcu it seems like you would continue with weekly dosing and you're probably going to maintain a safe protective titer.

And for IVIG we can look at what the potential implications of the dose and see if you might want to give a post exposure dose sooner. One of the big difficulties and one of the things that we looked at with the ACIP was, most of the post exposure prophylaxis is done by the public health departments and they don't do IVIG. That's typically referred -- I don't know and maybe Dr. Patel knows more, because when I was looking at all of this, this is what changed the

recommendations when we were looking at it.

The public health department said we don't really have the capacity to deliver IV. That's why so much is done IM, as painful as it is. But I don't know if that has shifted since the recommendations have shifted; if public health departments are now giving post exposure IV.

DR. PATEL: No, I don't think is has. That's a pretty resource intensive treatment to give to a patient. I think mostly public health works with each of those patients' physicians. Their patients are typically really well connected with their hospitals and their providers and so we work with it at that angle.

DR. BALLOW: Yeah, it wouldn't be from the health department, it would be from the provider. But remember, I made that statement with the realization that we may have to change our criteria for lot specification and the dropping measles antibody levels in the donor pool. It wouldn't be harmful to give an extra dose whether it's subcu or a partial IV dose; at least in this population.



DR. PAPINA: The calculations that I've seen don't indicate that you would need to give an additional dose in less than three weeks. The calculations for the IV seem to suggest that a titer of 240 was maintained out at least to three weeks. Is that a reasonable interpretation of the data you were showing?

DR. SIMON: Our data was subcutaneous and so it was maintained.

DR. VANDEBERG: And ours, it did look like both IV and subcu it would be to that 240 level.

DR. PAPINA: For how long?

DR. VANDEBERG: So really the time points we looked at were the worst case. They were before the next dose so that was the worst case, the bottom of the IV curve.

DR. BALLOW: But Dr. Sorenson. So if you've had a patient that had exposure to measles, would you give an extra dose or give them their regular --

DR. SORENSON: No, I would tell him that he is not going to get it or she. That's it. Have you ever seen one? No. You see. Wouldn't

you do the same? Ok, I already said enough you are probably tired of me but I think it's important to have a level of antibodies to this in minimum, but you may be setting it to high. And if that excludes a lot of gamma globulin because it doesn't reach that level, I would question that as a good idea. There are many other infections that are much more of a problem, other viruses instead of the measles.

DR. BALLOW: Another clinical immunologist that may want to make a comment about this question?

DR. SHEARER: William Shearer, Baylor.

DR. BALLOW: Dr. Shearer.

DR. SHEARER: Maybe I can help us here with a historical approach to this quandary. And that is I can't imagine they haven't sent out a survey in the past to gather the information about what's being currently treated or used for treatment. In other words, the amount in milliliters.

Is it possible to just get that information? In a prospective way you could

actually do this by proposing a protocol in which you (inaudible) of gamma globulin that's been pre-titered for the antibody in question. That sounds like a big project, but if we're going to face the possibility of reducing the antibody level down to a dose in a gamma globulin that's not efficient and doesn't do that job, it would be well worth it. That would require federal support I suppose but this impacts people considerably, including me. Thank you.

DR. BALLOW: Thanks, Bill.

DR. MISZTELA: Dr. Golding? Yes?

DR. GOLDING: Yes, you know I'm not seeing patients but I'm just thinking, you know, it's a rare disease, we're not seeing it, one immune-compromised person with measles. But I think in this population, if there was an outbreak and there were cases that could be a life threatening disease, to me, you do want some kind of safety margin both in terms of the 240 rather than the 120.

And I think Dr. Ballow's question whether 3 weeks is long enough, yes the data show that you're maintaining levels above 120 may be

even close to 240 at 3 weeks for the 400 milligram per kilogram dose, but that to me is as dangerously close to where you want to be. And with the variability of the assay, the variability of individual responses, the variability of the infectious dose, I wouldn't want to be there, I would want to be at a safer place, which is maybe 2 weeks after an IV.

I agree with a subcu that you're giving it weekly, you're maintaining a steady state at higher levels, so even the trough level after one week is higher. But with the IV I would say, why not after 2 weeks. Why take a chance when you can have a better safety margin? I don't understand that logic.

DR. PAPINA: I guess the one other consideration, because there does seem to be some variability in dosing even though -- I think Dot had said that the labels don't go below 300 anymore, but it sounds like, from some of the studies that were mentioned, that some clinicians are giving lower doses.

Certainly if a dose of 100 or 200 or even 300 were given, then post exposure, you'd want to

go with a dose of 400. So that would be 1 that's already in the recommendations and I think that would be worth emphasizing. If you have a dose -- that's basically what the recommendations say, if you've gotten a dose of 400 milligrams per kilogram than you don't need another dose. If your dose is less than that than you go ahead and give another dose.

DR. HAJJAR: So maybe I can answer a little bit about Dr. Shearer's question about the most recent dosing. We have some unpublished data that comes in from the latest IDF Foundation that looks at what is the current dosing. And in patients who are receiving subcu IG, in our data there is roughly about 23 percent of the patients who are receiving less than 300 milligram per kilogram.

And then for the IVIG patients roughly, again, there might be about 25 percent of the patients who are receiving less than 400 milligram per kilogram as there monthly dosing. While on the other hand you'd see -- hopefully this paper will be out soon -- that maybe roughly about 40 to 50 percent of are at the 400, 600

milligram per kilogram in both the subcu and IV.

Now unfortunately we will not have troth's in that paper because this is based on survey studies, so we don't have a correlating IGG levels that correlates with that. But it speaks to the fact that maybe a quarter of the patients with CVIB, and this is CVIB population, not any kind of antibody deficiency, are under dosed.

But speaking to the other point, would it be helpful if your individual patient gets exposed? Regardless of what is the time around their infusion, is to check the titers at this point and if it's below the cutoff point, we just extra dose them regardless. Because now there are products of subcu who are certified for every other week, and even the IQVI is approved for once a month.

So are we going to maintaining the levels, just saying that this is a subcu product and maybe, although maybe not, the most cost effective, but for this individual patient maybe more relevant to just check the titers for that person. Thank you.

DR. BALLOW: I didn't know that that

significant number of CVIB are maybe under dosed, well that changes the whole dynamic. So I know a wine manufacturer has, in the package insert, a comment about measles. I wonder if CFDA should consider, again, some kind of a comment to be placed in all package inserts with regarding this question, particularly as it relates to dose maintenance that may fall on the lower side.

DR. BLAESE: I just wanted to mention quickly that we've been talking about three week periods for IVIG but there are a number of insurers now that will not allow IVIG more than once a month.

DR. BALLOW: Any other questions?

DR. MISZTELA: (inaudible) it is beyond the scope. I think we are veering off, I think it's a -- we cannot answer this question; I don't feel anyone of us. Good.

DR. BLAESE: It wasn't meant as a question, it's just for information but in fact things are beyond our control and when the insurers will pay for things and so if you're basing your decision because patients are going to be receiving the material every three weeks,

and in fact they can't get it, they have to have it every four weeks it may change the calculation. It was my whole reason for bringing - -

DR. SCOTT: I think we can discuss more of this over lunch because we're eating into our time. Not our lunches right now. We are scheduled to come back at 12:35 and it is already 12:07, I propose that we come back at, let's say 12:45 because I don't have that much to say. So 12:45, we'll see you. Remember you can't eat in this room, but you can eat everywhere else. Thanks. And thanks to the speakers and the panel.

(Recess)

DR. SCOTT: Good afternoon. I think we'll get started. It's starting to get late. We'll begin the session on polio lot release testing for the potency of IG products. And what prompts this session is the fact that polio eradication, the effort to eradicate polio is becoming quite successful. And along with that success comes the need to quarantine or contain polio viruses in laboratories.

I will go over a little bit about the



polio virus lot release testing. So again this is one of the required tests in the code of federal regulations for the release of immune globulins. And it does measure product consistency and antibody function. I would point out that polio immune globulin was not historically deemed very effective. Some studies were done; the first study was promising, the next two showed little or no effect of polio immune globulin for post exposure prophylaxis of polio, and then the vaccines came along so of course nobody was looking at this and nobody produced it afterwards. The FDA and its vaccines panel in the 1970's also deemed it not to be effective. It's a category 3 product which means they did not think it should be licensed anymore. That's not to say it couldn't possibly work as post exposure prophylaxis, but it appears that the effects of polio immune globulin were weak. I make that point because we may not have the same concerns as we had for measles where we are still worried about primary immune deficient patients getting it. In fact, we'll learn a lot about polio virus persistence and excretion in primary immune

deficient patients later on.

The assays can be an in vitro or an in vivo neutralization test for polio antibodies and I've shown again, only this time with the types correctly specified, the specifications for Type 1, Type 2, and Type 3 polio. My understanding has been that there had not been wild type polio cases for Type 2 or 3 viruses since 2012. We are going to have some very recent updates now, so I'm going to skip through these slides rather quickly because you will probably be getting the most up to date information shortly from our speakers.

There were 70 cases of Wild Type 1 paralytic polio in 2015. These were in the adjacent countries of Pakistan and Afghanistan mainly. The live polio vaccine was replaced with killed vaccine worldwide in 2016, and there's some good reasons for this which are that live vaccine virus strains may persist in immunocompromised patients for years. And we've heard about some cases at FDA where polio excretion and sometimes disease was detected in a child with severe combined immunodeficiency and also an adult with CVID.

So the polio eradication obviously is global and is having a major impact. This is from an article in 2016 describing the global action plan with respect to what is going to happen to polio viruses in laboratories. We care about this because obviously it's laboratories where these potency tests have to take place. So the first step towards the eventual phased removal of all three vaccine types is related to ultimately completing destruction and securing containment. In this case, at that time of Type 2 wild polio viruses in facilities - - and facilities that do decide to or do wish to keep their polio viruses for logical reasons like making vaccines must be inspected for compliance with containment guidelines. And these containment guidelines you'll hear about more. The question about those is how difficult are they; can they be managed.

The first question we're asking is what are the advantages of continuing to use polio antibody levels as a potency specification. The second question is what are the drawbacks of testing in the setting of anticipated WHO biocontainment requirements. Once you hear more

about these I think it will be interesting to know the opinions, especially of the manufacturers but also of others in terms of how arduous these actually are. And the third question is can BSL 2, bi-safety level 2 assays for polio antibodies, provide analogous information to that of current neutralization tests, and are such assays amenable to validation. If not, we're asking the panelists and the audience to identify gaps in assay methodology that might need to be addressed.

So again, this is a second specification that I would say has caused us worry but for completely different reasons compared with the measles potency test. We'll be hearing from Dr. Oberste from CDC about the progress of polio eradication efforts and containment requirements post eradication. Dr. Patel, also from CDC will talk about polio disease, passive immune therapy, and infections in the U.S. in primary immune deficient patients. Dr. McKinlay, we're fortunate that he was able to come, will talk about polio virus excretion and the incidence of polio in primary immune

deficiency patients. This is a result of a global study that's very recent. And finally we will hear from Dr. Macadam from NIBSC about development in their laboratory of a hyperattenuated polio virus strain and validation of its use in antibody assays under reduced containment. I want to thank our co-chairs, Dr. Kreil and Dr. Levis for being here and running this sessions and I think we can go ahead and get started.

DR. LEVIS: Hi, my name is Robin Levis and I work in the division of viral products. I'm not Kostya Chumakov and I don't pretend to be, but I hope I can provide with others in the FDA appropriate perspectives with respect to the polio issues as they come up this afternoon. I'd like to introduce our first speaker this afternoon is Dr. Steve Oberste from CDC and he's going give a first presentation on the progress of polio eradication efforts and containment requirements post eradication.

DR. OBERSTE: Thank you. It's a pleasure to be here and have this opportunity to speak at this interesting and very important

workshop. So I'm going to give a little bit of background on the eradication program, where we stand, and talk a little bit about the containment requirements; so kind of why we're here.

First I want to acknowledge that I basically stole most of these slides from my WHO colleagues so they have kind of a standard deck that updates. Most of these are actually their slides so all credit goes to them; you can blame me if I say anything wrong. I'm going to kind of work through a couple of the key points that are in the polio eradication and an endgame strategy. I'm really only going to touch on the detection interruption and then on the certification. So I won't cover these other two today.

So this is the current situation for polio globally in the last six months. As you heard, the cases are restricted now to Pakistan and Afghanistan. Nigeria is still considered a potential endemic country because they had cases last year. That's for Type 1 only, so Type 2 has been declared eradicated as of 2015. The last cases were in 1999, so we're confident that it's gone to Wild Type 2. Type 3 has not been seen

since 2012 in Nigeria so it is likely eradicated as well; however, we do have outbreaks of Type 2 vaccine derived polio virus. So the problem of course is there's a - - it's a live attenuated vaccine and the vaccine can revert and reacquire neurovirulence. So there's a large outbreak in Syria and it's in the part of Syria that's been in the news, basically where ISIS is holed up right now so it's very difficult to access the over 50 cases. There are actually two separate outbreaks in DR Congo, one of which is relatively large; the other is just a few cases.

So two of these, the two larger ones, the dose was given sometime before we switched globally from trivalent oral polio vaccine to bivalent so in fact we haven't totally switched to IPV but the Type 2 component of OPV has been removed. So the good news is that means it's no longer possible for an immunodeficient person to get immunized or be exposed to Type 2, at least in most countries. The bad news of course is we still have Types 1 and 3 and Type 2 is still causing outbreaks. I'm going to talk about each of these kinds of blocks in a little bit more

detail, and some of these I'll go through pretty quickly because you have the slides. I just want to hit a couple of the high points.

So this is the situation last year and this year. You can see the reduction in cases. I should have mentioned that there are only a few cases in the last six months. And globally this year, there have only been 13 total cases of wild virus compared to 37 last year and 74 the year before, so we're definitely going the right direction. You can see where the cases are, and again, these are all parts of the countries that have been in the news recently. These are where all the conflicts are in Pakistan and Afghanistan.

In Pakistan specifically though the case counts have gone down dramatically so this is just three years ago where we had, you know, 50 cases a month. And now again, there are only, I think five, all this year. And they're restricted in just a few locations so we're at least optimistic that we may get a handle on these soon.

There's also environmentally sampling



as part of the surveillance system; there's both looking at paralyzed kids as well as looking in sewage. You tend to find positives in sewage and places that are reservoirs, not too surprisingly. The virus is excreted in the stool so you can find it in places with high population density and poor sanitation, so this just shows four different key areas and we do continually find it in the sewage which is a bit troubling, because we're not seeing a lot of cases. So we're wondering where those excreters are coming from.

In Afghanistan, very similar situation. What we can find though is that we'll have new transmissions, for example here in this north and northeast region of Afghanistan. One case in February but then he disappears. And so, we see a few spotty here and there; however, in the south region and in the east region it seems to be more sustained so that's where the real worry is in these areas where - - and this is mostly along the Pakistan border and where transmission does seem to be sustained and is continuing.

This just shows some of the issues.

It's really about accessibility. The vaccine works just fine. They do large numbers of vaccination campaigns. Pakistan, they're basically a mass campaign every month, but if you can't reach the kids, you can't immunize them. So the spots shown in red are areas that are simply not accessible to the vaccinators and in many cases to the surveillance as well. Those in pink are just partially accessible and some of the orange, there are still issues in certain parts of those regions. So that's really the biggest challenge that's faced and it all has to do with security and the various militant groups in the country.

The Lake Chad Basin in Africa is another area of concern, primarily in northern Nigeria and in fact, for the most part, even northeastern Nigeria and the surrounding area. So there's been no wild virus or vaccine derived viruses in 2017 detected there. The most recent case of wild was in northeastern Nigeria in Borno State last year. There was also a vaccine derived Type 2 virus in that same area; however, the vaccine virus was linked to viruses that had not been

detected in several years so implying that the virus is hiding somewhere. And again this is an inaccessible area so that's the real concern. This shows a little bit of the inaccessibility issue; exactly the same issue I just showed with Afghanistan so in this case the red hatching is inaccessible areas. Most of the northeast corner of Borno State is only partially accessible so same story; if you can't get to the kids, you can't immunize them.

Some of the priority activities moving forward are to try to expand activities in these areas that are difficult to reach. Try to come up with novel strategies, really track down the kids that are in some of these areas, particularly those that are going into camps for internally displaced persons or in host communities where people move to when they can get out. Make sure that immunization occurs there. Taking a look at all the islands in Lake Chad; there are apparently hundreds of islands. People live on some of those so getting to make sure that no people are missed where we can get to them. Strengthening things like surveillance and other issues in the

country; some of these places are very difficult to work in as you might imagine. And then just push routine immunization better so that kids get immunized at birth and not just in these large campaigns.

So I'll mention a little bit the Type 2 switch and the events that have been seen. So there have been some outbreaks. This just shows most of them, some of them. So as I mentioned, in April of last year there was the switch from trivalent vaccine to bivalent vaccine so a globally coordinated switch. The last doses were delivered in April and then there was a period, sort of a wash out period, where we were looking for the virus to disappear. It can be excreted in stool for up to a couple of months in immunized people. And not too surprisingly we did see some hot spots where the virus was not totally gone, either because there was poor immunization coverage which allows the virus to continue to circulate or in some cases it looked like there was trivalent vaccine that was used after the switch occurred. So people did not get the word, the practitioners did not get the word

that they had to switch. And so there have been a number of responses. In some cases we've actually had to go back and use monovalent Type 2 vaccine which has the undesired effect of then reseeding Type 2 into the community. But in the case of some of these outbreaks, there's no other choice. In fact, they used something like 30 million doses of monovalent Type 2 oral polio vaccine in northern Nigeria. There have been campaigns in Syria as well.

This just reiterates what I said about Syria so I won't go into that again. Again this is the area of Deir ez-Zor which is where the conflict is primarily occurring. And these other cases are more likely just exports from that area.

Talk about containment a little bit now, and that's really where the issue is for the immunoglobulin products. As you've heard there's a document that specifies how polio needs to be contained now that Type 2 has been eradicated. Ultimately this will apply to Types 1 and 3 as well. And the idea is that once we think we've seen the last case, there's a period

of three years in which we keep looking. And if we really don't see it and feel confident that it's really gone, then there's a certification process. And then after that certification process then the rules for containment will kick in. The idea is that either any existing stocks would be either destroyed, contained in a proper laboratory and I'll go into what that is a little bit here in a minute, or transferred to some other facility that has those correct biocontainment.

So this so called GAP III document is quite lengthy and has all of these different areas of coverage. I'm just really going to focus on a couple of them. Some of them are very simple things; maintaining an inventory, some basic biorisk management and biosafety. The real sticking point though is the facility physical requirements. So for example, and some of these again are easier than others, locating a facility in an area with high polio vaccine coverage, having immunization of the staff so in developed countries this isn't a big problem. We have very high vaccine coverage as you'll hear about in a moment in the U.S. and the same is true in most

of Europe. Having controlled entry to the lab; it's more or less a BSL III lab so it's a containment lab, a type of lab that does exist in a lot of places. Having standard decontamination for those sorts of facilities, pass-through autoclaves, that sort of thing, work flow. If they are animal facilities there are certain requirements. After total eradication of all three sera types there will be requirements for HEPA-filtered exhaust and effluent waste treatment, basically a kill tank so all waste that goes out, whatever goes down the drain, has to go to a kill tank. The biggest issue, the biggest sticking point, is currently there is a requirement for having a shower and that means shower out after the employees leave. If a facility is using a Class III biosafety cabinet which is basically a glove box, that's not required however most facilities don't have that and for anyone doing more than very simple kinds of manipulations, that's really difficult to maintain.

There are plans for a number of facilities to become what are so called Polio

Essential Facilities, meaning that it's essential that they maintain polio virus or eradicated polio viruses. And you can imagine these are - - the first obvious one is vaccine manufacturers. They have to have virus to make vaccines. It would also apply to places like CDC, other public health labs that are doing polio work. There are also a lot of research labs so we have the disadvantaged - - so it's good news, bad news that polio was actually the first human virus grown in cell culture and it's been a model for basic virology for 70 years; however, that means it's in a lot of places. So it's a very common model system in a lot of academic centers and other places, and so there are lots of labs that have this. So in the Americas the plan is to have

of these so called PEF's in 6 countries. You can see there are 39 throughout Europe and a few are in other regions of the world. And so that gets to be a bit of a problem in maintaining the integrity and maintaining these facilities.

There is a certification scheme that's been put out by WHO. Each country that is going



to host one of these facilities has to have a National Authority for Containment. They have consultation with the Global Certification Commission. There are different certificates, basically from participation which is more or less a gold star on your forehead that you've applied and intend to be one of these PEF's all the way to full containment and that you're totally good to go. For polio vaccine production there are specific other regulations which you might imagine. And I'm sure those in industry would recognize a lot of these things. For non-polio facilities because of, like I said, the virus can be excreted in stool for a long period, anyone who's collected stools in a time or place where polio was either circulating or the trivalent vaccine was used, they come under these guidelines as well so your diarrheal diseases labs and a lot of other labs. There's a lot of training being done on how to become certified.

Some of the barriers to implementation of containment and getting compliance, the timelines are extremely aggressive and that's a bit of a paradox because we've been talking about

containment for close to 20 years. But of course, it was never going to kick in until we were getting close to eradication. So it wasn't until 2015 when Type 2 was certified as eradicated that people finally got serious about this and so really, 2014 they said oh look, we have these new guidelines you have to follow and then the very next year say time's up, right now. So nobody was ready; literally, nobody was ready. There is no one who is certified to be a Polio Essential Facility right now. It's a very high bar so very few facilities either have a shower or have the ability to add a shower. As you might imagine, that's a very expensive proposition if you're doing it specifically for polio. Some of the IPV manufactures just don't have those facilities and it would cost millions to set it up. This also affects their quality control as well as production and that's really where the issue is for this group in terms of doing the testing because the tests for polio antibody are based on virus neutralization. So like a little bit like you heard for measles. And the reason for that is Elisa assays are highly cross reactive for all

the enteroviruses. There are so many enteroviruses, they totally cross react in a binding assay. So you have to have, at least currently, have to have live virus. And many of the contract labs or clinical labs that used to offer this kind of service just basically threw up their hands and said we can't use Type 2 anymore, we're not going to go through the containment process; therefore, we can't do it.

And so this also affects, of course, not just vaccine quality control and IG manufacturers, but things like clinical trials. So there are actually clinical trials for either new polio vaccines that would be used in a stock pile or for different formulations of current vaccines or different combinations, different schedules, that sort of thing, serial prevalence studies. So actually right now CDC has about 90 percent of the world polio serology capacity simply because we do have a facility even though we're not certified yet, we're on that path. So this is going to actually even impact eradication. And of course the reason we're here for the producers.

However, I want to emphasize that it is very important that we contain. There have been multiple incidences, some of which have been in the news. There was one earlier this year in the Netherlands at a vaccine production plant, Wild Type 2. So wild viruses are used to produce the inactivated vaccine. Fortunately it was in a pilot scale part of the facility, not in the full 3000 liter fermenters; it was only a few hundred liters, so bad but could have been worse. Basically two workers were in a room and it's not clear exactly what happened but at some point, someone looked down and said oh, there's virus on the floor and so someone was exposed. So fortunately it was only one - - one person was across the room so they weren't exposed, but this individual excreted for something like 28 days. And so this caused a major incident in the Netherlands. Closed down the production as well so it had a lot of impact. Just a few weeks ago in Belgium another manufacturer, an employee was exposed to Type

wild virus. So this person was isolated until stools were negative. There was

actually, you probably heard about the one a couple of years ago also in Belgium where they dumped like a liter or several liters into the river, because they were moving a big container and something - - I don't know exactly again what happened, they probably won't say really, but something spilled and they dumped something like ten to the thirteenth infectious units into the river. So bad things do happen and so it is important to have containment.

Priorities for the next few months for the program are to interrupt wild virus circulation and this circulating vaccine derived polio virus transmission in these areas that are either known to be infected or at high risk. Maintaining very high quality surveillance, especially getting into these high risk areas, but also to really accelerate efforts for containment which is moving along. And to engage some of the non-polio programs in this post-certification strategy implementation and in containment specifically. Thank you very much. (Applause)

DR. LEVIS: So it looks like we have

five minutes for questions so we can open the floor for comments and discussion. Please remember to identify yourself and your organization.

MR. KENNEDY: Michael Kennedy, FDA. I was wondering, polio viruses are now being used for experimental oncolytic activity. What do you think is going to happen with that?

DR. OBERSTE: Yes that's a tricky question. And in some ways, I might push that off to Allison Mawle who's the U.S. Polio Containment Coordinator, but that is being discussed, and I think that the one thing that is at least encouraging there and makes us feel a little bit better is that those kind of treatments are in very, very controlled environments. So certainly right now it's people who are really ill and so they're in basically a containment facility in the hospital; they're not out running around on the street excreting. And also the virus is being delivered generally, specifically into the tumor area so it's not even clear that they're going to excrete. There's clearly though not enough data to make decisions on that.

DR. MAWLE: Alison Mawle, CDC, So what Steve said, I would echo. As I understand it right now, those viruses are polio virus Type 1 and they're also significantly attenuated. Type 1's not under containment and we've got at least three years until that could even possibly be the case. So yes, we will be working with those groups to move forward.

DR. OBERSTE: And that actually reminds me to mention something, and you'll hear more about it in the last talk of the session is there is a possibility in the GAP III guidelines of being able to work with "more attenuated or safer strains." However, there's not necessarily a process on who's going to determine those are safer yet. There's a committee that's being put together and so if that happens, and so these particular attenuated strains, oncolytic strains, might be one of those so there could be others that would be used for other purposes. Thank you. (Applause)

DR. KREIL: Good afternoon. Thomas Kreil of Shire. I'm for PPT chairing this afternoon's session together with my co-chair

here and it's our distinct pleasure to ask back to the stage Dr. Manisha Patel. We heard her talk earlier about the measles epidemic in the United States. If one in a million sounds like a low exposure, I'm very interested to hear what she was to say about polio virus.

DR. PATEL: Good afternoon and hello again. For this talk I'll be providing an overview on the epidemiology of poliomyelitis in the United States. Of course, we don't have polio in the U.S. so this primarily be a review, but I will be sharing some new aspects of our surveillance system.

Since we discussed measles this morning I thought it would be interesting to start with a comparison of the two viruses. So first, polio is not as infectious as measles. The  $r$  number is lower so that means that for every case of polio you can infect 2 to 15 people but for every case of measles you can infect 12 to 18 different people. The herd immunity threshold is also lower for polio which is certainly a benefit in eradication strategy. But fortunately for both, again for of these pathogens, the vaccine



effectiveness is still high and greater than 90 percent for both of them.

Long before there was a polio vaccine, polio was primarily in the endemic phase with sporadic and low level of disease. Epidemic started to emerge in the late 1880's and the first documented epidemic in the U.S. was in 1894, and one of the largest epidemics in the U.S. was reported in 1916. This graph is looking at the number of poliomyelitis cases shown by the purple line and then using the left axis and the number of vaccine associated poliomyelitis cases or VAPP shown by the pink bars and using the right axis.

Since introduction of the polio vaccination program in 1955, the last indigenous wild case was reported in 1979 and the last imported wild case was reported in 1993 and then the U.S. was certified polio free in 1994. In response to the number of VAPP cases that were being reported in the 1990's, ripped the backdrop of no wild type virus circulation, the U.S. switched to an IPV only program in 1997 with no further distribution of OPV starting in 2000.

So the U.S. vaccination schedule for

infants vaccination schedule for infants and children is four doses of IPV at ages 2 months, 4 months, 6 through 18 months, and then

through 6 years. If however, there are infants and children that are vaccinated outside the U.S. and they don't have documentation, they are required to get vaccinated or re-vaccinated as per the current U.S. schedule.

And then to conform to the lab containment strategy that Steve was just talking about; serology is no longer recommended or used to document proof of immunity so these children should also get vaccinated again. Now if they do have documentation, special consideration needs to be made for those infants and children that received OPV and so if they received OPV after April 2016, all of those doses are actually considered, generally considered actually, all considered either to have been monovalent or bivalent. And therefore, these children will also need to be re-vaccinated.

For this segment I'm going to go through all of the polio cases that have been reported in the U.S. since the IPV only schedule which was

started in 2000. Just to first start off with some basic polio terminology. Vaccine associated paralytic polio or VAPP is a clinical syndrome in which the paralysis develops after receipt of OPV, in contrast to vaccine derived polio viruses, which is describing the virus which are strains that have mutated from the original OPV strain over time and have required neurovirulence. There are three types: Immunodeficiency related vaccine derived polio virus which results after a prolonged replicated of the VDPV's in persons with primary immunodeficiencies, circulating vaccine derived polio virus which results from person to person transmission; this is a rare event but may occur when populations are severely under-immunized. So this is when you introduce OPV into a community that does not have high population immunity. The virus propagates and then mutates within that community. And then the last is ambiguous vaccine derived polio virus. This is where the source is unknown after a thorough investigation. It can be isolated from people with no known immunodeficiency or sewage as Steve was

mentioning earlier. This is sort of a last designation so the other two types should be ruled out first before you would call something ambiguous.

So the first VAPP case was reported in 2005 and this was in a healthy unvaccinated 22 year old female from Arizona with travel to Central and South America. She had developed fever and malaise on March 2nd and then progressed to acute leg weakness four days later. The stool specimens that were collected on March 20th were positive for the Sabin strain for both Types 2 and 3 and the infant that was in the host family was actually vaccinated with the first dose of OPV four days before this patient had arrived and stayed with this host family. This was the first case of paralytic polio since 1999 and it was the first imported VAPP case documented in the U.S.

The second case was actually reported in 2009 but she started having symptoms in 2008. This is a 44 year old woman with common variable immunodeficiency. She was diagnosed in 1991 and was hospitalized for progressive ascending paralysis and multisystem organ failure and she

died on hospital day 92. Her initial cultures were negative but the stool specimen that was obtained on day 74 was positive for iVDPV Type 2 and this was at 12.3 percent divergence in the VP1 region from the parent strain. And I don't think - - Steve didn't go into this but generally there's a constant mutation rate with polio viruses and based on that they were able to ascertain that this patient was probably infected two years before, twelve years prior, and likely from her own child who had been vaccinated with OPV when he was a baby.

The third case was reported in 2013. This is a 7 month old boy from India, hospitalized in Texas for history of draining skin lesions that were refractory to antibiotics and he subsequently developed limb paresis. He was vaccinated with BCG and that was actually the site of where that draining lesion was, as well as two doses of OPV in India. He was diagnosed with SCID while he was in the hospital and his older sibling had also died in infancy following a rotavirus vaccination. And when they did chromosomal analysis of the parents, they found greater than

10 percent homozygosity. Stool culture was positive for iVDPV Type 1 with 10 to 12 nucleotide substitutions from the parents' strain. And unfortunately this baby progressed to respiratory distress and died.

You may recall that in 2005 there was a 7 month old that was - - it was an unvaccinated girl from an Amish community in Minnesota and she had been hospitalized on and off since July of that year for failure to thrive and diarrhea. A stool specimen collected on the 27th was positive for Type 1 polio virus with a 2.3 percent divergence in the VP1 region compared to the parents' strain, and she was also diagnosed with SCID during her hospital stay. And this actually launched a large public health investigation. They were able to detect VDPV in seven other unimmunized children in that community; 8 of 23 children tested from the 3 of 5 families. Not everyone actually agreed to partake in this investigation so therefore not everyone was tested. There were also other states that were in contact with this community. There were investigations that were done in those states as

well. They did not identify polio virus there either. But again, not all the families agreed to participate. None of the children developed paralysis, including the 7 month old, and it was thought that based on molecular analysis that circulation of iVDPV was at least two months before the infant's infection was detected. I just wanted to point out that this is really rare. These are all the cases that we have actually had reported in polio in the U.S. Again, a testament to high vaccination coverage as well as high population immunity.

I thought now I'd talk a little bit about surveillance. The U.S. does not conduct surveillance like other countries that do acute flaccid paralysis surveillance so usually these cases are triggered by astute physicians that recognize the key clinical features in a patient, collect the appropriate specimens, and then send them for testing. However, in 2014 you may recall reports of healthy children that developed paralysis usually over the course of a couple of days. And these cases looked just like paralytic polio, and in fact, in the early stages of the

outbreak they were called poliomyelitis cases. At the same time there were outbreaks of acute respiratory illness associated with EBD68. And even though there's not been an established causal link between AFM and EBD 68, this is actually an area of ongoing work at CDC to better understand the etiology. There was a temporal relationship between EBD68 and AFM that year.

So in response to that outbreak, CDC did initiate standardized surveillance and I thought I'd walk you through the evolution of the case definition because this does enhance polio surveillance in the U.S. So in 2014 a confirmed case of AFM was considered as acute onset of limb weakness with an MRI showing a lesion largely restricted to the gray matter in a patient that was less than 21 years of age. And these are some MRI findings that are characteristic of AFM but also as characteristic for poliomyelitis and you can see enhancement of the gray matter in the central region here which is the light gray area. And then if you look at this panel you may be able to make out the characteristic H or butterfly lesion which can also be seen in polio cases.



So in 2015 the Council of State and territorial epidemiologists actually adopted the standardized case definition for national surveillance of AFM. They did modify it. They added a - - well they dropped the age limit so now adults could also be included as part of surveillance and then they included a probable case definition which removed the MRI component because not all the patients were getting MRI's. And then in June of this year, focal was changed to flaccid, and another layer where every case would be reviewed by an expert panel neurologist. This is consistent with what we would do for polio surveillance; that was also added. I think it's important to note that, I don't have a flow chart up how case reporting occurs but states have - - if they have a case of acute flaccid paralysis, they should then report those to CDC and then each of those cases, the medical charts, the MRI images as well as lab testing is then reviewed by this expert panel and the cases are then classified. So in essence we might be doing some kind of quasi AFP surveillance now. There's no national surveillance for AFM before 2014, and so baseline

rates in the U.S. are unknown. And AFM is not nationally notifiable in large part due to the fact that there are not confirmatory lab tests to confirm a case. And so our state health departments have varying degrees of the type of surveillance they do. There are some states, like Washington state that makes AFM actually have mandated reporting and then some states don't do surveillance at all. But the majority do some type of surveillance.

So this is the number of confirmed cases of AFM from August 2014 through 2017, there were 305 cases reported. The majority of these, more than 90 percent, were in children. So a couple of things; one is you'll notice there's two peak years, 2014 and then 2016. The second thing you'll notice is that most of the cases are occurring in the fall which is also enterovirus season.

And then I just want to point out that while there was a respiratory outbreak outbreak associated with EBD68 in 2014, there was pretty limited EBD68 circulation in 2015 and 2017. There was some circulation in 2016, but it was

nowhere near the degree that we saw in 2014 and yet we still had a pretty large AFM outbreak in 2016.

So I think this is probably the part you're interested in is that, at least within this surveillance system, I will say that preexisting medical conditions are not systematically collected in AFM surveillance. Currently it's an open text field and so we're revising our data collection methods to better ascertain this. But at least what we were able to find when we read all the cases is that there were two heart transplant patients, two renal transplant patients, one HIV patient, and one patient with lymphoma. So none of our cases in our surveillance system were PID patients.

And then sort of a second tier of surveillance are seroprevalence surveys. This was conducted in 2009-10 through NHANES. For Type 1 the overall seroprevalence was 93.9. For Type 2 it was 97 percent and Type 3 was the lowest at 83.1 percent, and it also varied by age, but in general, the seroprevalence rates remained high. This study was done in Kansas City in 2012

to 2013, Type 1 seroprevalence was 90.7, Type 2 94.4, and Type 3 was 83.3 percent. The difference here is that they're also including the 2 to 3 year olds so this group had lower seroprevalence in general compared to the other age groups. But this group also has not completed their vaccination series so again highlights the importance of making sure that all of their IPV - - these kids receive all of their IPV doses.

So in summary, AFM which does include poliomyelitis continues to be rare; it's at less than a case per million in the U.S. The last VAPP case that was documented in the U.S. was in 2013. U.S. seroprevalence is high against all three sera types with antibodies lowest to Type 3, and these are lower rates in children who have not yet completed the series. And then U.S. surveillance for acute onset of limb paralysis was established in 2014. It was primarily so we can better understand the underlying cause of AFM because these are not polio cases, but it does provide infrastructure for systematic surveillance of paralytic polio as well. Thank

you.

(Applause)

DR. KREIL: We do have time for a few questions if there are.

DR. MACADAM: So given your very high coverage in the U.S. - - sorry, Andrew Macadam, NIBSC. Given the very high coverage you have, the chance of a case, an AFP cropping up are very low. Do you think there's a case for doing environmental surveillance for polio in this country?

DR. PATEL: I'm going to punt that to Steve.

DR. OBERSTE: That has in fact - - Steve Oberste, CDC - - that has in fact been discussed a little bit. Part of the issue of course is just the vastness of the U.S. and how many sites it would take to cover the population, so it's not really practical. And as you're implying, certainly in an IPV vaccinated population where they can become infected and the virus can circulate, that is something to think about. At this point, we're not really monitoring that though.

DR. LEVIS: I just had a quick question if you could comment on, because we know there are people who are secretors, immunocompromised people who have been immunized. Is there surveillance on those people? Are they ought to be identified and are being followed or - -

DR. PATEL: Yeah, you know it's always going to be hard because of what you just said; they're asymptomatic. And in the Amish outbreak they were identified because that patient actually had other things going on. I think that there's still pockets of susceptible people in the U.S., and we're not seeing spread anywhere else. And you would think at least with polio, you know, for every case that you detect there's probably hundreds of cases around that, and we're not having cases sort of pop up in other places so I think in general that we're catching as much as we can. But certainly, besides this AFP surveillance we're not sort of doing any viral surveillance around that. There's enterovirus surveillance and we do pick up what we can but not anything sort of systematically for polio per say. And I don't know, Steve, if you want to add

anything to that in terms of polio virus surveillance.

DR. OBERSTE: Steve Oberste, CDC.

Yes, there certainly long term excreters among antibody deficient people. The numbers are pretty small even globally for those who excrete over a long period so there are a number, and I think Mark McKinlay is going to touch on one particular study done abroad, but I think the numbers are such that there are people who will excrete for say three months, six months, a short period, and then they stop; just sporadically. Some will excrete a little bit longer. There are a few however who have excreted for many years. There's the one case in the UK that he's excreted continuously for 30 years and not being paralyzed. And so again, the risk is pretty low and in somewhere in like the U.S. or in Europe where the patients have access to immunology centers and clinics and get treated and they are watched closely, there doesn't seem to be very high prevalence of excreters.

DR. GOLDING: Can I ask - - this is Basil Golding, FDA - - were these patients, were

some of them treated with immune globulin?

DR. PATEL: I don't know. I was specifically looking for that information. These are all published reports so we would have to go back to the medical charts and that's possible, but I'm not sure.

DR. GOLDING: I also assume that the differential diagnosis would include Guillain-Barre and is that true? And because that is often treated with immune globulin.

DR. PATEL: I don't know the full work up for each of those patients that did present. Guillain-Barre is certainly in the differential diagnosis, even for AFM. Those cases don't have the characteristic MRI findings like with our paralytic polio cases. It's a different MRI finding and there are probably other components with the CSF findings as well as the type of paralysis. But certainly that should have been part of the differential.

DR. SCOTT: I have some of the case notes from the woman with the CVID and the diagnosis of polio excretion. What I found, it was Type 2, and what we had to do we actually



received a call asking if we could get a high titer lot, and people at the Center for Biologics called around to the different manufacturers to find out first of all who had Type

and did they have, you know, a higher titer lot, and in fact, a higher titer lot, I mean, the best lot they could select was selected and given to her. I don't think it helped. I think she also had a very confusing case, and I don't recollect if she had been receiving regular immune globulin. It's possible.

DR. LEVIS: Our next speaker is Mark McKinlay and he is at the Taskforce for Global Health and he will give us a presentation on polio virus excretion and incidence of polio in primary immune deficient patients.

DR. MCKINLAY: Thank you very much for the invitation to speak to you today. I'll be talking about a study that we did in collaboration with the folks that are shown here at that bottom, including the Jeffrey Modell Foundation, which is a leading immunodeficiency foundation pretty much around the world, the Bill and Melinda Gates Foundation, CDC, and the World Health

Organization. I'll also be - - so the purpose of the study that I'm going to talk about is to estimate the prevalence of excretion of polio virus in immune deficient patients, but I'll also talk a bit about what we know about the risk, and Dr. Patel talked about this as well, the risk to a person who's excreting polio virus what's the potential they can develop poliomyelitis.

So the bulk of my talk will be talking about the study that we designed and the outcome of the global study to determine the incidence of polio virus excretion in a subset of primary immune deficiencies and these are B-cell deficient patients, because it's known that prolonged excretion of enterovirus and polio virus is predominately in those patients who hypo-IgG, so very low IgG levels, and these are B-cell deficient patients. You'll also see that we talk about accommodation B-cell but also T-cell is another group of patients that we are interested in. At the end I'll talk about a summary that we had from Dr. Winkelstein at one of our meetings about his summary of the literature, and Dr. Patel's pretty much covered

most of these patients, in terms of what's the probability of developing poliomyelitis in a B-cell deficient patient who's asymptomatic.

In 2012 when I joined the taskforce - - which by the way, the Taskforce for Global Health is an NGO based in Atlanta. We work very closely with CDC and WHO on a range of programs including polio eradication. But in 2012 it wasn't really understood what the asymptomatic polio virus excretion rate was in these patients. All that WHO knew was what was reported to them and this tended to be individuals who developed poliomyelitis and then they were cultured and found to be excreting iVDPV. So there was a real need to try to understand this. Meantime, it was pretty clear that the number of patients who are excreting iVDPV was increasing. So I stole this slide from WHO and it shows the incidence of iVDPV isolation by ten year periods and here's the last ten years. You can see it's increasing markedly and mainly in the lower and upper middle class countries. So what's happening we think is that more and more of these patients are surviving and continue to be exposed

and excrete iVDPV. So the global partners that I mentioned noted that we need to really do a study and we undertook in 2013 to design that study.

The objectives of the study were to determine the prevalence of excretion in asymptomatic B-cell immune deficient patients and then through the work of WHO and CDC is to characterize how this virus evolved over time.

The partners that were involved here, Mark Palansch and Steve Wassilak from CDC, worked very closely with us in terms of writing the protocol and connected us with WHO, Dusmane Diop at the WHO Global Polio Lab Network. They did all the stool testing and sequencing in the study. John Modlin and the team at the Bill and Melinda Gates Foundation provided technical advice and also the financial support for the study. And then we worked very closely with Fred and Vicki Modell at the Jeffrey Modell Foundation and all of their sites of pediatric immunologists around the world that were involved in the study. And the Modell Foundation basically managed the interactions with the clinical sites. Our role as the taskforce was basically do all the behind

the scenes work and study management and analyze and write up the manuscript.

So, the study design. We were looking for patients six weeks of age or older that had one of these four diagnoses. So any of these common variable immune deficiency:

Agammaglobulinemia, severe combined SCID, or and late in the study actually about a year into the study, one of our investigators in Tunisia had reported a relatively high incidence of excretion, prolonged excretion of enteroviruses in patients with MHC Class 2 deficiency. So we added that group kind of late in the study, but you'll see it was a beneficial addition. These individuals needed to live in an OPV using country and had to be able to provide two stool samples over a four day period. In many cases these patients were out, pretty far out away from cities and it was quite a job to get those samples.

The assays were run, as I mentioned, at the GPLN WHO and the polio virus positive virus were sequenced, but we continued to take samples from these individuals until they became culture negative. As you'll hear we still have one

subject who is still excreting virus.

In picking the countries, I mean, Jeffrey Modell Foundation's pretty much in every country around the world, but what we wanted to do is really identify those countries which would have a higher prevalence of immune deficient patients. And one of the things that's pretty well known, particularly with these B-cell deficient patients is in countries with high consanguinity have a higher rate. So you'll see when I show you the results not surprisingly that a number of the iVDPV's come from these countries.

So in the study we had 19 different sites in 13 different countries, and you can see on these next two slides the country, the city, and the number enrolled. And you can see it's pretty variable in terms of the number enrolled. We were shooting for somewhere between 20 and 30 per site, but when Iran had a lot more subjects, we made the decision to include them in the study. So you can see we had multiple sites in some countries, in particularly Turkey.

So the study got rolling in January 2014. You can see here we enrolled 635 patients.

Basically we got data on

point something percent of the patients in the study so it was really excellent. So 635 represent all the individuals for which we had a lab result.

So what we know from the study population is the average age was about 13 years of age. The older group were the common variable and agamms and the SCIDs tend to be younger as you might imagine. We had a predominance of males, and this is mainly because the agamms are predominately seen in - - agammaglobulinemia's mainly seen x-linked disease in males.

So by immune deficiency classification, half of the patients were CVID and a good third were agammaglobulinemias, and the balance were SCID and MHC Class II. And as I mentioned, MHC Class II was a late addition to the study.

So this very busy slide, a few things, I'm going to break it down in the subsequent slides but a couple of key points. Number one is that two percent of the patients in this study were found to be excreting polio virus but more

importantly five or .8 percent were excreting iVDPV. And they're highlighted here and you can see those in red and as I mentioned, one patient, Patient 108, is still excreting virus as of an email of a couple weeks ago. So we're continuing to follow that individual and also seeing if they'd be interested in antiviral treatment, and I'll come back to antiviral treatment in a bit.

So now to break this down in terms of where were these patients. Basically only four countries did we find patients excreting polio virus and only three countries were they excreting iVDPV. So three of the patients were in Iran, one in Tunisia, and one in Turkey. The type excreted, not surprisingly, iVDPV is predominately polio Type 2 and also CVDPV's tend to be predominately Type 2 which is one of the reasons we removed polio 2 from the oral polio vaccine. Four out of the five iVDPV's were Type 2 polio.

We, in the study, wanted to collect data on non-polio enteroviruses and you can see here that a number of countries had patients that were excreting non-polio enteroviruses.



So to summarize, what we learned from this study, that we found 13 or 2% of the immune deficient patients were excreting polio; .8 percent were excreting iVDPV. And of these, 4 were SCID and 1 was MHC Class II so no agammaglobulinemias or no CVID's in our sampling. As Steve mentioned, we know that there are CVID's that can excrete virus for long periods of time and in the case of the gentleman in the UK, over 30 years. The iVDPV's were all identified in three countries; Iran, Tunisia, and Turkey and this has been helpful as we've been talking with WHO and CDC about how we're going to do surveillance to find, identify these patients going forward. Four out of the five were polio Type 2, four out of the five were under one year of age and only one patient continues to excrete virus.

Interesting to this group and I think this relates to - - 97 percent of the patients in our study were receiving IVIG or subcutaneous which was only a few percent, I think, of the total. So the vast majority were receiving IVIG. Nearly five percent were excreting enterovirus.

We didn't collect; follow them to find out how long they continued. And if you're interested, this study is now published in the *Frontiers in Immunology* this year.

So now I'll turn to what is the potential that an individual who has an immune B-cell deficiency would develop paralytic disease. We have what's called the Polio Antivirals Initiative that we're the secretariat of at the taskforce and where we're developing antivirals stop excretion in these individuals. And we asked Dr. Jerry Winkelstein from Johns Hopkins to come and tell us well what is the risk to the patient. We know there's a risk to the eradication effort, but what's the risk of paralytic disease in a patient. So Jerry reviewed all the information that he could find which was seven cases and I was waiting for Dr. Patel and saying, oh boy, I think I may have missed some here. But basically the seven cases include the one mother from Minnesota here who excreted for 12 years prior to paralysis. And the conclusion, take home message here, especially when you weigh that versus cases that we know of

a fellow in the UK, there's a case in the U.S. who I don't think we ever - - we tried to follow her; she's now in California somewhere. We're trying to find her so we can offer antiviral treatment. But what we can't say is what the exact risk is to an individual at any point in time. We just know that there is a risk.

So to summarize, the overall summary is that asymptomatic excretion of poliovirus in B-cell deficient patients definitely occurs at a much higher frequency than in paralytic patients. But exactly, you know, the overall data suggests that it was about .8 percent based on our study. We do believe that iVDPV excretors represent a significant risk to the polio eradication effort. This has been modeled by groups to look at what the impact will be and that we don't know what the risk is for that individual patient. That said, when we meet with immunologists and talk about the antiviral that we're developing, they all, virtually all, say they would recommend to their patients that they take a treatment and reduce their risk to zero.

One of the things that's going on right

with WHO is to really improve the way they look for these individuals. We need to find them because we at the taskforce have been, like I said, serving as a secretariat to develop two antivirals working by two different mechanisms to be able to treat these individuals and stop excretion. We have one antiviral that we've tested in a study, that challenge study, that we did in Sweden which showed a very profound antiviral effect but a relatively high rate of drug resistance development which is the reason why we decided we had to bring in another antiviral with another mechanism to reduce that rate of resistance. The single agents available now, in fact, we've treated two patients so far, and we plan to move very quickly as we can. We think in two years we'll have the two drug combination available for treatment. But the single agent's now available for compassionate use. So with that, I'll end and take any questions. Thank you. (Applause)

DR. MOND: What was the amount of IGA that those patients were excreting? Those who were on IVIG who were excreters, were they getting

average doses, lower than average, do you have any idea?

DR. MCKINLAY: I don't know. I don't recall there being anything said that they were getting any, you know, more than a standard dose. But that doesn't - - I can go back and look at that.

DR. MOND: Okay.

DR. MCKINLAY: Okay, thank you.

DR. SORENSON: Ricardo Sorenson. Was there any intrafamilial transmission so that other people in the family or in the household would have acquired polio?

DR. MCKINLAY: That is a really important question and one we don't really have a good answer to because by the time you find they're excreting, the household's presumably been exposed for some time. But that is one of the key questions. What is the transmission rate? The assumption we make based on animal models et cetera and the behavior in the lab is that the virus will be as transmittable but we can't really say. I don't know, Steve, do you want to comment or Dr. Patel?

DR. OBERSTE: Yeah so, I think it's a

theoretical risk, and like Mark said, it's likely that they've certainly been exposed and they could be excreting. What I will say is I'm not aware of any case in which it's been shown that a paralytic case has resulted from an iVDPV excreter, meaning that from a contact, there are no known outbreaks that have been seeded by an iVDPV excreter. Doesn't mean it doesn't happen, but I haven't seen one.

DR. MCKINLAY: And the concern of course is in the poorly immunized population if one of these individuals are present.

DR. SORENSON: Right. I mention it actually because there is a relationship between CVID and IGA deficiency.

DR. MCKINLAY: ADA?

DR. SORENSON: IGA. They're in the same families. One may have CVID another has IGA, and strangely IGA deficient patients are susceptible to paralytic polio.

DR. MCKINLAY: Thank you.

DR. KREIL: All right, it's very nice to see that we are well on time. I'd like to call to the podium Dr. Andrew Macadam. He's at the

British NIBSC, or shall I say the Great British NIBSC, part of MHRA and he is, I think they said, has intellectually fathered a molecularly crippled polio virus.

DR. MACADAM: First of all, thanks to the organizers for inviting me to this fascinating meeting. It's taken me out of my comfort zone to some extent, but that's always a good thing. So as an outsider to the field it occurred to me that the simplest answer to the question of how to do polio assays after GAP III's been implemented is to just change the code. But that's clearly a stupid answer to the question. Apparently it's harder to change the code than the U.S. constitution. So what I'm going to talk about instead is a potential alternative solution to the problem.

So back in 2015, we published a paper on an alternative approach to IPV, inactivated polio vaccine production using seeds that would be safer in a post eradication world. And these strains could well be useful in a different context, so in the context of doing laboratory neutralization assays for the same reason. So

the strains were designed to be hyperattenuated, whatever that means; I'll try and explain, and also genetically stable. And that was done on the basis of what we know, what we've learned about Sabin virus evolution over many years of study in not only our lab but other labs as well.

So what I'm going to do in this talk is try and show that that is the case, the strains are attenuated genetically stable. Secondly show that we've devised ways of showing that - - devised ways of working that ensure they remain safe and stable. Look at whether the strains are a suitable fit for purpose in the assays that we're talking about here; in other words, do they act the same way as the current strains in neut assays. And lastly describe the pathway that we hope will lead to being able to use the strains under lower containment than is currently envisaged on the GAP III.

Okay, so this is covering ground we've heard before but it just emphasizes that it isn't just you guys that have the problem. There are other, there are other situations where we're going to need live viruses after eradication so



vaccine manufacturers and serums, surveys, et cetera as well as immunoglobulins. And as Steve said, there is nobody currently who can meet the requirements of GAP III. So there's a conflict between the clear need to contain polio and to safeguard the successes of the eradication program. There's a conflict with the need for essential medicines and vaccines.

Under GAP III there is a mechanism where it actually allows for new strains to be assessed, so I'm just quoting here from it, and in red you can see that if there are new strains that come along that can be shown to be safer than current strains, then the suitable containment will be applied to them. The way they'll be assessed is by a committee of experts and that committee will be appointed by the people at the top of the GAP III implementation, a body called CAG which is Containment Advisory Group, and I'll come back to this at the end perhaps.

The strains themselves we called S19, not a very inventive name and it doesn't really mean anything, but that's what we call them. The essential properties are that they replicate in

cell culture, that means you can use them to make vaccines but it also means that you can use them in neut assays. We think they're unlikely to replicate in humans and I'll explain why that's the case. We know they're genetically stable and there's a whole sort of portfolio of strains that have different capsids depending on what use you might want. These include wild types and Sabins and all three sera types.

So this is a schematic of what the strains look like and they're modified only slightly from the Sabin 3 vaccine strain. So they're based on Sabin 3. The capsid proteins come, as I said, from either the three vaccine strains or the three wild type strains that are currently used in IPV or even mostly used in neut assays, I think, Mahoney is the most commonly used virus in these assays. The non-structural agent comes from Sabin 3 and there's a modification that allows the virus to grow in Vero cells, and I'm not going to talk about that anymore unless anybody's interested. Then the business end, the bit that controls the infectivity and the genetic stability comes from a virus called S19.

And I apologize straightaway for hitting you so late in the day with some RNA secondary structure, but it actually is quite important to how the things work and so I'm going to walk you through it hopefully without invoking too much insider knowledge. So the 5 prime non-coding region of polio virus is highly structured. Domain V, ringed here is crucial to infectivity in the human gut and to attenuation of the live virus vaccines. It's the site of attenuating mutations in all three live virus vaccines. This domain forms part of a larger structure called the IRES which is involved in initiating of translation of the genome. If you screw that up enough that the virus doesn't initiate translation, then that aborts infection entirely because it's the first step after uncoating the virus within a cell.

This is the S19 domain V and there are two key features that explain how it works. First of all, it's thermodynamically unstable, and that's as a result of multiple base pair substitutions from CG, the strongest CG base pair which has three hydrogen bonds to a weaker UA base

pair which only has two. So the result is that that particular domain is weaker. It falls apart more easily and as a - - there's a knock on on the function of that domain in initiation of translation. The second thing is that it's genetically stable, and that's because we've removed any UG base pair so there's no single nucleotide which there's no single mutation which would allow the virus to strengthen that domain. Any single change would weaken it, so it would be selected against. And as result, the S19 is very stable.

In contrast, Sabin 3 for instance here has a UG base pair there and this base pair is extremely unstable so within days of vaccinating an infant, the U is converted to a C and the structure is strengthened and the virus reverts to virulence. As a consequence of these modifications, the viruses are much less infectious and we've done this in two ways. We've looked in transgenic mice, expressing the human polio virus receptor and in (inaudible) macaques. In the transgenic mice, you only need about ten infectious units if you introduce them

directly into spinal cord to paralyze the mice. Sabin's strains you need a bit more, a few logs there's a bit of a range depending on the sera type. The S19 strains, you don't get any clinical response however much virus you put in. And ten to the nine is about the most you can get into five microliters which is the inoculum for an intraspinal infection. Monkeys are harder to infect orally than humans. That's been known for a long time. The infectious dose 50 for wild types is around a million cell cultured doses, ten to six PFU. Sabin's strains are less infectious as they are in humans. The S19 strains, however much you put into them, you don't get any evidence of infection in the monkeys by this route.

So I think this evidence is really crucial to our proposition that the strains are not going to be infectious in people. This along with what we know about how polio viruses grow in the gut and also the extreme temperature sensitivity of the S19 strains. So we are confident that the viruses are not going to be infectious in people. Now there is a question of whether we actually need to prove that and I

expect that we can return to that and discuss it later, whether it's actually feasible to do that.

The other thing to say is that domain V of the virus is the only thing that matters. You can change the capsids, you can change the non-structurals, you can put wild type sequences in. It doesn't matter. The virus is attenuated. For that reason, that's the bit that you really want to make sure is genetically stable. When we talk about stability, that's the region that we're looking at.

As I said, one of the aspects of stability is that to convert a UA base pair, or AU here, to a CG, you need two mutations at the same time. Any individual change will weaken that base pair to UG or a mismatch and the virus (inaudible). But the other thing is that even if it does happen, you only go here to a virus we've called S18. This virus itself is hyperattenuated and it doesn't cause any paralysis in mice at very high doses. So you've got an additional layer of safety there. And if we did look at it in a more diagrammatic way, the virus has to pass through these fitness valleys

five times before it can revert to a wild type phenotype or else it has to mutate twice at the same time, and of course, that's extremely rare and it has to do that five times. So that's the theoretical basis of the stability. But of course we've tested that in cell culture passage and found that to be the case.

This is an assay we devised relatively recently to, very sensitively, look for the kind of reversions that matter in these strains. So as I said, if you start with a weak UA or AU base pair what you worry about is that you'll pick up a double nucleotide polymorphism. That's why we christened it to DNP on the basis of, or with reference to SNP's. And the way we do that is we do massive parallel sequencing on a fragment of the genome that spans the Domain V. So we amplify the whole of that region, sequence it at huge depth, and then we map it to all possible variants. So each AU will construct a sequence in silico which has a CG or a GC there. And we will look for any sequence which has both those mutations. If you look for one or the other, it doesn't really tell you anything because those

viruses are not revertant. So you find a sequence which maps exactly to a revertant sequence and it's an extremely sensitive method.

And so this is just some early data we produced and the method has a sensitivity of around one in half a million. In this example here, we've got a coverage of two to three hundred thousand per base and we can show that the number of

(inaudible) like revertants within the population is no higher than background as shown by the plasmid control lab. What's more, even when you pass anti-viruses in this case ten times in different cell lines, there's no increase in the number of revertants.

So we have a sensitive method and we've used it to show the sequences are stable. What we propose to do is use that method to ensure that any laboratory that wants to work with these strains in the future can validate them as being safe and what they're supposed to be and not



reverted.

So if we move on to whether they're fit for purpose. If you consider that the viruses have the same capsid proteins as the pair in from which they're derived, so what we call S19 MahoneyP1 has the same capsid protein sequence as the virus Mahoney. If it had an antigenic difference then that would be quite something. We would have to explain it in a way that nobody understands so it would be exceptional. However, we do need to show that the viruses could be used (inaudible). And we've done two things. There's some work we've done at NIBS and we've been working with Thomas's lab at Shire and Maria who's also here to validate the use of these strains in neut assays.

So one of the things we do is we release IPV. And one of the release tests is a rat immunizicity test. You inoculate rats IM and then after 21 days you take the serum and you do neuts and you look at seroconversion and you compare it with a reference. So these are some data from a Type 3 IPV analysis where we've challenged with S19 or the reference virus in the

neuts. And they're indistinguishable in this assay. And in fact, if you look at two vaccines, these are Type 2's now, the potency that you get for the vaccines using the reference strain or using the S19 strain was pretty much indistinguishable.

We've also looked at a panel of human sera. These are individual lots and they were tested against Sabin 2 or S19 with a Sabin 2 capsid and you can see that there's no statistical difference between the results using the two viruses. So what they've done Vienna is we provided them with two of the strains in fact that we've devised. They've prepared working seeds which have been highly characterized and then used these to validate the immunoglobulin characterizations that they normally do there. There are several aspects to the way you work. First of all, and this is Thomas's slide and I think he's summarized it perfectly here, good virology practice is essential. So you, though the viruses are safe, you want to make sure that you don't do anything stupid. So you take your original viruses and prepare your working seeds

and at that stage incorporate them into hundreds of thousands of vials depending and then you analyze them and make sure they are what you think they are. So one of the things that you do is, as I said, is you deep sequence them to show that they are what they are; in other words, they're identity is right, the sequence of the capsid is right and also that there's no reversion of this double nucleotide sort that I mentioned before. And what we agreed was that if you did, you would throw it away and start again, because that way you can ensure that what you're working with is safe.

So as I said, they've established working seeds certainly for one of the types. And we've confirmed that there is no reversion at all and they've used this virus to do some preliminary studies on immunoglobulin lots, and these are the data here. The problem as I understand it is that all immune globulin lots have pretty much the same level of antibodies so it's very difficult to get a straight line when all your points are in the same place. But they've done dilutions of the immune globulins

and from this data it looks like there's a very good correlation between using the S19 version and the original viruses that they used normally. So that work is still ongoing, but it's looking very promising.

I'll skip that, I think. So the last section of the talk really is to talk about the most important or the most difficult aspect of this which is how do we get, how do we persuade WHO that we can use these strains under reduced containment. And the pathway, as I said, is there. It's in GAP III. There's a paragraph that tells you how it's done. Unfortunately the process is not in place totally yet. But we've set off on the path of our own accord and hopefully WHO will catch up with us when we get to the right moment. So the pathway is you validate whatever you want to do with the strains. So in our case, in the lab we want to do IPV lot release or research or whatever. For an immune globulin manufacturer you want to do neutralization assays; say you do an SOP and you validate the new strain against the old et cetera, et cetera. Secondly you do a local risk assessment for your

activity. And you base it on the preclinical, if you like, data that we've got and possibly any that you've got yourself in terms of the virus being highly attenuated and stable and unlikely to infect humans and very low risk of reintroduction to population et cetera, et cetera. You also use a seed lot system, so use a vial of virus which is highly characterized. You use it and throw it away so there's no risk of the virus going back to any sort of anything like a wild type virus. Once you've done a local risk assessment you apply to the national body which is the NAC as Steve explained. Not every country has a NAC, but at some stage they will do. That's the National Authority for Containment. And they will have to then submit their advice to the CAG which as I said is the Containment Advisory Group.

This is what we've done. We proposed that the strains, really on the basis on the evidence we have, the strains could be handled under Class 1, because if they're not infectious what's the worry. However, given that there is a remote chance of a partial reversion from the

S19 to the S18, we've seen it once in around 350 passages, we proposed to handle it under Class 2. And we put it in this to our UK Health and Safety executive or the legal body at the moment. They're not the NAC, the NAC is not yet formed, and we gave them the risk assessment, and they assessed it and they, as you can see here in this draft report; it's not actually been published yet, but they agreed that laboratory work we proposed to do could be undertaken at BSL2, so this is really good. Of course they recognized that this has to be rubberstamped, if you like, by the national authority, by the NAC. But the HSC, who as I say are the legal body and have been operating in the UK for many decades, that is what they would advise. But then the NAC has to go to the CAG and say this is what we advise and the CAG has to authorize that. And they will - - I'm absolutely sure they won't do that until the strains have been assessed by this expert committee. I'm nearly finished. Unfortunately the expert committee has not yet been formed. I understand that it's partially formed. There are about three people in it out of the three names

that have been nominated anyway. But hopefully by the time we get to that stage, there will be a process by which new strains can be assessed.

Anyway, I think I've probably said enough. I just want to acknowledge the people that did the work, both at NIBS and at Shire. And thanks for your attention. (Applause)

DR. KREIL: Thank you Andrew. You brought us perfectly well on time. There is even the time for a few burning questions if they have them before we need to break for - -

DR. LEVIS: With reference to your early study that you showed in mice and non-human primates with the S19 strains, did you look at other parameters such as viremia or biodistribution of the virus in those animals or any other indicators for pathology?

DR. MADADAM: Right. So we only looked - - the only other thing we looked at was seroconversion. Well we looked at virus excretion obviously. And so we looked at how much and then we looked at the sequence of what came out. And on the basis that there was no sequence variation. I mean, clearly when you're

putting ten to the twelve infectious units in one end, you're going to get some out the other end. But what did come out had the same sequence as what went in. None of the monkeys seroconverted, whereas we had some positive controls which were the Sabin strains and they did seroconvert. So we didn't look for virus anywhere else. That was the question.

DR. SHEARER: William Shearer from Baylor.

(Inaudible) in your brilliant talk. I have to be careful with my comments. It seems to me that - -

DR. MACADAM: Could you waive? I can't see you.

DR. SHEARER: It seems to me that one of the drawbacks to this line of research is that you lack sufficient number of samples. I mean, you're dealing with seven people who (inaudible) period of time and you were in somewhat the same boat when we were looking at SCID babies several years ago and we decided to do a newborn screening test, universal. And the incidence actually doubled over time. And so my question to you is



why not go to the SCID babies that are born and follow them because they're the ones that are likely to have this polio virus infection in their guts? Have you thought of this with a planned program to provide a better number of human species?

DR. MACADAM: Is this for me or for Mark. I guess it's a bit more for Mark.

DR. SHEARER: Whoever.

DR. MCKINLAY: If the question is are we going to follow the SCID babies or whoever the B-cell deficient that we know are excreting, the answer is yes and we're hoping to also offer them an antiviral and stop excretion.

DR. SHEARER: Where is that happening?

DR. MCKINLAY: Right now it's not happening anywhere because the antivirals aren't both developed; they won't be ready to start treating until the end 2019 so right now what we're trying to do is put in place ways that we can find the patients. We can offer them a single antiviral at this point in time, but then offer them two antivirals hopefully by the end of 2019.

DR. SHEARER: Is there a supply train

from the clinic to the laboratory that we just heard about?

DR. MCKINLAY: If the question's what's the regulatory process, that's a really, really good question. We're talking with the company that's developing that's developing - - it is based here actually in D.C. It's called Viral Defense and they're working with the FDA antiviral division, but they're also talking with EMA and involving WHO because ultimately what we want is that this drug would be stockpiled, this combination therapy would be stockpiled at WHO for distribution.

DR. SHEARER: Thank you.

DR. KREIL: With that I'd like to have another round of applause for all the speakers. Thank you very much indeed.

(Applause) With that we are ready for the break. I have consulted with our chairman here and she also felt that maybe we don't need a full hour of break so can I ask you please to be back at 3:15. Thank you.

(Recess)

DR. LEVIS: So I think we'll get ready to start our panel discussion. And I would like to invite the speakers from our last session to come and join us up here for the questions. All right, so I'll go ahead and open the floor to our panelists to start with our first question which is what are the advantages of continuing to use polio antibody levels as a potency specification? And any comments on potential alternatives to that?

DR. OBERSTE: I would maybe throw that as a question to the audience and, you know, what is, you know, your interest in having polio specifically, I could understand historically why it would be there, but given the very low prevalence and risk of polio in the U.S. and Europe, and most of your market probably, what is the importance of having polio in there as a specific target?

DR. LEVIS: Say that again, hon?  
You're on now.

DR. SHEARER: William Shearer from Baylor. I think any time science can open the

door to a mechanism it eventually, in translation, with medicine benefit patients, I think we should do it. You know, we don't have much of a problem in this country, but I think that we're, if you believe this, our brother's keeper, there's half the world that suffers from this. So it's scientifically quite appealing, and on a human level it's the right thing to do.

DR. MCKINLAY: So you're basically saying it's not such an issue for U.S. but mainly for the use of the product outside the U.S.?

DR. SHEARER: You got that wrong. I say we should go ahead with it even though those limitations exist for the U.S. A chunk of the world is dealing with polio and scientifically it raises some very interesting insights into mechanisms of viral infection and how it affects the human immune system. And at a humanitarian level it's the right thing to do to help other people in this world. That's my message.

DR. LEVIS: I would just follow up and say do we have any clinicians here working with a population where the polio potency is critical as part of the, and I know this is a U.S.-centric

population, but if anybody has any global information on any current use of the products with respect to the polio potency component?

Because --

DR. OBERSTE: From a therapeutic point of view?

DR. LEVIS: Yes, because I know we learned, you know, some of the early statements were that it wasn't therapeutically efficacious so.

DR. MACADAM: Yes, I suppose I could mention that. I was thinking of it early. So the long-term excreter in the UK has been treated a number of ways without any success. So I mean, he's been on IVIG all his life. He's very good at self-administering, and that presumably explain why he's fit and well 30 years on. But one thing that was done was he was given oral IG which is very high titer. Another thing was a ribavirin treatment, and the last one was some human breast milk. So there happened to be a human breast milk bank very close to where he lived. And this was screened for polio antibodies, and it was thought that since

maternal antibodies affect how viruses, how polioviruses take in the gut, it might work.

In none of these cases was the virus cleared. There were temporary dips in excretion levels but it didn't, in fact, alter the population, the virus population that was excreted either. So it didn't select out cleanse from --

DR. SORENSON: But you didn't say --

DR. MACADAM: -- it was more or less --

DR. SORENSON: -- if anything worked?

You mentioned three different --

DR. MACADAM: None of them worked.

DR. SORENSON: None of them worked, okay.

DR. MACADAM: None of them worked.

DR. LEVIS: So what -- you made reference to antiviral therapy that's under development. Could you just, just for out of interest, describe that a little bit for the audience?

DR. MCKINLAY: So we're developing two antivirals that work by two different mechanisms. One has been through a challenge study with mOPV1

and shown to be effective, but in that study, we saw high rate of resistance development, which is a reason we brought along another drug with a different mechanism. So right now we're developing the formulations because the second drug is not really pharmaceutically elegant, let's say to make it absorbed as well as possible. And the two products should be available to start treating patients by the end of 2019 is the current plan.

So right now, if we were to treat anyone it's with a single drug and if we do that, of course, we don't know what will happen. We know we've stopped excretion in some immune deficient, but, you know, the potential is that we create a resistant strain, and then we're left with one drug to stop that. So that's where we are. Does that answer your question?

DR. LEVIS: Yeah, just thank you for the additional background.

DR. SORENSON: So another way of looking at this is I'm not saying it's not important to know how much because you showed that none of the other have developing countries like

Mexico, I paid attention to that, Mexico, Colombia, Argentina, and Brazil, they didn't have this problem. So this problem occurs in places where nobody will be able to afford gamma globulin to begin with. So the point of saying it's not the big issue. It's better to develop other drugs that are for them. That's one world view.

DR. MCKINLAY: And just to make the point that follows on what Andy was saying that the five IVDPV excreters were all taking IVIG in our study, too.

DR. HAJJAR: Joud Hajjar from Baylor College of Medicine. I looked up that lady who had CVID who contracted the polio supposedly from her child. And that patient was actually on immunoglobulin replacement therapy at the time, and her IGG chart, according to the case report in New England, was actually in the 900 range. So that kind of argues that what was wrong?

I mean, this patient, on the other hand, seems to have the noninfectious complications from CVID. So she was on prednisone as well at 20 milligrams. So maybe we have to pay specific attention to our patients who are suppressed, as



well may be T-cell suppressed, because they have the noninfectious complications and maybe, of course this is one case, but our patients are living longer and getting those noninfectious complications. Maybe those are the ones that this becomes more relevant to them.

DR. GOLDEN: So Basil Golden, FDA. So there's a regulatory issue here as well. It's in the regs to test for polio. And I can understand that what people are saying is that this is not a question of efficacy of immunoglobulin. There is a question that it's not only in the regs but it's used, to some extent, to determine consistency of manufacturing. So you want your immune globulin to be functional, and the test is a neutralization test. There is a functional assay, and to some extent it's testing the function of your antibody.

So I'm not saying in the future we couldn't substitute it with another test or find a way around this but it is a regulatory problem from that point of view.

DR. LEVIS: Can I ask just for one clarification? Did you say there's no

specification for the result? It just needs to be reported, or there is a --

DR. SCOTT: There is a specification in the regulations to IUs per mil. It might say units actually. I would also point out that we haven't actually officially come to this, but if we do decide to get rid of one of the tests that it's in the CFR, there's another part of the regulations very close to that, 21 CFR 640.120 which provides alternatives for that section. And that is that if an alternative is justifiable, you can take it. So technically speaking, we could probably get rid of one of those specifications.

But we'd need to have a reason, and we would probably want to have a replacement that we think, for various reasons, is better or more relevant. I think also, on a different tack, the information about that we're hearing about the immune-deficient patients who are excreting, and nevertheless, getting immunoglobulin, that suggests either the dose isn't as high as it could be, or that it just isn't going to work in this way. And isn't going to work is pretty

consistent with the idea that it also didn't seem to work in post-exposure prophylaxis.

The one thing that I don't know, and people with a lot more expertise might have an idea of, is whether immune globulin is going to prevent extension of the virus to the nervous system.

DR. MACADAM: I mean I think there's evidence that IVIG does protect the individual. I mean, this guy's been going for 30 years and he's perfectly fit. When I said it doesn't work, I meant it doesn't work in clearing the virus. So he's still infected but he's not got polio.

DR. LEVIS: Okay, and then Thomas --

DR. OBERSTE: To follow up on --

DR. LEVIS: Oh, sorry.

DR. OBERSTE: Okay. To follow up on that, yeah, it's generally from, I think, studies back in the fifties, it's consider that even any titer for polio is protected from disease, basically a one to eight titer, it protects from disease. However, there's no such thing as sterilizing immunity.

So you could have serum titer of

whatever and you're not protected from, obviously, an infection of the gut. And even people who have had multiple doses of OPV can become reinfected. Now they may excrete shorter period and at a lower titer, but they're still going to become infected and excrete. So in that way it's a little bit different than, say, the measles situation or certain other situations.

DR. BALLOW: So there's a paper by Alain Fischer published in one of the pediatric journals a number of years ago where they looked at their patients with XLA with regard to enteroviruses, maybe not quite the same. But they found that if they dosed low those XLA patients, x-linked agammaglobulinemia, were very susceptible to getting enteroviral meningoencephalitis.

But they used a higher dose, somewhere up at 800, 700, 800 milligrams per kilo, then they could protect those individuals against developing enterovirus. So yes, there is some information available about these groups of viruses preventing neurologic disease. The GI manifestations are totally different and I don't

think it's that much of an issue in this country with polio, even though data was presented.

You know, once we took the oral polio vaccine off the market that made a major change. We are having more problems now with norovirus in patients with immune deficiency. And perhaps some of those antivirals that you're developing will be, no, they won't be active against, okay. Too bad, because that's a real problem now is norovirus.

DR. LEVIS: Thomas, did you want to --

DR. KREIL: And if I can add on this whole discussion on the efficacy, I thought it was intriguing, if I understood it correctly, that this lady with the COVID who was treated with Igs only developed the paralytic consequence of the infection once the virus had a 12 percent mutation of the surface proteins. So maybe that was immune escape that allowed it to access the nervous system and cause the paralytic complications, or the virus sufficiently drifted so that with the 12 percent I think it was, right?

DR. HAJJAR: Yeah, again Joud Hajjar from Baylor. The patient in the report changed

products 60 days before she became symptomatic. So one of the points of discussion is that maybe the titers were higher in the other product, and after she changed, after 60 days, that was one of the causes. But obviously, there was hypotheses; you might have more insight about what was done for that patient, Dr. Patel, no?

DR. KREIL: No, I do not, but actually, I wanted to say something really different, because the question, as it is phrased, I would almost like to revisit the question. So what are the advantages of continuing the use of antibody levels? I think that's one for polio. And the other is, as a potency specification, because there seems to be pretty wide agreement that the efficacy of IG against polio is probably not the major thing. And certainly, given the incidents of the virus in the U.S., it is not.

And that's why I wonder, should we not talk about antibody function rather than potency? And for me to confirm the activity of every lot of IG and maybe use for that an assay where we have a lot of history so that we can see the continuity of the product quality, that, in itself, is a

value. Totally disrespectful of the fact whether it's protective against a virus that is not in circulation anyway; it's a different purpose I think.

DR. LEVIS: Okay. I think we'll go on to the next question which is what are the drawbacks of testing in the setting of anticipated WHO biocontainment requirements? And I would add on to that does anyone here, now what we've learned this afternoon, does anyone hear have experience with getting the WHO biocontainment requirements up and running, if you could just talk a little bit about your experiences with that?

DR. OBERSTE: Yeah, I would say both Andy and I have some experience with that since we have to do it in our own labs. And it's a lot of work. Some of it is the same kinds of things you would do for virtually any lab documenting all your procedures and that sort of thing. It's the things we all do anyway.

The biggest issues, I think, are, you know, currently with the requirement for a shower, because not every lab has that even a

BSL-3 lab doesn't necessarily have to have a shower. And that's, obviously, very expensive if you're in a building that, you know, you have to start drilling holes in concrete and such to put one in.

In our case, we do, in fact, have a shower in at least part of our lab. So we're actually able to use that. But at a lot of other labs, that's not the case. I would say that's probably the biggest hurdle.

Now once we get to full eradication then you have the things like the effluent decontamination and the HEPA-filtered exhaust air, and some other things that will kick in which make it even worse. In some places, some institutions, they have a BSL-3 lab that might be a shared lab in some cases. But in those cases they're doing very small amounts of polio work. And so it's easier to go into a single room or a couple of rooms and do things.

You know, in the case of my lab, we have an entire floor of a building and so it's, you know, something like 9,000 square feet of space. And so it's a much bigger deal to try to convert



that. In fact, we can't convert all of it over to this kind of containment. So that's really the challenge.

And to be able, to do that for, you know, one assay or for, you know, in some cases say a vaccine manufacturer even for one product, in the case of polio, a product they're probably not making a lot of money on, you know, it's really not feasible. And so that makes it very, very difficult. If there are ways around that, then I think that will help a lot.

DR. MACADAM: Yes, well, I agree with all of that. I mean, what it impacts on is the capacity of you to work really. Everything's harder to do so it takes longer. You can do less work.

But there are a few other wrinkles there. There's some things which are much harder to do under containment. One is animal work. It's not actually required for new tests, but for instance, we do these neurovirulence tests in mice intraspine inoculations. They are really difficult to do under those conditions. We don't even do them yet.

So and then with the manufacturers, for instance, certainly vaccine manufacturers, their QC labs are usually multiuse. So if you're going to turn it into a category three lab, you're going to have to make everybody, the QC for every product is going to have to be carried out under that containment. And you've got the investment and you've got the time where the lab's out of use. I mean, my impression is that most of them just aren't going to do it. They've said no.

DR. LEVIS: But what does that mean if they say no, that they're --

DR. MACADAM: Well, currently they hold all the cards. Because either you get -- if you insist that they make vaccine under GAPIII, they don't get any vaccine. So you either have vaccine or GAPIII.

DR. OBERSTE: And the other issue is that, you know, the way it's set up is all of these regulations are basically pushed down to the country level. So the country actually has to have this national authority for containment and enforce it. There are lots of countries that don't have any laws, this one for example, that

would impose, you know, these regulations on a facility.

And so there are countries where there are specific biosafety, biosecurity laws that, and even some that are specific for polio, and so they have some teeth to enforce. Other countries not so much and so that -- it makes it difficult because then you have the situation where you might have a facility that says no, we're not going to follow this because we can't, and but we're going to continue to make our product, and you can't stop us. But then you still have them as a risk.

And so I tell people, you know, that is true, but you don't want to see your picture on the front page of the "New York Times" that says, you know, academic lab spills wild polio virus into the Hudson River. You know, that would look bad, and so that's really all the enforce we would have in some cases.

DR. KREIL: So can I maybe ask a question? I mean, we are focusing here only about wild-type and maybe Sabin virus even. But then if I read from Andrew's slide, in that GAPIII

agreement it also talks about novel strains and how they could be reviewed, and then adequate controls applicable to their containment might be defined.

And as I understand it, then the strains that Andrew has developed would look to me like a couple of thousand-fold or even more orders of magnitude less pathogenic than even the vaccine virus we have put into the mouth of our kids. Shouldn't that be a convincing case for the WHO?

DR. MACADAM: I'm not going to say not that, am I? It would move me on to question three here by the sounds of it.

DR. KREIL: I mean, what are the drawbacks of testing? I would argue none so long as we convince the WHO that there is even after the eradication certain strains of polio that are not going to pose any threat, and therefore, should be still okay to work with. And then there is no drawback, I would argue.

DR. LEVIS: But it sounds like that's almost what the answer has to be if you're really going to get the level of resistance from the people who are going to have to implement the

GAPIII containment saying no, right? I mean, I presume those dialogues are going on now at the table at WHO in terms of the authority to say yes or no to the, you know, or what the strength of the document is with respect to the GAPIII requirements.

DR. MACADAM: I think that's right. I mean, I'm not there at the table so I mean maybe CDC can comment more about that. But I mean, I think the GAPIII has had several purposes, and the way it was written, which is extremely stringent, was with the express purpose of discouraging anybody to work with polio, certainly for any trivial reason. Like, for instance, at university practicals or something like that, and it more or less it's had that effect. Anybody who doesn't need to use polio has stopped.

They've destroyed their stocks, the ones they know about anyway. And we're down to, more or less, the essential facilities. So at this stage I think it's probably always been in their view, and Steve was saying this to me earlier that GAPIII would be changed, because it's achieved its primary purpose and now it has

to achieve a secondary purpose which is to be a practical useful document in a post-eradication world.

DR. OBERSTE: Yeah, and as Andy said, you know, there is admission that eventually there will be some changes and, again, it was meant to be very stringent, and I think now there's the realization, like, with many things, you put down something, and then there's something comes up that maybe they hadn't anticipated. And a different situation, and so there are some changes in the way both for, you know, polio labs and for non-polio labs who might have, you know, a real disease lab that has 10,000 stools they've collected that are really important for a different public health reason. You don't want to destroy those, but at the same time, you want to make sure they're handled safely.

So there is a process for trying to at least minimize the risk, or assess the risk, and then look at mitigating the risk. And so I think that will be going on and these new strains are one way to do that. Again, the process is just

now being put in place to start looking at those, but hopefully soon we'll know something more.

DR. KREIL: And just for final comment on that, I mean, so oftentimes we hear about this risk-benefit ratio. We cannot lose sight of the fact that IGs have been designated by WHO as essential medicine. So there is a few thousand kilograms of IG used every month in this country, and part of the release requirement is testing polio antibody titers.

So there is now a safe way of it, I fail to appreciate why it should be difficult to find a practical way forward to that. And I will say, too, that not knowing any of the WHO politics, I understand that they need to work through the national authorities, so the national MOHs for enforcement. And we have made the experience that there is national MOHs if you seek to dialogue and explain how those strains can be safely handled and serve the purpose to release an essential medicine to the market. And then we have found them extremely supportive and I think there will be feedback given to the WHO about how to actually live up to what they have put into the

GAPIII agreement themselves.

DR. OBERSTE: You make a really good point and, of course, this happens not just with this issue, but with lots of issues in WHO and governments and everywhere else. You'll have two different mandates that, in some ways, are mutually exclusive. And so you have to find, you know, they're both important. You have to find a way to make them match.

And so this product is, like you say, is an essential medicine. You have to find a way to get it out to the patients. But at the same time we don't want to have, you know, virus dumped into the river. And so we have to find that balance, and there has to be a way to make that work in the end. It's just the path between here and there that's a bit difficult sometimes and kind of bumpy.

But I think now there is starting to be some movement. So there have been some small changes. So just as an example, probably kind of a trivial example is that originally, nucleic acid was considered containable. So because polio is a positive strand RNA virus, so by



definition the RNA is infectious. However, I think we all recognize that, you know, you're not going to be drinking RNA. So for infectious for a human it's really not a very high risk.

You can introduce it into permissive cells and, you know, make a virus. And so there was a ruling that just in the last few months that, in fact, isolated nucleic acid, as long as you promise you're not going to put into permissive cells outside of a containment lab, you could extract RNA and then do molecular, whatever molecular testing you wanted to do. And so there has been already some movement in that direction recognizing that there are some parts of the original GAPIII that we can modify without substantially increasing the risk. And that's, I think, where we're going.

And again, the next meeting is just in about three weeks, so the end of this month, and hopefully, they'll start to tackle some of these other issues.

DR. LEVIS: We'll go on to the third question which is can BSL-2 assays for polio antibodies provide analogous information to that

of the current neutralization tests? And are such assays amenable to validation? And if not, identify gaps in assay methodology that would need to be addressed.

DR. MACADAM: I would turn that question around and say can validation assays be done under BSL-2? I don't think the validation is a big challenge. I mean, it'll take time, obviously, but all you're doing is comparing one strain with another and seeing if it performs equivalently. The challenge is to get agreement to do it under BSL-2. But that's my view.

DR. KREIL: So and as you have kindly included in in here, Andy, I mean, we have taken a look whether wild-type can be replaced by the hybrids he noted, and the results are fully equivalent. It's just like replacing one region in the assay by another, nothing else changes. So it would even, from a regulatory perspective, I think, be a fairly trivial change if that were to be pursued.

So currently we've done this under BSL-3 with all the bells and whistles and blah, blah. Having made the proposal, though, that

this virus in principle should be handled under BSL-3 and we have, 2, excuse me, BSL-2, and we have made that proposal with our national MOH. We've informed that so while we're using BSL-3 we believe that it should be handled BSL-2.

DR. OBERSTE: Yeah, and I agree for the S-19 strains that Andy described as well as there are two novel type 2 OPV strains that are candidates, vaccine candidates, that have been in a first and human trial, and completed that trial, and are under final analysis now. We've also shown that those strains behave similarly, at least in terms of aneugenicity. And so and you would guess that if you designed the strains, you know, rationally, you should be able to have equivalent aneugenicity. So this is not a shock.

And so it really just takes some appropriate bridging studies to show that you have equivalent aneugenicity and so now you can use these other strains. And it's all just going to come down to whether there's an approval to do that and what is the bar? So as Andy showed, there are standard neurovirulence assays in the transgenic mouse, and those are well-accepted now

and with years and years of experience.

Similarly for the monkey neurovirulent studies, they've shown the genetic stability over time.

And so the question is well, what other data would a committee want to see, if anything, that would convince them that these strains are now safer than the existing statement strains and could be used outside of a high-containment under BSL-3. I'll also add that, you know, that's still in a neutralization format.

We and several others have looked at other kinds of assays. So as I mentioned in the ELISA format there's so much cross-reactivity that's really difficult to do, so in the standard ELISA that doesn't really work. There's been some work with some engineered pseudoviruses that are not infectious. There's some issues with those as well. So those may or may not work in the long run.

NIBSC and with some work with FDA have actually developed a competitive ELISA which actually shows some promise. So that might be another avenue. Again, it would take some very fairly extensive bridging studies to show that

it's equivalent, but there are probably a couple of possibilities that could be developed here in the next couple of years.

Now of course, the issue is you don't necessarily have an unlimited time to get these in place. So that's really an issue. So as I said, you know, OPV cessation is expected to be about a year or two after certification of eradication. That's about 2021. So at that point, type 1 and type 3 would be contained. So certainly type 1 can be used now, and, you know, if a manufacturer could switch from type 2 to type 1, I know given all the challenges with that, that would at least buy a few years while all these other things get worked out.

DR. LEVIS: Dr. Scott?

DR. SCOTT: Well, timing is exactly what I was going to ask you about because if the GAPIII comes down on type 1, and we don't really have a plan, then we have a bit of trouble over here in our area of the woods.

I have another question also. I think that you said that if let's just say for the sake of argument that S-19 is accepted by WHO, one of

the things I believe you said is that seed bank maybe was a term you used? It would be tested, and I got the impression that it would, if they didn't have any signs of the beginnings of, you know, this progression of mutations, then they would be okay to use.

And how do you envision this would actually work? So it seems to me that each vial, each small aliquot would be used once, and the rest thrown away. So if immune globulin manufacturers make, say, collectively I don't even know how many thousand lots are made just for the U.S. There's a lot of lots getting made just in one year. How is that actually going to work technically? Will you have gigantic loads of or you see what I mean? There might be a need to passage it some more, and it would be kind of unusual to use the original version the whole time. And it would be kind of unusual for them to go back and deep sequence, you know, their stuff if they passage it, although, obviously, it could be done.

DR. MACADAM: Yeah, it's a very astute question and we have considered that. And I

think there are probably several answers. So if you were, for instance, a large manufacturer who is going to do a lot of tests, then you would probably to have a large seed bank of your own.

If you're a small company, you wouldn't want to put the effort into doing that. So there might be somebody else who provided a bank that was available to others, and that might be us, or it might be somebody else. So I think there are a number of different, well, those are two, but you could think of other ways possibly as well.

The other thing is that each assay only requires 2 logs per 50. It's not a lot of virus per 50, I mean, if you add it all up you can grow polio to 10 to the 9 per mill, or at least with these strains, at least 10 to the 8, somewhere between 8 and 9 anyway. So you can make an awful lot of diluted vials from not that much. So a large bank would not actually be unfeasible.

DR. LEVIS: I had an administrative question. Once you get the WHO's certification that the S-19 strains or some of the other ones that are in development are going to be okay as alternatives, then you have the responsibility of

going to the NRAs of each country? Or is there some kind of coordinated acceptance of this in terms of the change in the assays? And has that been part of the discussions?

DR. KREIL: So I think the one big issue is can you get WHO to allow you post-eradication to continued use of the virus. For everything else, for the regulatory purposes, I think it's quite straightforward, really, because on a global scale, there is one regulatory authority you need to discuss the exchange of a reagent, a critical reagent, in your assay with. And we all know what the validation package looks like that we need to make available to the FDA so that they feel comfortable that the performance of the assay has not changed.

It's really, I mean, the "hurdle" is making WHO comfortable that post-eradication we can continue using, for example, an S-19-like virus.

DR. LEVIS: Any other discussion points for -- okay, well, thank you very much. And I think we'll draw our panel to the close. And then the chairs for this morning's session



will come up and we'll just do a, the chairs will do a quick summary of the day. Thank you.

DR. SCOTT: I'd just like to make an announcement that the shuttle back to the hotel for the speakers will be arriving at 4:45 instead of 5:00. We tried to move it up a little more but that is the time they gave us. It's for the speakers actually.

If you came over on the shuttle, you're welcome to go back on the shuttle. There are a few extra spaces so if some speakers walked over in the morning and want to go back in the -- come back on the shuttle this evening, that's also fine.

DR. MISZTELA: Good afternoon, everyone. We will proceed now with the session one summary. So I'll start with an easier bit and then hand it over to my clinical colleague. So we have heard this morning that measles remains a rare disease in the United States due to successful vaccination program which assures good level of herd immunity. And so far for patients with primary immune deficiency it has been not a threat. It is of concern, of course,

but so far not a single reported case of measles infection in primary immune deficient patients has been reported.

We have also heard that studies have shown that there is a steady decrease in titers of measles antibody in plasma donors that is likely to have reached a steady state or will reach a steady low state as we continue. Especially in the younger donor population which constitutes the majority of the plasma donors. The high-titer populations are those who have experienced a natural measles infection. This population will decrease; therefore, what we will be left with is plasma donations, plasma pools with a lower titer of measles antibodies.

We have also heard from a study that's the revaccinations of donors does not yield what we were hoping to as in it's a transient twofold increase in measles antibody that after about six months returns to what we have seen before. So it's not a viable option to increase measles antibody titers. So the question remains if the FDA will, or would like to uphold their lot release criteria for measles testing. We will

not be able to release plasma lots especially for IV, IG, and intramuscular IG when current specifications are used. So and this will, in consequence, lead to a possible problem with supply of immune globulins for these patients.

DR. BALLOW: So my summarization is it's kind of more of an opinion from what I got from the first session. So as my colleague said it sounds like we're eventually as a donor pool for plasma products, we'll reach kind of a steady state based just on younger population that's just been immunized and have not had natural measles. But I encourage the manufacturers to collect data so that we're not caught short by surprise going forward. That, in fact, we're very close to this kind "steady state" measles antibody level on our donor population.

That will make it easier for the FDA to make a decision going forward that at the present time it sounds like I challenge the panel that we can reduce the release specifications to 0.3. And I think it sounded like the panel was comfortable with that. Achieving -- given the right dose of gamma globulin, achieving a level

of 240 milli-international units per mil of measles antibody. I didn't hear anyone contrary to that suggestion. But again, I think we just need to be careful in monitoring the donor population going forward.

With regard to steps for those immune deficiency patients that perhaps are exposed to measles, just a couple of thoughts. One is to ensure that the family members are vaccinated, and perhaps, that something the Immune Deficiency Foundation can stress through their various publications and communications. That it's really important to have all family members immunized.

With regard to giving an extra dose or changing the timing of the dose, I, for one, as a clinical immunologist, because it's kind of an emotional issue, if a patient came to me and said I have been exposed to measles, what am I going to do? I will probably take a more aggressive approach, perhaps a more conservative approach, and either if they're on IV, moving up the timetable, or if they're on subq maybe giving an extra dose.

I was struck by the fact that a survey suggested that perhaps significant proportion of patients with CVID are underdiagnosed, I'm sorry, under dosed, and then we have that other variable that some of the patients with CVID do not have normal cell-mediated immunity, and that's a factor that we don't understand at all with regard to susceptibility if we're changing our potency of these specifications. So that's kind of my thoughts on this morning's session.

DR. SCOTT: I think we can take comments if people have anything to add. I would just add that it was interesting to me that we discussed the total dose of immune globulin that patients are getting, and that one might make -- use that. That one might be able to use the doses that are being given in a sense, what's recommended, to help increase the titers in the patients. And that was something really that had not been discussed by us before. And I don't think it's necessarily that there's a right answer or best answer. But it's sort of a concept that we hadn't really given thought to. I would just add that was interesting in addition to the

list of other things, other potential solutions that we did write down in that massive question four.

DR. BALLOW: Yeah.

DR. SCOTT: And we didn't discuss labeling enough because we ran out of time. But now we know the shuttle is not coming for a little while. And so I think we might address that because it always comes up in our internal discussions, why can't you just label the titer and let clinicians decide? Or why can't you just have some products that are especially for some IGIV lots that are especially for PI patients, or called suitable for PI patients in this respect, and not worry about the other lots because they can go to people who need the immunomodulatory indications.

So there's that and it's a bit complex. And I think that it would be helpful for us to understand logistical or practical reasons that that might not be a good idea, or might be a good idea compared to some of the other ideas. That's wasn't very articulate but let's talk about labeling.

DR. BALLOW: But, Dawn, I don't think it's necessary at this point to have a hyper immune immunoglobulin preparation. That puts a lot of burden on the manufacturers. I think what's more important is that to guide physicians on what the appropriate dosing is as replacement immunoglobulin therapy in patients with primary immune deficiency disorders.

And so therefore, you might review the package inserts for the various products to make sure that, you know, I said before somewhere between 400 and 600 milligrams per kilo as a starting point would be probably suitable and accomplish what we want to accomplish. It might also be advantageous, perhaps, to put an addition in the package insert with regard to measles exposure. I know one manufacturer; I think it was Grifols, if I remember right, has something in their package insert along those lines.

So you know, with some careful wording I think it would be, again, a good guidance point for physicians who are not as experienced in taking care of some of these patients.

DR. MISZTELA: I think manufacturers,

I remember Dr. Simon touching on the issue of labeling high titer lots or producing these. I think the main issue was how to do this in practice because the population which has a high titer naturally, per se, is going to decrease even further. And then to hold these lots for a long time for what we have all agreed is a rare eventuality of a measles outbreak in the PID patients. I think from a practical point of view from a manufacturer's I would have to pass it on, but I think it would be extremely challenging.

DR. SCOTT: Well, I think our concept, I'm sorry; I think our concept of labeling was more than just to put the titer, to indicate what the titer is, not to say this is a hyper immune. And just some random lots will come up higher at least for the time being, but I don't see that lasting indefinitely as those recovered plasma donors really age out.

DR. KREIL: If I can maybe offer a comment here? So you're suggesting something with a number that you're putting on a label. So I think there might be an inclination of people to always take the higher number in some ways.



And in reality, we are talking about an event that has a likelihood of one in a million. Now in this country, something like two, three percent of the population have gone through West Nile virus infection.

Would that be the more relevant number? Or which other numbers do we wish to see on that label, too? It's going to be, I think it's a very convoluted label at some stage, no?

DR. SCOTT: This is exactly what we talked about at the last workshop, but I brought it up because I think it's important for us to understand what makes it feasible or infeasible. Because generally we do not favor labeling specific titers because it begins a sort of competition and the exact titers may not matter. It just may need to be a bit higher or a bit lower in any given case.

So you know, it's sort of there's a lack of precision there.

DR. KREIL: And I guess nobody would challenge a need for information, the desire for more information. I think what the problem is though for any person who receives IG treatment,

we don't know if they walk out in their backyard what virus is going to face them. Are we going to have the right number on that label that morning to make the right choice for that afternoon? I think it's going to suggest a level of information that, in reality, is not going to be able to carry its weight.

DR. BERGER: Mel Berger, CSL. I think we have to remember a little bit of the history of how we got the guidance on licensing which is that there were, as I understood it, as I experienced it, in order to have well-defined endpoints for clinical trials, we have very stringent definitions of a few infections we expect IVI or IGG to control in immune-deficient patients.

And so then we say, okay, you have to have less than an average of less than one serious bacterial infection per patient per year in order to get your IGG product licensed. And we don't have criteria for moderation of bronchiectasis or total elimination of sinus symptoms, or other infections which are very difficult to define.

So when we say the people are under

dosed or we say we should change the dosing recommendations, the dosing recommendations are that in order to have a product licensed, you have to meet this criterion, and then we say things and we try to teach our colleagues and so on that dosing needs to be individualized according to a patient's need and clinical situation. And clearly, just as Tom pointed out, different people have different residual immunoglobulin production. Immunoglobulin is not the be-all and end-all of the immune system. And certainly people have different levels of exposure. And all of that has to be figured into a patient's clinical need. So I don't see how much we can do with labeling.

DR. GOLDING: This is just my -- Basil Golding, FDA. So this is just my personal opinion hearing the discussion is that I gathered from this morning's session that if we talk about a 400 milligram per kilogram dose and the .3 level, that for the near future we probably going to be okay in terms of measles prophylaxis.

It may be a time point in the future where the level goes even below that, and we start

seeing failed lots. I think the idea of labeling maybe hasn't -- changing the label or putting the titer on the label that we're not there yet in terms of necessity, but we may eventually get there. And I would also like to point out that we do have products, the FDA has licensed products that do have the potency on the label.

I mean, we regulate clotting factors like factor VII for hemophilia and you do have the actual potency on the label so the physician can give the dose based on the potency of that vial that he has in his hand, he or she has in his hand. I don't see why it would be so difficult, maybe not now, but if there is a need in the future to put some more information about the potency testing on the carton or it would be so difficult if you want to calculate the dose more carefully. I don't think we've reached that point yet but it's something to think about. And I'd like to hear from other people in the industry why that is such, is that such a burden something?

DR. DEMARIO: This is Lucy DeMario from ADMA Biologics. To put the potency on every vial, I can see that having some issues carrying

out lot to lot. However, would FDA consider if you say that these lots are above X? So let's say we, you know, when we have a hot lot, we define that a hot lot is over .5 or .6 or whatever the number may be that we can define that as a hot lot. And when we have a hot lot, we can label it as, in some way that identifies it as a higher titer measles lot without it being it's exactly X.

DR. GOLDING: You know, I think that's some reasonable thing for us to think about and, you know, maybe an easier way to do this. So and again, I don't think we need to do that today or tomorrow. But if we start to see a lot of failed lots, you know, if 20 percent or more, a lot of failing because of the .3 and the 400 milligrams per kilogram, then we may want to think of some kind of solution that allows you to differentiate between lots that meet the measles standard and lots that don't.

And the lots that don't maybe have to meet a different -- have a different label. And those can be used for conditions where you're not treating patients with immune deficiency, but you're treating patients with ITP or CIDP or

whatever other neurological or other condition that doesn't require protection against an infectious agent.

DR. MOND: Just to that point, I think, Basil, transparency in label is always a good idea. I don't know what the implications are by putting titers in there, but I think it's a good idea for a physician to know what he actually is putting into the patient, whether it's measles, diphtheria, or strep, or whatever he's putting in, it's a good idea for him to know what it is he's putting in. The implications are not always clear because, obviously, it depends on the inoculum and the state of the patient, the age of the patient. But transparency and revealing what the product is I think it always a very good idea.

DR. BALLOW: No, as a clinician, I am not enthusiastic about this because let's just say you put on the label oh, you know, what the antibody titer to measles is. You know how misleading that will be to the clinician? Then they'll assume that, you know, there's a lot of antibodies, pneumococcal and pneumococcus in

there or lots of antibodies to haemophilus influenza type B. You know, they'll make all kinds of assumptions just by, you know, labeling it as such. So I think it's going to lend more confusion than enlightenment.

DR. MOND: You've already made assumptions that when you have a certain titer it'll be protective to a patient. Assumptions are made based on labels. So assumption is if it has this titer it's going to be okay for the patient. In fact it may not be. It depends on the dose you give to the patient. It depends on what his immune deficiency is. It depends on what the inoculum is.

So a patient will make assumptions based on medical judgments not simply based on a number that's put into a package insert.

DR. CERVENAKOVA: Larisa Cervenakova, PPTA team. I would like to come to comparison of the labeling for factor VIII, for example, or calculation factor, or whatever other factors, and immunoglobulins. In case of calculation factors, we do deal with protein. In case of immunoglobulin used for particular uses, we are

dealing with the virus to participation. It is a little bit different setting and very much more complex thing than just replacement of calculation factor.

So I think that it is probably correct to provide information about coagulation factor and activity and so on, but whether it is correct to provide the titer for the measles, I don't think so because we still don't know how much of immunoglobulin we need to kind of go treat of the virus in the body especially in immune deficient patients.

DR. MISZTELA: I think if there are no further questions or comments?

DR. BOYLE: Maybe one more comment. John Boyle, IDF. Just since we've been talking about the efficacy issue and clearing measles in a hypothetical case, as an end user and, you know, as Dr. Golding was talking about today or tomorrow, just one thing to put out there is while we, of course, are concerned about measles and any of the other conditions, you know, that may be affected with the antibody replacement, as someone who's lived through shortages as well of



immunoglobulin, I just urge everyone to think about the timing since we've already been talking about the, you know, some lots that, you know, are not making it to prime time. That, you know, those of us, you know, and certainly there are many who use for immune modulation which are on label, you know, such as ITP, and I know more and more the CIDP.

There's certainly lots of off-label uses, but we cannot afford, in the PI community, to have this drag on, you know, and the sort of an issue where we reach that tipping point with the loss of lots. We have to have enough of the plasma as has been discussed before, that there's just not enough of. We do have to have enough of that for the population here. So as people consider whether there should be, you know, lessening to the .3, while our community is concerned with all sides of it, we are also just plain concerned about the supply issue because it's what we rely on, so just wanted to put in that plug.

DR. MISZTELA: Thank you. I think with these concluding remarks I will terminate

the first summary. Thank you.

DR. KREIL: Thank you. So this is going to be the report of this afternoon session and Robin has kindly allowed me to take the stand here on behalf of both of us summarizing the session. The good thing is with the bus now late and the labeling squared away, I'll have 25 minutes that I do not intend using.

So on polio, there has been a lot of discussion about the efficacy of IG even against measles where there is a lot of evidence, frankly speaking, as compared to polio. And while there has been a discussion of whether IGs are a futility limiting polio virus replication to the gastrointestinal tract maybe where we see the shedders for years and years without developing any neurological complications, then I think in general the efficacy of IG against polio virus is even less proven than against measles virus. And that's why probably talking about efficacy in relation to the polio neutralization test that we perform on the lots is probably not the right word really.

Because in reality, what we were trying

to ascertain here, I think more, is the biological activity of every single lot they would reproduce. So it's not just a certain grams of protein that is in there, but these antibodies that are in there are indeed capable of doing what we expect them to do and that's one example for neutralization of all the viruses that might be contracted in the backyard in the afternoon. Bless you. We're testing for polio virus neutralization.

So about that antibody function, the question was asked so was it the benefit of continuing to test for polio virus. And I think there is an element that I certainly can have some warm thoughts about and that is continuity. I think we've seen these antibody titers determined over years and years and years, over different product generations, over changes of many factoring processes.

For all of these we have sort of monitored the effect on final product activity through the measles and the polio virus testing. And therefore, I think, to some degree, polio virus neutralization assay while of limited, if

any, clinical relevance, I think in terms of functionality confirmation for a specific lot, I think, does have a certain element of trustworthiness. I mean, we've been using it for so long. We understand it well.

There is never any titer program in that release. The assays rope us and everything else. So I think if possible then I would see from that perspective some utility I guess.

Now with the eradication, the WHO apparently have had different thoughts. The wish to eliminate the work with polio virus, and I think we all should be glad that they are trying to do that. I think this whole polio eradication campaign, the saving the last child in the world, an effort that has been some many billions and countless hours of volunteers around the world, we cannot possibly put that at risk by now leaking virus in whatever river.

And so the intention to contain the virus, ultimately, is certainly the right one. Now nothing in life, I've come to understand with the years is black and white. There is always shades of gray. And while it would be perfectly

the right thing to do to eliminate the use of any wild-type virus, and maybe even of the current vaccine viruses that we know may revert, at some stage, to become something more ugly, I think we should not allow the WHO to, in the black or white scheme, eliminate the use of all polio virus.

I think there is technical development and we have heard some of them from both Steve and Andrew that have resulted in polio viruses that are so apathogenic that really we should not be concerned about using them in the lab. And I shall assume that at WHO people are not ill-intentioned. They're just very busy with what they are trying to do and rightfully so.

But I think there just needs to be more of this interaction until they come to appreciate that really those viruses are not getting into the airway. And they will still allow us to do what we think is right for our purposes. So it's just a matter of increasing and foster that interaction.

I did mention that the national implementation of everything that the WHO is trying to achieve will require the collaboration

of the national MOHs. I would argue the other way around. If the national MOHs would encourage the WHO to really revisit and actually live up to what they've put into their GAPIII already, then I think both sides could ultimately get what they want.

I think we've seen today that there is at least one solution that we have reviewed in more detail, the S-19. To me the most compelling feature of these viruses, frankly, from everything that we know is that they're orders of magnitude less pathogenic than the virus we've been putting into the mouth of our kids. To me that's a pretty strong argument.

And I think it's just a matter of, again, making sure that both sides understand each other. And I think longer term it's going to be a lot more impactful, if not the plasma products industry which I'm sure that the WHO is very familiar with. But some of the national MOH stakeholders would support that dialogue with the WHO because I think that would maybe accelerate the region of a state where there is more certainty on the plasma products industry. Can

we use these new strains to still do the same thing? And we'll also, I think, generate more certainty for even the FDA and just fostering that dialogue, I think, is something that I believe should be a next step maybe.

So and without having exhausted the 25 minutes, I think that's as much as I would like to summarize for this afternoon's polio discussion. If there is any labeling discussions we need to have here or --

DR. SCOTT: I'm sorry about that. I just thought it should be gotten out. I want to thank everybody for your attention and your expertise and certainly the co-chairs have done a terrific job, the staff. And we'll see you tomorrow at 8:30. We have a big agenda tomorrow and we have to be out of this room at noon. So be prepared to think fast. Thank you.

(Whereupon, at 11:57 a.m. the  
PROCEEDINGS were adjourned.)

\* \* \* \* \*

CERTIFICATE OF NOTARY PUBLIC

COMMONWEALTH OF VIRGINIA

I, Carleton J. Anderson, III, notary public in and for the Commonwealth of Virginia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

**Notary Public, in and for the Commonwealth of  
Virginia**

**My Commission Expires: November 30, 2020**

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