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Center for Biologics Evaluation and Research (CBER)

152nd Meeting of the

Vaccines and Related Biological Products

Advisory Committee (VRBPAC)

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"This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO".

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PROCEEDINGS (8:05 a.m.)

Agenda Item: Welcome

DR. MCINNES: Good morning. I would like to call the meeting to order. I would like to welcome the members of the panel and the committee and the participants and the public who are attending today as well as the audience who is viewing via the webcast.

I would like to invite the members and consultants to introduce themselves. Please include your name, your institutional affiliation, and perhaps a few words about your expertise. We could start. Let me start actually with Dr. Heine and very special welcome to you. Thank you.

DR. HEINE: Phillip Heine. I am a maternal fetal medicine specialist from Duke University who also has a research interest and clinical focus in reproductive infectious diseases.

DR. GILBERT: Peter Gilbert from the Fred Hutchinson Cancer Research Center. I am a statistician who works on clinical trials for different vaccines, mostly HIV, but also for other vaccines.

DR. KOTLOFF: I am Karen Kotloff from the University of Maryland, Center for Vaccine Development. I am a pediatric infectious disease physician, principal

investigator of the Vaccine Treatment and Evaluation Unit at the Center for Vaccine Development.

DR. SPEARMAN: Paul Spearman. I am chief of infectious disease at Cincinnati Children's Hospital. I am a molecular virologist and also work through the VTUs to do vaccine trials and very interested. Thank you.

DR. BOK: Good morning. I am Karin Bok from the National Vaccine Program Office at HHS. I am a vaccine scientist and my specialty is maternal immunization of vaccine safety.

DR. SCHRAG: I am Stephanie Schrag. I am from the Division of Bacterial Diseases at the Centers for Disease Control and Prevention. I am here just for today because I also lead CDC's group B strep program.

DR. SUN: Wellington Sun, director of Division of Vaccines, Office of Vaccines here at CBER.

DR. GRUBER: Good morning. My name is Marion Gruber. I am the director of the Office of Vaccines Research and Review at CBER.

DR. GREENBERG: Good morning. David Greenberg, head of medical for Sanofi Pasteur and adjunct professor of pediatrics at University of Pittsburgh, history of vaccinology in pediatrics through seniors.

DR. MONTO: Good morning. I am Arnold Monto. I am an epidemiologist at the University of Michigan, School of

Public Health, mainly working on respiratory and other acute infections.

DR. SHANE: Good morning. I am Andy Shane. I am the interim division director of pediatric infectious diseases at Emory University and Children's Health Care of Atlanta. Thank you.

DR. JANES: Good morning. I am Holly Janes. I am a virus statistician at Fred Hutchinson and I work in HIV prevention efficacy trials.

DR. SAHLY: Good morning. Hana Sahly, Baylor College of Medicine, trained and practicing adult infectious diseases with a research interest in clinical vaccine development at the VTU as with other members here.

DR. MCINNES: Mr. Toubman, I believe you are on the phone. Can you hear us? Sheldon? Can you hear us? We cannot hear you. If you are on mute – was he muted? We have a lovely seat here for you with your name on it. I want you to know you are not forgotten. When we can make contact with you, we will circle back.

I am Pamela McInnes. I am the deputy director of the National Center for Advancing Translational Sciences, one of the newest institutes at the National Institute of Health. I am extremely privileged to be chairing this meeting. Dr. Edwards was not able to be here. I thank you for this opportunity.

Let me pass now to Serina to introduce yourself.

MS. HUNTER-THOMAS: Good morning everyone. My name is Serina Hunter-Thomas. I am the designated federal officer for VRBPAC.

DR. MCINNES: We will move to administrative announcements and conflict of interest statement.

Agenda Item: Administrative Announcements, Conflict of Interest Statement

MS. HUNTER-THOMAS: Good morning everyone. On behalf of the Food and Drug Administration, the Center for Biologics Evaluation and Research and VRBPAC, we would like to welcome everyone to this meeting. It is my pleasure to serve as a designated federal officer for the 152nd VRBPAC meeting.

The committee management specialists for this meeting are Rosanna Harvey and Joyce Mercer-Dickens. The committee management officers for this meeting is Casey Stewart, Julia Marie Keller, and Jeanette Devine. Thank you for the small village that is takes to put these meetings together.

Today's session has two topics, one that is open to the public in its entirety and one that is partially closed, which is Topic II. And the meeting topics are described in the Federal Register Notice that was published on April 26, 2018.

The FDA CBER press media representative for today is Miss Megan McSeveney. Megan, if you could please stand for a moment so that everyone can identify with you. Any press or members of the press can reach out to her as needed.

The transcriptionist for the meeting today is Mr. Chanda Chhay. He is from CASET.

I would like to remind everyone to please check your pagers and cell phones and make sure that they are either turned off or in silent mode. When making your comments, please first state your name and speak up so that your comments are accurately recorded for transcription.

Dr. McInnes, I would like to make a personal statement to thank you for your longstanding dedicated service to VRBPAC. You will be truly missed as this is your last meeting with us. Thank you so much.

DR. MCINNES: We are happy to have had Mike Levine join us. Welcome. We have gone around the table, Mike. Each person introducing themselves, saying their name, where they were from and what their interest is, their expertise perhaps for this committee. Welcome and let me ask you to do the same please.

DR. LEVINE: I am from the University of Maryland School of Medicine from the Center for Vaccine Development

and Global Health, the CVD. I am interested in vaccines, every aspect thereof.

DR. MCINNES: Sheldon, have you joined us by any chance? We will move on.

MS. HUNTER-THOMAS: We are going to proceed now with the conflict of interest disclosure statement for topic one for this meeting. The Food and Drug Administration is convening today for the 152nd Meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

Dr. Pamela McInnes is serving as the chair of the meeting for both Topics One and Topic Two. This meeting will have two separate conflict of interest disclosure statements read prior to each topic session that will occur during this meeting.

The entire meeting for Topic One will be conducted in an open session in which the committee will discuss approaches for demonstrating effectiveness of group B streptococcus vaccines intended for use in pregnant women to protect the newborn infant. This topic is determined to be a particular matter involving specific parties for PMI-SP.

With the exception of the industry representative, all participants of the committee are

either special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this Advisory Committee's compliance with federal ethics and conflict of interest laws including but not limited to 18 US Code 208 is being provided to participants at this meeting and to the public. This conflict of interest statement will be available for public viewing at the registration table.

Related to the discussions at this meeting, all members and consultants of this committee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouse or minor children for the purposes of 18 US Code 208 and their employers.

These interests may include investments, consultants, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment. The FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws.

Under 18 US Code 208, Congress has authorized FDA to grant waivers to special government employees and

regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual service outweighs his or her potential financial conflict of interest. However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 US Code 208.

Dr. David Greenberg is currently serving as the industry representative for this meeting. Dr. Greenberg is employed by Sanofi Pasteur. He is the industry representative that acts on behalf of all related industry and bring general industry perspective to the committee. Industry representatives are not appointed as special government employees and are non-voting members of the committee. Hence, industry representatives are not screened and do not participate in the closed sessions and do not have voting privileges.

Mr. Sheldon Taubman is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee and hence do have voting privileges and they do participate in the closed sessions.

Dr. Stephanie Schrag is employed by the Centers for Disease Control and Prevention. Dr. Schrag is a regular government employee and is serving as a speaker for this meeting. Dr. Schrag has acknowledged her expertise on the group B streptococcal disease and has clarified that she is not involved in any clinical trials involving GSK or Pfizer.

At this meeting, there are regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks in the interest of fairness that they disclose any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

Dr. Judith Absalon and Anneliesa Anderson are both currently employed by Pfizer and will be serving as guest speakers for this meeting and will make presentations. Drs. Absalon and Anderson have acknowledged having financial interest in or professional relationship with Pfizer, an affected firm for this meeting.

Dr. Shabir Madhi is employed by the University of Witwatersrand, Johannesburg, South Africa, and is serving as a guest speaker for this meeting and will make a

presentation. Dr. Madhi has acknowledged having financial interests in or professional relationships with some of the affected firms identified for this meeting, namely Pfizer. Additionally, he is involved in clinical trials related to GBS vaccine development and epidemiology that are funded by Novartis.

Dr. Carol Baker is employed by the Baylor College of Medicine and is serving as a guest speaker for this meeting as well. She will make a presentation. Dr. Baker has no financial conflicts of interest with any of the affected firms for this meeting.

Guest speakers are not special government employees. The FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms, its products, and if known, its direct competitors.

We would like to remind members, consultants and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement and their exclusion will be noted for the record.

This concludes my reading of the conflicts of interest statement for the public record related to Topic One.

DR. MCINNES: Thank you very much, Serina. This is a very special day that we have finally come to after really quite a long journey to speak very specifically about endpoints for prevention of group B strep disease in infants.

The topic is titled approaches for demonstrating effectiveness of group B streptococcus, otherwise known as GBS vaccines, intended for use in pregnant women to protect the newborn infants. We have quite an array of speakers and discussions. I would like to invite Dr. Cara Fiore from the FDA to present the introduction from the agency and the presentation of the questions.

Agenda Item: Topic 1: Approaches for Demonstrating Effectiveness of Group B Streptococcus (GBS) Vaccines Intended for Use in Pregnant Women to Protect the Newborn Infant

Agenda Item: FDA Introduction and Presentation of Questions

DR. FIORE: Thank you so much for coming out today. I am Cara Fiore. I am in the Division of Vaccines and Related Products Applications within the Office of

Vaccines Research and Review and the Center for Biologics within the FDA.

Today, we are going to talk about the evaluation of effectiveness of vaccines intended to prevent group B streptococcal disease in infants. I am going to give a very brief introduction and background to this.

Over the next few minutes, I am going to go over the bacterium that is group B streptococcus, which is Streptococcus agalactiae or GBS. I am going to go over very briefly at a high level of group B strep vaccine development. And I am going to present today's invited speakers and present the advisory committee questions that we are asking the Advisory Committee to opine on.

Today, we will discuss the approaches for evaluating the effectiveness of group b streptococcus or GBS vaccines in preventing infant disease in the context of maternal immunization.

Group B strep or GBS is a gram positive, diplococcus opportunistic pathogen. GBS has a variety of virulence factors that contribute to its pathogenesis. Group B strep expresses pili proteins, human lysine and other toxins that facilitate colonization and invasion of its hosts. Additionally, it is encapsulated. It has an outer polysaccharide. The capsular polysaccharide is a

critical virulence factor such that acapsular mutants have a decreased pathogenicity.

Serotyping of GBS is based on the capsular polysaccharide. To date, there have been ten clinically relevant GBS serotypes that have been identified: Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX. Antibodies to the capsular polysaccharide have been shown to be protective in animal models and human studies. These studies were done early on by Carol Baker and Dennis Kasper, dating back to the 1970s.

As I mentioned, we will discuss evaluation of the group B strep vaccines intended for maternal immunization. Maternal immunization in this session refers to vaccination during pregnancy. It is the passive protection of the infant using antibodies passed from the vaccinated mother to the unborn child with antibodies remaining active early in the neonate afterbirth. Currently, there are no vaccines licensed for maternal immunization in the US specifically to protect the infant when administered to the pregnant woman.

A GBS vaccine for maternal immunizations has been identified as a priority by the World Health Organization. On November 13, 2015, we had the VRBPAC topic of considerations for evaluation of safety and effectiveness

of vaccines administered to pregnant women to protect the infant.

Today's discussion will focus on the evaluation of group B strep vaccine effectiveness and the FDA will not present any product-specific information.

I am just going to go over very briefly at a very high level product development for group B strep so far. Historically, there have been polysaccharide-based vaccines developed for group B strep. And although these polysaccharide-based vaccines illicit an immune response, they did not provide robust protection in humans. Based on published literature, a present approach would more likely be a polysaccharide conjugate vaccine where the polysaccharide is conjugated to a carrier protein, thereby eliciting an improved immune response.

Another approach could be approaching subunit vaccines.

Because there are ten clinically relevant serotypes for group B strep, a vaccine would likely be multivalent to provide wider clinical coverage. The approaches that we discussed today will inform group B strep vaccine development.

Now, I am going to go over today's invited speakers and the topics that they are going to speak about. Dr. Darcie Everett is up first. She is from the FDA and she

will frame the discussion of potential study endpoints, including a spectrum of clinical disease.

After Dr. Everett, we will hear from Dr. Stephanie Schrag. Dr. Schrag is an epidemiologist with the US Centers for Disease Control and Prevention. And the title of her talk is group B strep young infant disease burden, trends and prevention strategies: high income countries.

Dr. Carol Baker will be up next and she is from the Baylor College of Medicine. Her talk is entitled GBS conjugate vaccines: early development and correlates of protection.

Dr. Shabir Madhi will be joining us via WebEx. He is professor of vaccinology in South Africa. The title of his talk is clinical and immunological epidemiology of group B strep disease and colonization in low and middle-income countries.

Lastly, we will hear from Pfizer. Pfizer will present two different talks. They will discuss their group B streptococcus maternal immunization program.

Now, I am going to go over the questions that we are asking the advisory committee to opine on. The first question is in addition to laboratory confirmed early or late onset disease, what additional clinical disease endpoints, i.e. unconfirmed and confirmed fetal or infant

endpoints, maternal endpoints, could be considered to demonstrate vaccine effectiveness. Please discuss their strengths and limitations.

The second question is could immunological endpoints, i.e. functional and ligand binding antibody levels, be used to demonstrate vaccine effectiveness. If so, please discuss their strengths and limitations.

And thirdly and lastly, could colonization be used to demonstrate vaccine effectiveness? If so, please discuss its strengths and limitations.

With that, I would like to introduce Dr. Darcie Everett.

Agenda Item: Evaluation of the Effectiveness of Vaccines Intended to Prevent Group B Streptococcal Disease in Infants

DR. EVERETT: Good morning. I am Dr. Darcie Everett, medical officer at the FDA. I will be presenting on the evaluation of the effectiveness of vaccines intended to prevent group B streptococcal disease in infants in order to frame the Advisory Committee's discussion about study endpoints.

Today I will be providing some background for the discussion by giving an overview of the spectrum of clinical disease caused by group B streptococcus or GBS. I will talk a little bit about current prevention strategies.

I will then briefly discuss licensure pathways that may be considered in the development of GBS vaccines.

Finally, I will discuss endpoints that could be considered for pivotal studies to demonstrate vaccine effectiveness. This will include clinical disease endpoints, immunologic endpoints, and colonization.

I will start with an overview of the spectrum of clinical disease caused by GBS in young infants and pregnant and postpartum women. As Dr. Fiore discussed, GBS is an encapsulated gram-positive bacterium of which ten serotypes have been identified. In most cases, GBS is a commensal organism that colonizes the genital and gastrointestinal tracts of healthy adults. Globally, it is estimated that approximately 18 percent of adults are asymptomatic carriers based upon assessments of colonization in pregnant women.

Although most colonized individual will not develop disease due to GBS, it is an important cause of invasive disease particularly in certain groups. GBS is the leading cause of morbidity and mortality in neonates and young infants and also causes disease in pregnant and postpartum women.

Five serotypes, serotypes Ia, Ib, II, III, and V, account for approximately 97 percent of invasive disease in infants worldwide.

GBS disease in the infant is categorized by the age of the infant and disease onset with disease manifesting in the first week of life known as early-onset disease and disease manifesting from one week to three months of life known as late-onset disease.

In early onset disease, GBS is transmitted directly from a colonized mother to her fetus or infant. Transmission occurs via an ascending infection in utero usually after rupture of membranes, but GBS invasion can occur through intact membranes.

Transmission can also occur during passage through the vagina, but usually this results in asymptomatic colonization of the infant.

Because early onset disease is often the result of peripartum invasion, early onset disease usually occurs within the first 24 hours of life. The most common clinical syndromes are sepsis without a focus, pneumonia or meningitis.

Late-onset disease occurs between days 7 through 89 of age. And the infant may acquire GBS from colonized household members or the community. The common clinical syndromes are sepsis without a focus, meningitis, and less commonly other focal infections such as cellulitis, pneumonia, septic arthritis and osteomyelitis. Late-onset disease is more likely to present as meningitis than early-

onset disease and serotype 3, which is associated with an increased risk of meningitis, is more common in late-onset disease.

Case fatality for early-onset disease used to be as high as 50 percent, but has improved with advances in neonatal care. In November of 2017, a series of 11 articles describing the burden of GBS disease in infants and pregnant women was published in Clinical Infectious Diseases. Our guest speakers contributed to these articles and much of my data on background incidence and impact is taken from this series.

In this global meta-analysis, case fatality for early-onset disease was 5 percent in high-income countries, but was as high as 27 percent in Africa. Case fatality for late-onset disease was 4 percent in high-income countries and 12 percent in Africa.

Data on long-term outcomes in infants with invasive GBS disease has focused on neurodevelopmental outcomes in infants with GBS meningitis. The November 2017 meta-analysis estimated that worldwide 32 percent of GBS meningitis survivors had neurodevelopmental impairment at 18 months of follow-up, including 18 percent who had moderate to severe impairment.

As stated previously, a large majority of infants born to GBS colonized women do not develop invasive

disease. Risk factors contributing to the development of early-onset disease have been well characterized. The primary risk factor and virtually a prerequisite for early onset disease is maternal GBS colonization. Heavy maternal colonization and maternal GBS bacteriuria, which may be a marker for heavy colonization, are also risk factors for early onset infant disease.

Other risk factors are preterm delivery, premature or prolonged rupture of membranes, chorioamnionitis, as determined by maternal intrapartum fever, and prior delivery of an infant with GBS disease. Deficiency in naturally acquired maternal anti-capsular polysaccharide antibody is also a risk factor for infant disease, which you will hear more about later in the presentation and in our guest speakers' presentations today.

Risk factors for late-onset disease are not as well as characterized as for early onset, but maternal colonization, preterm birth and HIV are risk factors for disease presenting from one week to three months of life.

In addition to early and late-onset disease, invasive GBS disease can also cause stillbirth, which is fetal death resulting in an infant who was born with no signs of life after a specified gestation. In the United States, stillbirth is defined at or after 20 weeks. The

World Health Organization defines stillbirth at or after 28 weeks of gestation.

GBS is known to cause stillbirth with transmission occurring through the same mechanism as early onset disease, an ascending infection in utero in a colonized pregnant woman.

In observational studies attempting to quantify the contribution that GBS makes to stillbirth, varied diagnostic techniques have been used to identify GBS-related stillbirth. But a generally accepted definition is isolation of GBS from a sterile site in a stillbirth infant.

In the November 2017 series, a meta-analysis estimated that based on the studies including data since 2000, 1 percent of all stillbirths in high-income countries and 4 percent of stillbirths in Africa were associated with GBS.

GBS can also cause maternal disease in pregnant and postpartum women, leading to infections of the urinary tract, the genital tract causing chorioamnionitis and postpartum endometritis and bloodstream infections.

In observational trials that have attempted to quantify the burden of maternal GBS disease, invasive disease is generally defined as isolation of GBS from a sterile site in a pregnant woman or women up to 42 days

postpartum with clinical symptoms such as fever. This definition does not include nonsystemic infections such as maybe the case with pyelonephritis or chorioamnionitis.

In the November 2017 series, a systematic review meta-analysis found limited data quantifying the burden of maternal invasive GBS disease in high-income countries and no qualifying data from low or middle-income countries.

Based on the limited data from high-income countries, case fatality for pregnant and postpartum women was estimated to be 0.2 percent. However, risk to the fetus or infant was greater with an estimated 7 percent of pregnancies in which the woman had invasive disease ending in stillbirth or miscarriage and an estimated 2 percent of infants born to women with invasive disease dying within the first month of life.

GBS has also been implicated in other clinical outcomes such as preterm birth and neonatal encephalopathy. But the bacteria's exact contribution is not known. In the November 2017 series, a global meta-analysis estimated the relevant risk for preterm birth with maternal GBS colonization to be 1.2 in cohort and cross-sectional studies and the odds ratio to be 1.85 in case control studies.

In this analysis, preterm birth was associated with GBS bacteriuria in cohort studies with a relative risk

of 1.98. It is not known whether these results are due to confounding or whether GBS bacteria can cause preterm birth without necessarily resulting in invasive disease.

Neonatal encephalopathy has been associated with GBS disease and mortality is approximately twice as high in infants with neonatal encephalopathy and GBS isolated by culture or molecular assay from a normally sterile site compared to cases not associated with GBS.

Prevention of GBS disease in infants has evolved over time. Currently invasive disease can be prevented with the use of antibiotics administered during labor.

There are two general approaches for identifying subjects to whom intrapartum antibiotic prophylaxis or IAP is administered. The risk-based approach identifies candidates for IAP based on maternal risk factors for having an infant with early onset disease. Risk factors used to identify women are the same risk factors for early onset disease.

The culture-based approach screens pregnant women by rectovaginal culture late in pregnancy and all GBS colonized women are given IAP.

Countries that have adopted policies for GBS prevention and IAP administration have chosen different strategies. Some have opted for the risk-based approach in

both high and low-income countries and others have opted for the culture-based approach.

For countries in which the risk-based approach has been employed, recommending bodies have selected different risk factors in order to determine who should receive IAP.

It is important to note that in countries in which a GBS vaccine study may be conducted, there may be a different standard of care for intrapartum antibody prophylaxis for GBS prevention than that used in the United States.

In 1992, different guidelines for IAP were issued separately by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. In 1996, consensus guidelines recommended that clinicians use one of the two approaches to GBS prevention but did not specify a preference.

In 2002, the recommendation was revised to universal screening by rectovaginal culture for GBS colonization at 35 to 37 weeks gestation and treatment of all colonized women with IAP.

Since these recommendations were made, the incidence of early-onset disease depicted by the red line has declined. But the incidence of late-onset disease, the blue line, has remained relatively steady.

Despite the demonstrated success of IAP in preventing early-onset disease, there are limitations to currently available prevention methods. Even the most aggressive prevention strategy, the culture-based approach, has not eliminated early-onset disease and has not affected late-onset disease incidence.

Invasive disease can occur prior to the onset of labor and administration of IAP, for example, as might be the case in GBS-related stillbirth.

Antibiotic administration does have its own adverse effects including allergic reactions and concerns about the emergence of antibiotic resistance. However, the risk benefit of IAP is favorable.

Lastly, both approaches can also be costly and logistically difficult to implement particularly in the setting of low-income countries.

As a consequence, there has been widespread support for the development of a vaccine against GBS disease. Because there is active transfer of maternal antibodies across the placenta particularly late in pregnancy, it is thought that a strategy of immunizing pregnant women will have the greatest impact on preventing infant disease.

Now, I would like to switch gears somewhat and give a brief overview of vaccine licensure. My point in

presenting this is to remind you of the framework that is available to approve vaccines. Rather than focusing the discussion on the best pathway for licensure, we would like to focus the discussion on possible study endpoints. But I do want to give you some background information on some of the things that the FDA is thinking about when we are making decisions regarding licensure pathways.

At the time of a biologics licensure application, the FDA reviews data to ensure the product is safe and effective. It is expected that the demonstration of vaccine safety and effectiveness will be based on adequate and well-controlled trials. These trials can be conducted within or outside of the United States.

Among the licensure pathways that are available to the FDA to license vaccines, traditional approval and accelerated approval are pathways that would potentially apply to licensure of a GBS vaccine. Traditional approval is used when vaccine effectiveness is based on a clinical disease endpoint or a well-established precursor of the clinical disease endpoint of interest.

For example, rotavirus gastroenteritis was a clinical disease endpoint to evaluate rotavirus vaccine effectiveness. Cervical intraepithelial neoplasia of grade 2 or greater, a well-established precursor for cervical

cancer, was used as a clinical disease endpoint to evaluate HPV vaccines.

Sometimes an immune marker can be used as a study endpoint to demonstrate vaccine effectiveness by the traditional approval pathway when it is well established that the marker indicates protection from disease. For example, antibody to hepatitis B surface antigen above a certain threshold has been established as a marker indicating clinical benefit and has been used to support traditional approval of hepatitis B vaccines. Often an efficacy trial is used to establish an immune marker as an accepted marker of disease protection.

An accelerated approval pathway is available for serious conditions for which a product addresses an unmet medical need. This would apply to a new vaccine against GBS. In this pathway, vaccine effectiveness can initially be demonstrated using a marker that is reasonably likely to predict clinical benefit. In contrast to the traditional approval pathway, there is some uncertainty regarding the ability of the marker to predict effectiveness.

An example of an endpoint that was used as a basis of an accelerated approval licensure is pneumococcal antibody titer above a specific threshold as measured by opsonophagocytosis assay, which was used to support

approval of pneumococcal conjugate vaccine in adults for prevention of pneumonia.

As part of the accelerated approval pathway, the sponsors require to verify and further describe clinical benefit with an adequate and well-controlled trial that is preferably ongoing at the time of licensure or alternatively conducted post-approval.

Again, I will remind you that the focus of this discussion is not to decide which of these pathways is appropriate. But this information is presented to orient you to the types and rigor of data that are used to support licensure.

Now I am going to move on to the major topic for discussion today: how to demonstrate vaccine effectiveness for GBS vaccine and more specifically, what study endpoints are appropriate for this.

This is an outline of the potential study endpoints I am going to discuss. I will start with clinical disease endpoints, in particular, infant disease and GBS-related stillbirth. I will also discuss other potentially relevant clinical disease endpoints. Then I will talk about possible immunologic endpoints. Finally, I will discuss colonization as a potential study endpoint. My talk will focus on clinical disease endpoints as some of the other

invited speakers will discuss other potential endpoints in more detail.

Infant invasive disease would be an appropriate clinical outcome to evaluate in a GBS vaccine trial. While earlier late-onset disease could be evaluated separately, a combined endpoint of invasive disease identified at 0 through 89 days of age would be clinically relevant.

A general case definition that has been used for collecting observational data and has been proposed for vaccine trials is isolation of GBS from a normally sterile site in a sick infant. Infants with a clinical history consistent with invasive disease for which GBS was isolated from sterile site postmortem might also be included in this definition.

Use of a combined endpoint of both early and late onset disease would be anticipated to reduce the required study size compared to either earlier or late-onset disease alone as I will show you in the next couple of slides.

Incidences of both early and late onset disease in the US are relatively low. Based on data from 2016, the Centers for Disease Control and Prevention estimated 0.22 early-onset disease cases per 1000 live births and 0.25 late-onset disease cases per 1000 live births.

Study size estimates have been published in the literature by our guest speakers. Based on an incidence of

early-onset disease in the United States in 2014 of 0.25 per 1000 live births, these estimates suggest that if one were to conduct a study in the United States with a primary endpoint of early-onset disease only, a study size of greater than 200,000 could be anticipated.

Globally, the incidence of infant disease is estimated to be higher. In the November 2017 series, early-onset disease was estimated to occur in 0.41 per 1000 live births worldwide and in 0.71 per 1000 live births in Africa. Late-onset disease was estimated to occur in 0.26 per 1000 live births and in 0.65 per 1000 live births in Africa.

In some of the published literature, incidence rates higher than these pooled estimates have been reported. For example, in a South African study, incidence of early and late-onset disease of 2.7 per 1000 live births has been reported. Based on this figure, a study in an area with a similar incidence with an endpoint of early and late-onset disease may require 25,000 to 33,000 subjects.

Calculations of sample size are dependent upon many factors, including incidence of disease, the proportion of disease caused by serotypes contained in a candidate vaccine, the expected vaccine efficacy, the threshold set for the lower bound of the 95 percent confidence interval around the point estimate of vaccine

efficacy, power, the proportion of subjects that are eligible for evaluation, in other words, those in the protocol population, and a sensitivity of identifying cases, for example, for each case, whether a blood culture was collected and the influence of factors that affect culture positivity.

The study size estimates provided were drawn from the article reference on the previous slide. They make assumptions based on the factors that affect study size. Estimated sample sizes may differ if any of these factors are altered. But these were shown just to give an idea of study sizes. Factors affecting study size and their estimates would require discussion with FDA.

However, based on the estimates of study size by disease incidence, it seems that a study conducted in the United States or other high-income countries could be difficult to conduct due to the size requirements and that an efficacy study conducted in a location or locations with a higher incidence of disease such as in lower and middle-income countries may be more feasible.

Moving back to possible clinical disease endpoints. Because GBS-related stillbirth is thought to be caused by a similar pathologic mechanism as early onset disease, GBS-related stillbirth could be a clinically relevant outcome to evaluate. An inclusion of this as part

of a combined endpoint might be expected to reduce study size.

As mentioned previously, a definition that has been used for observational studies and suggested for GBS vaccine trials includes GBS isolation from a normally sterile site in a stillbirth infant at autopsy.

Beyond early and late onset disease, the incidence of other types of invasive GBS disease such as GBS-related stillbirth is not as well described even in the United States and other high-income countries.

A systematic review looked at the incidence of GBS-related stillbirths and did not pull data because definitions of stillbirth and diagnostic assessments for GBS varied significantly but identified eight studies all in high-income countries reporting GBS-related stillbirth rates of 0.04 to 0.9 per 1000 births. Most of those studies reported data from before the year 2000.

As I previously mentioned, GBS is estimated to be associated with approximately 1 percent of stillbirths in high-income countries and approximately 4 percent of stillbirths in Africa. This is based on a meta-analysis from the November 2017 series that identified six studies reporting this information for six countries.

One advantage to including GBS-related stillbirth as part of an endpoint would be the potential to reduce the

study size. Challenges to including this as a study endpoint include the ability to conduct an autopsy and acceptability of conducting an autopsy. Given the limited data on GBS-related stillbirth, there may be limited information on the background incidence of GBS-related stillbirth where the study is conducted.

Additional case definitions for clinically relevant outcomes of infant disease have been proposed and are potentially more sensitive, but less specific than culture-confirmed invasive infant disease, which is represented by the smallest circle.

Possible or probable GBS sepsis in infants represented by the middle circle has been defined as an infant with clinical sepsis and GBS surface colonization with no other cause of sepsis identified.

The larger circle represents clinical sepsis, which might also be considered an outcome of interest. This could be defined as clinical signs of possible serious bacterial infection by the World Health Organization, but it has low specificity for GBS disease. In a similar way, one could consider evaluating the effect of a GBS vaccine on all stillbirths.

These outcomes may be easier to identify in many settings globally. However, vaccine efficacy may be

underestimated in a trial using endpoints that are not specific.

In addition, other types of disease endpoints have been proposed as potentially relevant outcomes to evaluate. Maternal invasive disease might be expected to be affected by a GBS vaccine, given that the timing of maternal GBS disease is usually during labor and delivery or postpartum.

A reduction in invasive GBS disease in pregnant and postpartum women might be considered a clinically relevant outcome and might support vaccine licensure.

The incidence of maternal disease was evaluated in the November 2017 series, which found few studies reporting the rate of maternal GBS disease even in high-income countries and that definitions and units for reporting differed between the studies.

They estimate an incidence of invasive maternal GBS disease of 0.38 per 1000 pregnancies based on only one recent study reporting maternal disease with pregnancies as the denominator and an incident of 0.23 per 1000 pregnancies resulting in a live or stillbirth based on three recent studies.

All of these studies were conducted in high-income countries and no studies in lower and middle-income countries qualified for inclusion in the meta-analysis.

Other outcomes affecting the infant to which GBS has been linked include preterm birth and neonatal encephalopathy. An evaluation of the effect of a GBS vaccine on these endpoints might be considered relevant and they might be considered particularly as supportive evidence of effectiveness.

Now I am moving on to endpoints other than clinical disease endpoints. This is just to make the point that words such as correlate of protection and surrogate mean different things to different people. I would like to stay away from using these words as much as possible. I will try to refer only to markers that are well established to predict protection from disease and markers that are reasonably likely to predict protection.

FDA has approved vaccines using markers well established or known to predict clinical benefit via the traditional approval pathway and using markers reasonably likely to predict clinical benefit via the accelerated approval pathway.

As I mentioned earlier, an example of an established immune marker of clinical benefit is antibody to hepatitis B surface antigen titer above a specific threshold. An example of a marker considered reasonably likely to predict benefit is pneumococcal antibody titer above a specific threshold as measured by

opsonophagocytosis assay, which was used to support approval of pneumococcal conjugate vaccine in adults for protection against pneumonia.

Determination that is specific immune endpoint can be considered a marker predicting clinical benefit, relies upon scientific evidence, an understanding of the disease process, and an understanding of the vaccine's mechanism of protection.

The strength of the evidence supporting the ability of a marker to predict clinical benefit determines whether it is a well-established or reasonably likely marker and consequently which licensure pathway is appropriate.

Assays that could potentially be considered for immune markers for GBS disease include a ligand binding assay to measure total anti-capsular polysaccharide immunoglobulin G or IgG or an opsonophagocytosis assay to measure functional antibody.

In the case of GBS, multiple observational studies, some of them conducted by our guest speakers, have examined the relationship between serum, serotype specific, anti-capsular polysaccharide IgG and infant GBS disease. In these case control studies, infant and/or maternal serum IgG titers obtained from cases of early-onset disease or early and late-onset disease were compared to titers of

controls who were born to mothers colonized with the same serotype, but who did not develop disease.

These studies show an inverse association between naturally acquired serum anti-capsular polysaccharide IgG titers and the odds of developing infant invasive disease for serotypes Ia, III, and V.

This has led many to propose that anti-capsular polysaccharide IgG could be considered an immunological endpoint for a clinical trial assessing a GBS vaccine. In these studies, different thresholds are suggested by the authors, which provide similar estimates of risk reduction for invasive disease. These levels vary by serotype and by study. Different assay techniques and lack of standardized reference sera make comparability between these studies difficult. Threshold suggesting reduced risk may also vary by study population. Inclusion of late onset disease in the case definition might also be anticipated to affect the suggested threshold.

Finally, thresholds for some serotypes have not yet been proposed.

Despite the inverse association observed between serotype specific anti-capsular polysaccharide IgG and infant disease, some infants in these studies develop disease despite high maternal or infant serum

concentrations of antibody, suggesting additional factors may play a role in protection from infection.

Measurement of functional antibody has been used as an immunologic marker to demonstrate vaccine effectiveness such as the pneumococcal opsonophagocytosis assay.

Opsonophagocytosis assays or OPKA for the GBS serotypes have been developed to measure functional antibody to GBS. The host defense mechanism for opsonophagocytosis precedes from opsonization, which is antibody and complement deposition on the capsular saccharide of the bacterial surface to phagocytosis and intracellular killing of bacteria by polymorphonuclear leukocytes. This assay may mimic the in vivo process of complement mediated bacteria killing.

Most of the seroepidemiologic studies of invasive GBS disease mentioned on the previous slides evaluated total IgG titers. But in one of these studies conducted in Europe, opsonophagocytosis was assessed. This study found that most, but not all of the mothers of infants with invasive disease caused by serotypes Ia and III had OPKA titers that were not measurable, suggesting lack of functional antibodies as measured by this assay may be associated with susceptibility to disease.

This study also found that in a subset of mothers colonized with GBS serotypes Ia, Ib, or III who delivered infants without invasive GBS disease, maternal OPKA titers positively correlated with serotype-specific anticapsular polysaccharide IgG, providing support for the use of IgG titer as an immune marker.

As you discussed the use of immunologic markers either total anticapsular or polysaccharide IgG titer or functional antibody titer, please consider whether the marker can be used to predict clinical benefit. What is the certainty regarding the marker's ability to predict protection? And is it possible there are differences between a vaccine-induced and a naturally acquired immune response to GBS?

Finally, I am shifting back to clinical endpoints to discuss colonization. GBS colonization has been suggested as a possible endpoint as it is an indicator of potential for clinical disease. While colonization or carriage has not been used to date to license any vaccine, the committee is likely aware of the success of other vaccines in reducing carriage by vaccine serotypes noted post-approval, for example, as has been seen with pneumococcal conjugate vaccine. This may lead one to consider whether a GBS vaccine could result in similar

reductions in maternal or infant colonization along with reductions in disease.

The November 2017 meta-analysis found that worldwide GBS colonization in pregnant women was estimated to be 18 percent with regional variation of 11 to 35 percent. Other studies have shown that approximately 50 percent of infants born to colonized mothers will become colonized. And without intrapartum antibiotic prophylaxis, approximately 1 to 3 percent of these colonized infants may develop early onset disease.

As you discuss the potential for colonization to be used as a clinical endpoint for a trial to demonstrate vaccine effectiveness, please consider the following points. Which endpoint of colonization would be the most appropriate to evaluate? Could maternal colonization act as a marker for early-onset disease and could infant colonization act as a marker for late-onset disease? Would clearance of colonization or prevention of acquisition of colonization be evaluated? This question is closely tied to the question of who would be vaccinated, for example, all pregnant women, women colonized with GBS or women not colonized with GBS. At which time points would one need to perform assessments? An effective GBS vaccine against invasive disease might have different effects on colonization in that it could completely eliminate maternal

or infant colonization, reduce it or have no effect on colonization.

Lastly, please consider the complex interactions between the colonizing bacteria and the host immune response.

That concludes my presentation. I now would like to remind you of the questions for the advisory committee. Number one. In addition to laboratory confirmed early or late onset disease, what additional clinical disease endpoints, in other words, unconfirmed and confirmed fetal or infant endpoints and maternal endpoints, could be considered to demonstrate vaccine effectiveness? Please discuss their strengths and limitations.

Number two. Could immunological endpoints, in other words, functional and ligand binding antibody levels, be used to demonstrate vaccine effectiveness? If so, please discuss their strengths and limitations.

Number three. Could colonization be used to demonstrate vaccine effectiveness? If so, please discuss its strengths and limitations.

DR. MCINNES: Dr. Everett, thank you very much. I think we have time for some questions if there are any questions from the committee for Dr. Everett, any clarification on anything.

DR. EL SAHLY: Thank you for this presentation. One question regarding late-onset disease. You mentioned that horizontal transmission seems to play a role. Given that we will be vaccinating the mothers for the purposes of this vaccine under consideration, do we know that the horizontal transmission that occurs after birth in these children is from other household members or is it also only the mother?

DR. EVERETT: It is my understanding from the literature that there have been cases reported of transmission from other members, in particular, from the community I think in certain neonatal units or well-baby units that have reported transmission that were case clusters that were similar serotypes and not from colonized mothers.

DR. EL SAHLY: As I hear this discussion, it seems that inclusion of late-onset disease is critical to reach a reasonable sample size to answer some of these questions. If we are not sure that it is coming all from the mother or what fraction possibly is coming from the mother, it is going to be hard to gauge an adequate sample size.

DR. MCINNES: Any other questions? Dr. Greenberg.

DR. GREENBERG: Thank you for your presentation. I have a question. It is related to slide 27. It is the target. Most of the data presented were proportions of

infants where the mothers were colonized, et cetera that then resulted in invasive GBS both in their early onset and late-onset disease. My question for this slide because of the questions that the committee has been asked to consider, if one takes all clinical sepsis, let's say all clinical early on sepsis among newborn infants, then what proportion of that piece of the pie is due to GBS? Because if clinical sepsis without culture confirmation is to be considered then obviously we would need to have some understanding of what proportion of the whole universe of early onset clinical sepsis unconfirmed would be actually due to GBS.

DR. EVERETT: Thank you for that question. All clinical sepsis or alternatively culture negative sepsis would have a low specificity for GBS as there are other bacteria that can clearly cause this. I think some of our later presentations might actually touch on this point and I am sure it varies by location that the study would be conducted and the diagnostics that occur in that location.

DR. GREENBERG: Not easy. This might be a question for a later speaker. Do you understand why the proportions are so much higher in Africa?

DR. EVERETT: I think that reason is probably multifactorial. I am sure that Dr. Madhi will have much to say about this. I can say that it is my understanding that

they employ a risk-based approach to antibiotic prophylaxis. I would assume that that has something to do with it. Colonization rates might be different. Serotypes might be different. But I would definitely leave that question to some of our later speakers.

DR. MCINNES: Thank you, Dr. Everett. One more question. Dr. Bok.

DR. BOK: Great presentation. Thank you. A couple of questions. Is there any way to quantify colonization? I understand it might be difficult, but I just wanted to know. Second, do you know how long antibodies stay in the neonates if the mother has antibodies because we are talking about early onset and late onset? I am just trying to gauge how long can we expect an infant to have those antibodies if the infection might be coming from other sources.

DR. EVERETT: To your first question, to quantify colonization, you mean in an individual or in a population?

DR. BOK: Like we do with diarrhea or gastroenteritis and you have a severity score or something. I am sure it is not like viremia or anything.

DR. EVERETT: I believe – it is my understanding form the literature that you can quantify because they have had cutoffs that define heavy colonization. I am sure there

is probably someone in the room that might be able to better answer those questions then me.

DR. MCINNES: There surely have been efforts to do this. I would say it is a nonspecific science at this point. We have not really honed in. But certainly, you see descriptors in the literature of heavy colonization. You see light colonization. I think actually we may have some of that addressed as we move on also.

I am going to move on now, Dr. Everett. Thank you very much indeed. We are back on time. I would like to invite Dr. Stephanie Schrag to present on group B strep young infant disease burden, trends and prevention strategies in high income countries.

Agenda Item: GBS Young Infant Disease Burden, Trends, and Prevention Strategies: High Income Countries

DR. SCHRAG: I think I was just supposed to begin and say my disclosures, which is that I am not part of any clinical trial as part of Pfizer or GSK's work and also to say that I do serve on two working groups convened by the World Health Organization that address issues related to maternal group B strep immunization.

But I was asked today – I think this talk is not going to directly give you new ideas about alternate endpoints, but instead I hope will motivate you to think really hard about that because I was asked to really focus

on the unmet medical need remaining around group B strep in high-income countries. And because we are VRBPAC, I am going to focus on unashamedly on the US and then at the end, shift a little bit to other countries.

We are actually this year marking the 60-year anniversary of the emergence of group B strep sepsis in infants. We do not fully understand still the reasons for this emergence, but it was first noted in the US in 1958 and over that next decade. And the US was particularly I think hard hit by this emergence. We had high incidence rates, as high as two per thousand live births and pretty high case fatality rates at that time. I think this has led the US to take a pretty active approach when it comes to prevention.

As Darcie showed, I will just try to go quickly for slides that overlap with information she showed. In this pre-prevention era, most of the disease was in the first week of life, what we call early-onset disease. About 80 percent occurred then. Late-onset disease in the US had a median onset around one month of age, but you can see that it does spread out over the three-month time period. There is a little bit of disease after the third month of life in the infant age group, but it really drops off.

If we look a little closer at early onset disease in the US, again, this shows the point that most of the

disease is happening on day zero. It is happening very early, which is part of the reason that we would think of a maternal immunization strategy because it is definitely too early for infant vaccination.

Also, as Darcie mentioned, one of the main risk factors for early-onset disease is maternal colonization. Globally, this ranges from 10 to 30 percent. In the US, it is around 20 to 25 percent of women colonized. There are some subpopulations that are more affected. In relation to one of the recent questions, we do in the US see higher colonization rates among African Americans and globally higher colonization in women with origin from Africa.

The colonization is usually transient and the GI tract is the main reservoir. As Darcie mentioned, early-onset disease is acquired vertically and there are few different ways this occurs. The group B strep can ascend into amniotic cavity during labor and there can actually be aspiration of the bacteria. There can be exposure during passage through the birth canal. And also group B strep can sometimes cross intact membranes, sometimes even before the labor period resulting in utero infection and sometimes stillbirth.

If we start with a colonized mother, the transmission dynamics suggest that about half of the newborns will be colonized and then about 2 percent will go

on to develop the severe early onset infection. This is just a reminder that in this instance as with some other infections, the exposure is a bit more common than the serious outcome that we are trying to prevent.

Unfortunately, shortly after group B strep emerged, clinical trials and a couple of well-designed observational studies demonstrated that intravenous penicillin or ampicillin given to group B strep colonized women is highly effective at preventing this first week of life disease, this early-onset disease.

One of the trials was actually stopped early because of overwhelming efficacy and the effectiveness estimates are 86 to 89 percent. We have a very strong intervention available in the US for early onset disease.

Work began when group B strep emerged also towards a maternal vaccine. And Carol Baker will talk about some of that work that she pioneered because we are still waiting for that vaccine to become a reality. Most of the debate in the US has focused on how best to target women for intrapartum prophylaxis. And Darcie mentioned that the two strategies that are primarily used a risk-based approach, monitoring women for the sorts of observable clinical risk factors shown here or late antenatal microbiologic screening for group B strep colonization.

We have been able to show using US data that this screening approach is 50 percent more effective than the risk-based approach because it captures group B strep colonized women who do not present with the risk factors.

Under both of these strategies, the concern is that a fairly large portion of deliveries will be exposed to antibiotics. There has been a wish to try to narrow this to the extent possible. But what we have seen in the US, what we do know is that we went from about 12 percent of deliveries before group B strep prevention being exposed to antibiotics to now about a third of all deliveries getting this exposure. If you think of four million live births a year, that is a lot of antibiotics and it is not usually a public health wish to have a lot more exposure than might be needed.

Additionally, we have to – because bacteria are always evolving, we cannot rest on our laurels and feel comfort that we will never have an issue with antimicrobial resistance. And more recently, there is a growing appreciation that there could be some unintended consequences of disrupting the newborn microbiome right at this time of birth when the microbiome is forming. I think these are the concerns around an IAP strategy that I would also encourage people to keep in mind as you think about maternal group B strep vaccine.

In terms of the actual US policies that we have used, two of our main professional organizations, the AAP and ACOG, came out with initial statements in the early 1990s, some that live on because they were conflicting. One of the roles CDC played in 1996 was to bring the different stakeholders together to the first consensus guidelines in the US. This one was recommending either the risk-based or the microbiologic screening-based approach to identifying candidates for IAP. We were essentially an apropos at that stage.

By 2002 through accumulation of evidence, we transitioned to a universal microbiologic screening strategy. And then in 2010, we have updated that guidance with some small refinements. That is the policy.

I want to give you a feeling for how well implemented the policy is in the US. I think high-income countries have the opportunity to implement some complex strategies that are not possible in all parts of the world.

What we saw in the US through a large labor and delivery record review that we conducted in ten different states is that there was a rapid transition to universal screening after the 2002 guidance came out. We reviewed labor and delivery records from 2003 and 2004 births so just in the years immediately following. We found that the proportion of deliveries screened increased from 48 to 85

percent with 98 percent having their colonization status result available at labor. Very rapid transition.

We also saw an improvement in the proportion of women with an indication who actually received IAP under universal screening. You can see here that 85 percent of women with the indication received IAP.

We are dealing with a situation in the US of strong implementation. In 2008, we did a thorough review of our early onset cases in these ten areas to try to look for missed opportunities for prevention. While we did find some, they are in the tough areas of the guidelines where improvements may be difficult. I think we have maxed out in the US in terms of how the good the implementation is going to get.

Switching then to look at the impact on disease, the main tool that we have for doing that in the US is the active bacterial core surveillance system. This is a cooperative agreement between CDC and the ten areas shown here on this map. The surveillance actually began in 1989 in three sites. We have the benefit of longitudinal trends for group B strep from the prevention time until now.

Right now, the catchment areas encompass about 10 percent of US births. And the case definition that we use in this surveillance is group B strep isolated from a

normally sterile site. For infants, this is virtually always blood or cerebral spinal fluid.

Darcie showed you an older version of this graph. I have added a few more years on here. This is the 25-year picture of invasive early and late onset group B strep disease in the US. As Darcie pointed out, the early onset disease has declined. It has actually declined by greater than 80 percent over this time period. And late onset disease has stayed fairly stable between about .25 to .4 cases per 1000 live births.

I want to pause for a moment and just talk about this Y-axis, the incidence rate, just because I know some of the VRBPAC are not always thinking about young infant diseases. I just want to point out that instead of using per 100,000 population, which is often the common measure for disease incidence, we are using per 1000 live births. It is a different entity and it is also a different order of magnitude if you are thinking why is this disease so rare. We are looking at something different.

I am going to spend a little time later in the talk focusing on the recent period so we can really dig into the remaining disease burden. But for the next couple of slides, I just want to take advantage of the power of ABCs to look at the trend over time data. Here, I am summarizing 16 years of serotype information from ABCs. We

collected isolates from group B strep in seven of the ten surveillance areas. I have listed two time periods here, 1999 to 2005 as an early period, and then 2006 to 2015.

The top row in this slide shows early onset serotype distribution and the bottom shows the late onset distribution. What you can see first of all comparing the top to the bottom is the point that Darcie raised earlier that serotype III, which is this gray slice of the pie, is more common in late-onset disease than early-onset disease. This has been the case from when group B strep first emerged and has stayed stable.

The other large serotype here, the blue slice, is serotype Ia. Another thing you can see if you look at across instead of up and down is that the serotype distribution has been quite stable over time. Early onset serotype distributions have not really changed.

With late onset in this more recent period, we see a slight increase in serotype III and a slight drop in serotype Ia. And one of the exciting things we are able to do now through this system is whole genome sequencing starting in 2015 of all of the GBS isolates. We will be able to see strain and clone differences that are not apparent at the serotype level to try to understand the dynamics behind these changes.

In the table that is at the right of this slide, this just gives you a feeling for the US that with a vaccine with the five leading serotypes, we would have about 93 percent coverage of the disease-causing strains. And with a six-valent vaccine that added serotype IV, we would get above 99 percent coverage of the young infant disease causing strains in the US.

Still thinking longitudinally, I want to talk for a moment about antimicrobial susceptibility that we see in the US because this is also the issue I said where bacteria can change. We have to continuously monitor for this. I think the real threat to the IAP strategy and also to treatment of group B strep disease would be the emergence of beta-lactam non-susceptibility. Penicillin and ampicillin and cefazoline are really the cornerstone of the agents that we are using for prevention.

Group B strep historically has been pan susceptible to this class of drugs and similarly in our ABCs among infant isolates, we did not have any non-susceptible isolates through the year 2015. But this has now changed. I wanted to point this out to the group that in 2016, we had three non-susceptible isolates, invasive isolates from infants, two from early onset, one late onset. Although they were the same serotype, they have

different penicillin-binding protein modifications, which suggest independent evolution of the non-susceptibility.

With the first quarter of 2017, which are our most recent period with whole genome sequencing, we found one additional non-susceptible isolate that again is a different modified penicillin-binding protein. Different serotype.

When we look at our adult invasive isolates, this is just for context, but we have much larger sample size of adult strains than young infant strains through our surveillance. We now see 1 percent of adult strains are non-susceptible to beta-lactams. The emergence has happened although it remains very rare.

In terms of resistance to second line agents for IAP, these have been common for some time. Already our policy has had to evolve to take the resistance into account. But as of 2015, 49 percent of the infant group B strep isolates are resistance to erythromycin and 26 percent have constitutive resistance to clindamycin.

I am going to shift now from this longitudinal look to try to focus on this more recent period 2006 to 2016. And this slide has a few different graphs. But my main purpose is to show you that there are some infant populations even in this time period and you ask where we have really brought the disease burden down that are

disproportionately affected by invasive disease. The first graph in this series is just showing overall early and late onset disease.

But then the next two graphs are showing – the first is early. The second is late – are showing the incidence rates stratified by gestational age. You can see that preterm infants have much higher incidence than term infants.

And the last two graphs in this slide are stratified by race comparing black infants to white infants. This also shows that black infants remain at higher risk of early and late onset disease compared to white infants in the US. I think the hope with any new intervention that may come online at least from our public health standpoint would be that we could also reach and protect some of these disproportionately affected groups.

Focusing on the current case characteristics in the US of invasive disease, I wanted to highlight a couple of things that I think could make maternal immunization a challenging strategy so they are worth keeping in mind. The first is while early onset disease still has the vast majority of cases on day 0 of life, the median age at onset for late onset disease in the US is 34 days. If you look at the interquartile range, we have about 25 percent of the cases happening after 49 days of age. I think the question

that was raised earlier is relevant is if we are relying on maternal IgG that is transferred to the infant, there will be some decay over time and it will be necessary to keep high antibody levels for a long time or else we will have some portion of the late onset group that will be hard to reach.

Similarly, gestational age could affect maternal immunization strategy just in the amount of time available to get adequate concentrations of IgG transfer to the infant. In the US right now, 20 percent of our early onset cases and 33.6 percent of the late onset cases occur at a gestational age less than 35 weeks. These may be harder to reach infants. Again, there is a lot to see in terms of the dynamics of the antibody rise and antibody transfer.

Current case fatality risk in the US has actually risen a little bit from what it was when I first started working at CDC. I think this is because of the slight increase in the pre-term infants that are affected. They have much higher case fatality risks. But overall, it is now 5 to 7 percent in the US.

In terms of syndromes, the distributions are shown here just confirming that for late onset disease, this is where most of the meningitis is happening. It is still mostly associated with serotype III and that

bacteremia without a focus is still the main syndrome for both.

Below this table, I show you the estimated US cases for a single year 2015 based on our data. We estimate 840 early onset cases and 1265 late onset cases. And then you can see below that, the associated national deaths in that single year.

This to me represents an important unmet medical need, but it can be a little hard to think about how to put this in a context. I talked to my pertussis and RSV colleagues before coming here to try to help us think about this a little bit. What I am showing here are – I have limited it to infants less than three months of age. I am showing the disease burden for group B strep with our most recent year of surveillance for pertussis from 2012, which was the peak year for infant disease and it was actually the year that led to the maternal Tdap recommendation. And then also average RSV hospitalizations. This is based on the study that was from 2000 to 2005.

What you can see in the first data column in this data is that in terms of incidence rates and in parenthesis it is the estimated total US cases for a year. Group B strep and pertussis looks somewhat similar in terms of their incidence rates. RSV has a notably higher incidence

rate, which is actually more similar to what group B strep would have looked like in the absence of IAP.

Then if you look to the other columns in the table, I am trying to give you some sense of severity of the infections. I think what you can see there is that group B strep stands out with the case fatality risk with over 100 deaths a year. For infant pertussis in the year that really led to the maternal Tdap recommendation, there were 15 infant deaths in that year. For RSV, the case fatality risk is not zero, but it is extremely low and therefore quite difficult to estimate.

To look a little bit more at the severity, I think Darcie did show some of the data about sequelae among group B strep survivors. In addition to the high-case fatality, there are lasting consequences of surviving an infection. This is pulled out from that group B strep global disease burden update and that came out at the end of last year. This is limited to the high income countries. And, again, the main message here is 18 percent of group B strep meningitis survivors have moderate to severe neurodevelopmental impairment at 18 months of follow up. I think there is a wish right now to also get follow up information for longer periods when the full spectrum of the impairment can be more readily assessed.

I also want to point out and I think this comes back maybe a little bit to the end point challenge the committee will face that I am not showing you some information on what may be important additional disease burdens that a maternal vaccine could prevent. I am not showing you those data from the US because these are difficult endpoints to capture right now, not because they are not important.

Maternal group B strep disease – I think the challenge here is that women particularly I think postpartum are often treated empirically and are not cultured. We are going to have a real underestimate of the disease burden. Our ABC surveillance does capture invasive cases associated with pregnancy or postpartum and we estimate right now and this is certainly an underestimate approximately 175 maternal invasive cases per year. And then the group B strep associated stillbirths that were also discussed are difficult to capture in a surveillance because we do not in the US at least typically have performed pathology on the stillbirths and understand the potential infectious causes that may have contributed to them and certainly not in a way where GBS could easily be identified.

And then just as a last slide about the US, I wanted to point out that although we do not yet have a

vaccine so we cannot be very specific in modeling, we have done some early cost effectiveness modeling of a potential maternal group B strep vaccine in the US. I think this is an interesting situation to think about because we do have screening in IAP in the US. We do have one prevention strategy in place.

This model that we did compared a range of different strategy options. While it confirmed that screening and IAP does a good job of preventing early onset group B strep at a cost of about $70,000 per QALY compared with no prevention, the analysis also showed that maternal group B strep immunization with some assumptions about a vaccine can prevent early and late onset group B strep at a somewhat lower cost per QALY.

The challenge with the vaccine is that if the coverage is typical of current maternal vaccines in the US, it would need to be highly effective to prevent more cases than screening and IAP. It may be that actually the maternal Tdap recommendations will help the US strengthen the maternal immunization platform and lead to increases in coverage.

What this analysis found was that a combination strategy that offered vaccination to all pregnant women and then offered screening in IAP to women who remained unvaccinated would prevent more disease than either of

these strategies alone at cost per QALY similar to screening and IAP.

For the last few slides, I am going to shift from the US focus to looking at the experience in a couple of other high-income countries. I have borrowed here results from a survey that Kristy LeDoare conducted as part of the global group B strep disease burden update.

The colors here are just showing you the different strategies that countries have adopted for group B strep prevention. This bright red is countries that are using microbiologic screening. But there are some high-income countries in this more orange/salmon color that are using the risk-based approach. I am going to focus on some of these risk-based countries as I have just told you so much about our screening experience in the US.

This is a slide about trends in early and late onset disease in United Kingdom and Ireland. It comes from their surveillance. The graph that is on the left of the slide is showing the trend over time from 1991 through 2009. This light blue line is late onset disease. The darker line at the top is early onset disease.

The first point is that UK had a lower rate than US, quite a bit lower than US even in this early 1990s when US was at 1.8 per 1000 for early onset disease. UK was at .3 per 1000. But I think the more concerning trend that UK

is seeing right now is a trend towards an increase and that is further supported by the table on this slide, which includes a data point from 2014 to 2015. Right now, in the UK, the early onset disease incidence is twice what it is in the US whereas the US started out at this high rate of 1.8. I think that the UK is concerned about the increase. They are also seeing some trend towards an increase in late onset disease. They are a country that has been using the risk-based strategy, a fairly narrow version, and have recently slightly expanded the risk factors that they are using.

This next graph also shows experience with invasive young infant GBS disease in Netherlands, another country that introduced risk-based strategy. They introduced is in the late 1990s. The red line here is early onset disease and the green is late onset disease.

Again, one point is the incidence rates here are much lower than what they were in the US even before any prevention was in place. There do appear to be some geographic differences that I think cannot all be explained away just by case ascertainment or surveillance methodology.

What the Netherlands has seen though that concerned them is again this trend towards an increase in both early and late onset disease. They were able to show

and this is in the bar chart next to the graph that this appears to be associated with an increase in one particular clonal complex 17, which is associated with some hypervirulent factors in group B strep. They have actually gone on to do further analysis and shown that there is a particular subclade that has been in an expansion mode. That may explain this increase in both early and late onset disease that has been occurring for them recently.

And then just the bigger, global picture for high-income countries from this global disease burden update. The point estimate across all high-income countries is .46 per 1000 live births with a somewhat higher than US early onset incidence and some lower than US late onset incidence for where we are currently.

The serotype distribution from this broader look is quite similar actually to what we saw in US with maybe slightly more representation of serotype III, which again is the big slice that you are looking at in this pie.

Just in conclusion in terms of the high-income country experience and where we are today, I think I would say there is a remaining disease burden of significance. This in the US is despite an 80 percent decline in early onset disease. We still have notably more deaths than infant pertussis and a similar disease burden compared to infant pertussis in the US.

For UK and Netherlands, we also are seeing this concerning increasing trend in young infant group B strep disease. We are interested in looking right now in the US whether we have the same strain that the Netherlands had because we are concerned it could lead to expansions and late onset disease in the US where we do not have a prevention strategy right now.

Additionally, I do not think that further major declines are going to be likely through improvement in IAP. We remain vigilant around IAP policies and I think there are some refinements that can be made that would benefit, but I do not think we are going to see a significant translation into prevention of disease burden. It definitely does not reach the late onset portion of the disease.

A third point is that beta-lactam non-susceptibility has not emerged and we are even seeing it in infant invasive strains. It is extremely rare right now. But if it is to become more common, it could threaten both the current prevention and also treatment strategies.

And then finally, I think the issues around the antibiotic exposure, the IAP is the main prevention tool are concerning. And these long-term consequences of newborn microbiome disruption need more research and understanding. We, at CDC, have been able to fund two large observational

studies that are trying to look at the association between IAP and risk of obesity later in childhood, which is one of the outcomes of concern. I think we need more information here.

And then I just wanted to throw in – this meeting is definitely focused on maternal vaccine to prevent infant disease. But I just wanted to make sure people are aware that there is also a very large adult non-pregnant group B strep disease burden in the US that has been increasing over time. Right now, we estimate an incidence that is higher than that for adult pneumococcal disease. It is an important burden with over 27,000 cases and over 1500 deaths. I think in terms of unmet medical need, this is also one that is out there for this pathogen.

I just would like to acknowledge in particular the ABCs team and one of our staff people who have helped with some of the recent analyses. I will stop there.

DR. MCINNES: Dr. Schrag, thank you very much. We do have time for some questions. I will start with Dr. Kotloff.

DR. KOTLOFF: I am wondering how you factor in the preventable disease burden, infections that occur in prematurity where infants are born before sufficient maternal antibody may not be transferred to them to prevent disease. I guess there also may be some prevention of

prematurity through the vaccine. But I am just wondering what type of impact are you predicting prematurity will have on vaccine effectiveness.

DR. SCHRAG: I think it is a good question and I think part of the reason I wanted to show – there are two questions rolled into that. One is whether a vaccine could actually prevent or some portion of preterm deliveries all together because the group B strep may be part of the cause of the preterm delivery. I think that Darcie showed some of the data on studies trying to assess that. It is a little bit equivocal right – it is hard to put an estimate on that. We may need to do vaccine probe studies essentially once a vaccine is licensed to really understand if a vaccine will be able to prevent some portion of preterm deliveries.

In terms of protecting infants that are born preterm from invasive disease, I think I wanted to highlight the portion of infants that are born preterm because they may be a more difficult group to reach. I think you are correct about that.

And one thing we do see with intrapartum prophylaxis, which is a different intervention, is at least for early onset disease, it is just as effective for preventing disease in preterm infants as term infants. IAP has led to reductions in – if we stratify it by term and

look at the incidence rates, we are seeing the same kind of declines in preterm, but we still have disparities in incidence that persist. I think for a vaccine it is a challenge.

DR. MCINNES: Thank you.

DR. EL SAHLY: Thank you for this presentation. One question regarding the difference in incidence between African Americans and white in the US. Can the difference be explained by the difference in uptake of IAP or delivery of IAP to these minorities or should we thinking about other factors?

DR. SCHRAG: I think we need to be thinking about other factors at least when we look at key measures, for example, proportion screened, proportion positive, and proportion getting the IAP. That looks similar by race. We did quite a bit of looking at that after the transition to universal screening because we were concerned.

But I think there could still be some intervention delivery differences that are subtle or, for example, that are harder to pull from those high-level variables that may affect quality of care.

I think there is also some higher risk of disease for reasons we may not fully understand and maybe Shabir will talk a little bit more about those. But we definitely see higher maternal colonization. We do not fully

understand what is leading to that. And it may be that with some of the antibody studies, we start to get clues also. I think it is multifactorial.

DR. MCINNES: Thank you. Dr. Heine.

DR. HEINE: Thank you for all your work in this area. It has been very helpful. We have used it over the last 20 years to really change and make an impact.

I think that one of the issues that has come up is that we use antibiotics so frequently in obstetrics around the time of delivery to prevent infection in the newborn that I believe that when you look at culture positive only in the newborn, you are really looking at a tip of an iceberg because we have influenced the results so much with our antibiotics and labor. Are you tracking – and I know this is a holy grail of what is suspected neonatal sepsis, how you identify it, but are you working towards a common language of that and tracking it in the ABCs?

DR. SCHRAG: ABCs is in invasive bacterial diseases surveillance system. It is not set up in an easy way to track syndromes that are not culture positive. As you are saying, the case definitions are also really challenging to come up with.

What we have been able to do for the US – at least one concern we had at an earlier phase was that maybe we were preventing the culture positives like what you are

saying. There are the antibiotics. They are sterilizing the blood culture. But maybe the disease burden has stayed flat and it is just shifting over to be this culture negative still ill baby. We have done some look at administrative data at hospitalization discharge data and discharge code. That, in a sense, is a very crude clinical definition of sepsis.

We have been able to show that there were declines actually in that very broad entity during the time period in the 1990s when the invasive disease declines were so dramatic and that it was otherwise flat in the earlier period and after that. I think there is some sense that we are not just shifting the disease from culture positive to culture negative, but it is very difficult through a platform like ABCs to track those nonspecific endpoints. We have gone to the administrative data.

DR. MCINNES: Thank you, Dr. Schrag. I think we are going to move on in the interest of time. Thank you again.

It is both a privilege and a pleasure to welcome our next speaker, Dr. Carol Baker, who is going to address us on the early development and correlates of protection for GBS conjugate vaccines.

Agenda Item: CBS Conjugate Vaccine: Early Development and Correlates of Protection

DR. BAKER: With the chair's permission, may I answer a couple of questions? With regard to late onset disease – there has been some questions about late-onset disease. Let me tell you that the late-onset disease and early-onset disease is basically bloodstream invasion. Whether it is acquired from the mother, from household context or the rare nosocomial horizontal transmissions in nurseries, it is a sufficient amount of antibody that is the theoretical aim.

Hannah, that is a great question because you would have to longitudinally call it – culture that baby and all contacts to really hone down on your question. We know that the mother pre-IAP horizontal transmission from the mother was in 50 percent of the late onset cases before we had any intervention. This is the mother at the time of delivery in persistent colonization.

The other comment about prematures. Please remember that most babies are born at term or near term. That maternal antibody transfer is passive beginning at 17 weeks gestation. Depending on the amount, you get passive. And then active transport begins at 32 weeks. When you look at babies less than 32 to 34 weeks, number one, it is a small percent of the total births that are at increased risk of GBS disease. But sufficient amount and we do not know this, any of us, even me, of an antibody could be

protective, not just by the mechanism of preventing preterm delivery, preterm labor, but by the mechanism of passive transfer. No question. If you are born at 22, 23 weeks gestation, you are not going to get sufficient amount of antibody and probably the mother has not been immunized then.

Thank you very much for inviting me to this meeting. I am thrilled. I do have a couple of declarations of interest. I am a former consultant of Pfizer, but I am always confused whether they want life time potential conflicts, three years, one year, current, but that is the information to declare here on this slide that I have been a consultant of Pfizer and that terminated in August of 2016.

I am going to begin with thank yous first to the National Institute of Health, Allergy and Infectious Diseases for the RO1 grant that began six months after I became a faculty member at Baylor College of Medicine and then contracts and working. You will see extensively under the contract.

Dennis Kasper, who was a fellow with me at the Channing Laboratory. I left. He stayed. He bemoans the bad winters. I bemoan the bad summers. And his group at Harvard Medical School. Morven Edwards, my first postdoctoral fellow, who stayed in the team of the Strep Lab at Baylor.

Marcie Rench, who has been research associate since 1982. Clearly, she is a loyal person and could have gotten a job anywhere else.

I am going to talk about four things and thank you for the wonderful presentations because I am going to get to skip a bunch of my slides and shorten my talk hopefully. First, a little bit about the pathogens and population at risk, which you have heard a lot about before. Vaccine design and assay development. Now remember, this is early vaccine design, early development. And our Phase 1 and Phase 2 trials. And then some comments about correlates of surrogates. What is the holy grail of protection? I think the holy grail of choosing protection is some combination of reasonably gettable things to lead us to a vaccine trial that would be quite unique compared to the standard – hundreds of thousands or less, 50,000 of people in the typical efficacy trial.

Even though Dr. Schrag said that GBS emerged in 1958, I want to tell you I was not in medical school in 1958. I was in medical school quite a bit later after that. And GBS was a bovine pathogen. It caused epidemic mastitis.

Human disease was first described in 1938 in the UK. Dr. Lancefield's name is on that paper. An obstetrician in the UK sent a hemolytic isolate to Dr. Lancefield. She

had done the grouping system and there were three puerperal sepsis cases, so pregnant women, due to GBS.

But really my first case was in 1969 when I had a three week old come in with late-onset sepsis and meningitis and died. This was caused not by anything called group B strep at the time, but it was a beta hemolytic organism that was susceptible to penicillin and it was susceptible to a bunch of other antibiotics, making the fact that the lab called it an enterococcus, even to this non-microbiologist, a little suspect. I began to collect the isolates, wrote a letter to Lancefield who was an emeritus professor at the Rockefeller. She invited me to come to the Rockefeller, a non-paid, non-officially named mentor and a person who changed my life forever, both personally and professionally.

We know this organism colonizes the lower GI tract as a commensal in men and women of all ages. Also, infant colonization can be acquired. Children have GBS colonization in the GI tract that persists. It significantly increases as you become sexually active. But this is a commensal with secondary colonization of the genital tract. It is a common commensal. I have talked to literally thousands of pregnant women and tried to convince them that this pathogen is normal in so many people.

You have seen the capsular types. When I started out, there was Ia, Ib, II, and III and we are now up to X capsular types. And type V has become prominent.

This is a 1980s cartoon. We do know and we did know even back then that capsular polysaccharide was a major virulence factor and so was beta hemolysin. Beta hemolysin is very important in pregnancy-related perinatal losses. But, again, back then, only antibody to the capsule was associated with protection against both animal disease and early and late onset disease. This cartoon updated would show you many, many virulence factors that are surface proteins.

Just a comment about GBS polysaccharides. It is not like haemophilus influenza type B. It is not one PRP thing. It is multiple capsular types. We are up to type IX. The prominent clinical ones have been discussed especially in adult disease type IV is becoming prominent. Not so prominent in baby disease, but we have to consider it.

Look at Ia and Ib. Lancefield – these are isomers. Lancefield in 1934 distinguished these using antisera and mouse passage experiments. They have one linkage side chain that is different. And I do want to mention that if you immunize adults with Ia conjugate vaccine, you will get lots of Ib antibodies and vice versa. These are binding antibodies. That is why binding must be

contained with a functional assay because the binding antibodies elicited by Ib do not function in vitro to kill B strep Ia strains. Other cross reactions will be discovered, but they must be acknowledged given the likelihood of the similarities.

All of these polysaccharides have a terminal sialic acid. That was my gift to Dennis Kasper. This English major said I know that type III strains have sialic acid. Indeed, all of them do. But the one for type III in particular dictates the protective epitope and that is extraordinarily important because you take away that sialic acid terminal side chain and you have a type XIV pneumococcus polysaccharide. But if you immunize to protect against type III group B strep, you do not get protection with type XIV pneumococcus. This is really important stuff to be thought about as we go forward with a vaccine. See how optimistic I am. As we go forward in a vaccine. Some of these cross reactants could be very important to protection in vaccine trials.

I cannot tell you how many people do not understand this. This is one disease in terms of pathogenesis. In early onset, you have maternal colonization. You can have amnion invasion either silently so the membranes are intact or clinically, the membranes are ruptured. You have lung aspiration. And from the lung,

you get secondary bloodstream invasion. Or the baby going through the birth canal becomes mucosally colonized at mucous membranes in the respiratory tract later in the GI tract and you have bloodstream invasion. The same thing with late onset disease. The baby gets colonized either in the lower GI tract or in the respiratory tract and then in the GI tract, you have transcytosis into the bloodstream like you have with late onset E. coli or any other neonatal early infant disease. The bloodstream is the main place of attack of invasion. If you have sufficient antibody, you can block that problem.

Populations at risk have been well discussed: pregnant women, neonates and young infants and the elderly. The elderly are becoming more precious to me as I continue to remain on earth like some of the people in the audience, maybe even on the panel. Very important disease burden I am sure globally as well as in the United States, but we do not care about them today. We do care about them ultimately.

These are babies with early onset disease. In the upper panels, late onset disease. In the lower panel, this is what a brain looks like when you die of late onset meningitis. This is still after all of my career the most frequent pathogen in infants less than two months of age. This has been going on for – approaching five decades. It

is now the most common cause of meningitis in pediatric patients. Great blessings and good fortune to the introduction of Hib and pneumococcal conjugate vaccines in the United States that this now is the most common pediatric pathogen even though it goes away before year of age.

The mortality has been decreased. You have heard that. In one study that looked at patients from a minimal 3 years to 12 years of age, this is a collaboration between Vanderbilt and Baylor published a couple of years ago. This was very intense neurocognitive evaluation. And 19 percent of these children had global retardation, hearing, visual loss, basically skills where learning was virtually was impossible. Thirty percent more had more limited disabilities including deafness, behavioral or learning disabilities. That leaves you with a little more than half that were "normal" by this intense evaluation.

This is an old slide, but it makes the point that led me into an academic career. If this is horizontal transmission for early onset disease, why do we have all these exposure of babies for colonization and yet we have such a low attack rate for disease? Why?

The second thing that was – this is why Lancefield invited me. I had these strains in my apartment taped up with scotch tape. GBS lives on blood agar plates

for weeks and months. I mailed them to her in the US postal mail like a birthday present. She had at that time only one type III strain in her entire collection from abroad and 12 of my 13 strains from the cerebral spinal fluid were type III. She was very interested in type III, as you saw. Remains an extraordinarily important pathogen globally.

Antibody was one of the things and in this early paper, these were – people forget this. This was maternal sera that were assayed from babies who had early and late onset disease and a sufficient amount of antibody and it appeared to be protective.

I get a little local interview and they said – I was saying maternal vaccine. They looked at me like I was strange because we had no recommended vaccines for pregnant women in the United States. They said when do you think a vaccine will be made. I said five years. I have said five years every time I have been interviewed in the past four decades.

This is a better study also using the same assay with the same conclusion. The 29 cases there are babies with early and late onset disease compared to the 43 healthy neonates. But all these women were colonized at the time of delivery. You see that there was a significantly higher antibody concentration in women who had healthy

babies, but exposed their baby to type III versus the cases.

Two comments. Look at all the 43 that had very low levels of antibody. Enough antibody is important, but clearly there are other factors. One of the factors is density of colonization. There was a question about this. This is very hard to get at. It can be done by streaking plates and picking colonies. But it is a very difficult. And heavy colonization is just a higher inoculum. It is like an animal model. If you give a higher dose, it may be lethal in the mouse. If you give a lower dose then you may remain healthy. That is part of the answer, but not all. A sufficient amount.

These earlier studies were done with the radioactive antigen-binding assay because a lysis had just begun to be talked about. This is an assay that binds IgG, IgA, and IgM so all isotypes. We know that only IgG crosses the placenta. It was frustrating to do this.

And the other problem was the lower limit of detection was one microgram per ml. You got the bottom and you could not have really better sensitivity. I was very interested in who the truly antigen naïve adults were in terms of antibody concentration.

One of the things that Dennis learned – I started with the type III is that sialic acid moiety is absolutely

crucial. If you leave it there and if you desialyate it, the organism is not virulent. If you leave it there, but change its change, its epitope, there is not protective immunity. You have to have it intact for functional OPKA. That is very important actually to all of serotypes, but especially type III.

Why do we use tetanus toxoid? Two reasons. I had met people who had actually gone to Haiti and eradicated neonatal tetanus by immunizing pregnant women through village workers. I thought cool. Two diseases. Tetanus and group B strep.

The other reason is that the protein available – we went to various people that had proteins for conjugation, commercial entities. They were very afraid of the word pregnant women. We got this from the Massachusetts State Public Health Laboratory as a gift and used that.

The target population. We have heard about. But I have always been interested in protecting the pregnant woman, the fetus, as well as the neonate and young infant. We have heard a lot about the potential impact.

Dr. McInnes, try not to get sleepy because Pamela McInnes was at NIAID and was my first program officer. Dennis Kasper and I participated in these trials. They went on a long time and did some things and that is what I am going to talk about.

But one of the things is that ELISA was available. We wanted to make IgG specific ELISA, but we wanted to be very careful and crafty. One of the literature discrepancies in levels of antibody is ELISA assay methodology. We wanted a quantitative assay. We compared it. You will see in a minute to our established radioactive antigen binding assay. We wanted to be very specific. That meets the appropriate epitope sticking up there for antibody to bind it. We wanted something that would correlate with in vivo function in terms of animal – I am not going to present it. I saw Pfizer's slides. They are going to tell you the model that works beautifully. And in vitro opsonophagocytosis and killing.

I really wanted to know who had been primed by GBS antigen or a cross reactive antigen in nature so that we could see who would get a booster response or who would need maybe two doses.

And then all these phase I trials, phase II trials, looked at both in vitro function and in vivo preclinical before we use these in humans.

The ELISA here – we developed from monovalent immunized adults from five to seven high responder people, a standard human – that is what we use to generate a standard curve.

This was quantitated again by quantitative precipitant assays, which is very difficult and I am glad I did not have to do them. Dr. Kasper's lab did that.

Then we tested both conjugate vaccinated and uncoupled type III capsule immunized adults and some unimmunized adults. We basically got using the ELISA both vaccine induced and natural antibodies. We got the same quantitative results.

This is just a comparison with the ELISA and the RABA. You see that the RABA, which are the black dots. It is hard to see. When you get down to one microgram, you pretty much cannot tell. We wanted better sensitivity, but a high correlation with an R value of .92. This is just the standard curve going down there into the .0 micrograms using the assay.

We started with Phase I and Phase II trials. Basically, the Phase I of monovalent conjugates to give you – read the whole five years of literature. It was basically comparing the monovalent conjugate, polysaccharide coupled to tetanus versus uncoupled polysaccharide versus placebo and bleeds before 2, 4, 8 in 26 or 52 weeks after immunization. Our Phase 2 trials were dose response studies, using three different doses of the conjugant vaccine. We did one bivalent vaccine trial. We tried alum or no alum to see if there would be adjuvant effect and did

not find that with type III. That was the only one that was tested. We also for type III did a booster dose and it was not needed.

What have we learned? We got pretty much 95 percent four-fold rise response rates with a single dose in nonpregnant women. As I say, in one monovalent, no need for aluminum hydroxide as an adjuvant. We will see the placental transport. It was theoretically available because the dominant isotype was IgG. But for type II and type V, we also got IgM and IgA responses.

This is just summarizing things. I put red bars around everything that I think is important. And in type III, I spent years of my life on. A four-fold increase in these trials if we use 12.5 micrograms of the polysaccharide. These were chosen based on the significant dose response studies.

The bivalent trial. The only thing to show you here is in the red box is that this is the bivalent vaccine. You look at IgM. We are measuring the type II response. You see that we do go from 0.6 GMC before immunization to 13 at four weeks post-immunization. This persists. It does drop down.

The half-life to give you a ball park idea of from a peak at four to eight weeks, you end up with about half the antibody concentration, the IgG concentration at

26. And then it kind of levels off. It is very similar at one year too.

But look at the IgM responses here. Substantial IgM and IgG for the type II. We did not see this with Ia, Ib, III, and we saw it to a lesser extent with type V. Just something to keep in mind.

This is function. On the first panel, you have type II function log kill before and four weeks after immunization with the type II monovalent vaccine. The white bars are immunization with the type III vaccine. We would expect killing. And then gray bars are the II-III. A good response with the monovalent as well as the bivalent. And then the next is the type III. The black bars again immunized with type II. The white bars type III where you would expect any significant rise. And then the gray bars, the bivalent, very similar findings.

I just want to emphasize that with all these tetanus toxoid conjugates in all our trials, we correlated function with binding antibody.

Again, just to remind everybody who does not think about the gift of maternal IgG, the half-life is very important. Dr. Schrag mentioned pertussis. The half-life of maternal pertussis antibody is estimated at 35 days. Very rapid decay of pertussis antibody for mothers. That is fine

because then we are going to immunize the babies at age 2 months and go forward.

Group B strep is a disease where we do not have to immunize again like we will have to with RSV infant disease. But for measles, we do not begin immunizing until 12 months unless there is a huge risk because maternal antibody to measles lasts a very long time. We need to know both the height of the maternal antibody and how long it is actually going to go. Again, my estimate for late-onset disease based on our very small maternal studies is it is about 42 to 46 days. Not as short as pertussis, but again it is going to depend. Enough antibody and that is the question. How much is enough?

We did this pregnant women's study. You see Dr. McInnes' name. Do I have to declare a conflict of interest? This was prospective, randomized, double-blind, placebo-controlled. Even the husbands had to give informed consent. That is another story. Thirty low-risk pregnant women were enrolled. We did have to give placebo. This was at a mean of about 32 weeks, but the beginning of immunization was 30 weeks and ended at 33 weeks. And 30 percent were ethnic minorities.

Here is the maternal immune response expressed as GMC. The blue is the conjugate. The red is the placebo. I

have felt like showing my patients – saying would you rather be blue or red. This is not a political statement.

This is reverse curves for the placebo in red and the TT. Depending on what you think is the protective level of antibody, you will see in a minute that I say for type III, it is .5. All but one of these women had protective levels of antibody after immunization.

Now, I am throwing this in. My Pfizer colleagues will have to forgive me. What is a GBS type III naïve adult? It is very important because if you are primed, you need a single dose and you will respond. If you are primed, good. If you are not primed, you may need two doses.

This is the lower limit of detection in our assay. These women I just summarized. We had one woman who had undetectable, who had an antibody response of 37 four weeks after immunization. Another woman who had an antibody response of 8 micrograms. Some that were lower. The blue highlighted tells you that this woman did not respond. This is a nonresponder. She did not have enough antibodies to transfer and that is why it is undetectable at one and two months in the babies.

I do not know the answer to the question, but I think this is a very important question. The vast majority of people with low antibodies will respond to a single dose and sometimes they will respond to a remarkable degree.

Same study. These 20 women that got the vaccine. We get a lot with the polysaccharide, IgG, subclass 2, and it does not transfer as well as subclass 1. But we get plenty of 1-2 to end up with these levels. Something to remember. If the mom is 10, the baby will be about 7 in the cord blood and then you have decay and obviously placebo people stay low.

This is a study that should not be right here. I will come back to that. Forget that slide. It should not be in that order.

This is function and this was actually using endogenous infant complement. And complement levels in the infants take months to fully mature. But using the infant – this is the placebo infants followed one and two months, log, kill. You look at the incredible kill. In fact, it was a little higher at 2 months even though we knew the antibody was declining because complement is now being made by the baby. Function will improve with the maturity. Even though late onset disease – let's say for early onset disease that the protective level is one or five or whatever even though it is going to go down significantly at two or three months. The complement that is required to kill these organisms in vivo may be maturing enough. It is an important question to be thinking about.

Correlates of protection. A huge study done by the National Institute of Child Health and Human Development. They looked at – it is sort of a case control, but it is very different than my control study I am going to show you in a minute. It said that you would see an association with protection at 5 micrograms for type Ia and 10 micrograms for type III.

I will just tell you. There was a huge argument in the literature after this was published. We actually exchanged serum with the investigators. The bottom line was the same in that enough antibodies were correlated with disease protection. This was early onset disease only. But the magnitude of information was about 10-fold off. We think this was all a use of an appropriate antigen to bind to the ELISA plates. People can read about it if they really want to agonize.

The bottom line here is that we have to have agreed upon assays and that is being developed. We have to have agreed upon standards, assay procedure and we are going to get to a consensus of correlate protection sooner or later.

This was published. This is a prospective gathering of cases of matching of controls for Ia, III, and V. We picked these three because they are the most prevalent cases. The controls were matched by ethnicity

because we know that ethnicity influences density of colonization of risk and we also match by age because younger women are more likely to have a GBS, if you are less than 20 affected cases given risk factors and everything else than older women. And then of course exposure at the time of delivery with the capsular type.

What we found here is for types Ia and III, we had enough cases in control to show that antibodies of greater than or equal to .5 or 2 for type Ia were protective. In other words, there was a significant risk reduction. For type V, there just were not enough cases. There was a trend, but nothing statistically significant.

I am going to skip this one and move on to the last information. This is not published except as an abstract, but it is of interest because the SPIN Study wanted to look at the influence of monovalent conjugate vaccine on the acquisition of colonization in non-pregnant sexually active women.

Can a conjugate prevent acquisition of vaginal colonization? These women were enrolled to be very sexually active, given the clinics that they enrolled in. Healthy nonpregnant.

This is the study. 1525 were screened twice to have no GBS colonization of any serotype. They met other inclusion criteria. If they did, we lost a lot because of

colonization and other reasons. They were randomized. A little over 300 patients got tetanus diphtheria vaccine. This was pre-Tdap when this was done. TD was the control vaccine. The other got the monovalent type III conjugate.

These women were cultured and bled often. You can count up all the months that they were cultured and had blood samples. The primary endpoint in the study was time to first vaginal type III colonization. The secondary endpoints were several but included the proportion of positive swabs. These women were swabbed both at the vagina and rectum and they were processed at a central microbiology laboratory.

I can tell you that in this large group of women over 300 that the vaccine response was what we would expect. It peaked at 12 months at 12.6 micrograms with the confidence interval as shown there and remained quite low in the Td vaccine group.

Adverse events were similar. That is because the Td conjugate is the main culprit for causing local inflammation after the injection. There were no SAEs.

You cannot see this slide. Isn't that nice? I am going to have to tell you that the primary endpoint was time to first vaginal acquisition. You cannot see that, but it is in the box on the left-hand side. That is the time to first positive. And the top number is 35 percent vaccine

effectiveness against preventing type III vaginal acquisition over an 18-month period of time. The second number is 42 percent effectiveness at preventing rectal acquisition over an 18-month period of time. Both numbers were statistically significant.

Down on the bottom what you cannot see is basically an adjusted model where the statisticians looked at multiple things that would affect effectiveness, race, heavy colonization or light colonization, the microbiome, healthy or adverse, sexual activity, months since immunization. And, again, you see for interestingly according to the adjusted information, rectal acquisition again was statistically significant with an almost statistical significance for vaginal. Modest efficacy at preventing vaginal acquisition.

I will tell you. We did great for type III, but at the end of the 18 months, we had the same prevalence of total GBS colonization in the two populations because nature avoids and other serotypes filled in and took their place. Clearly, we need a multivalent vaccine if we are going to target colonization.

The conclusion here is that maternal immunization to prevent perinatal disease could modestly reduce acquisition of GBS during pregnancy thereby reducing fetal

and neonatal exposure in addition to the maternal antibody protection.

What do we know today to sum up? We know that CPS is an essential virulence factor for infant GBS infant, actually, for perinatal disease. We know that sufficient amounts of conjugate vaccine-induced IgG in all the studies against these polysaccharides are functional in vitro and protective in animal models. We know that given a half-life of about six weeks, maternal immunization could prevent most early-onset and late-onset disease at least theoretically.

We think that antibodies of capsular polysaccharides are protective, but we need appropriate quantitative epitope specific assay to determine the protective concentration. We need assay agreement and consensus. We need functional assay agreement and consensus because not all binding antibodies may kill this organism. Both serocorrelates if you use immune correlates and colonization should be considered as endpoints.

Some people think this is a sunset and it is. But I interpret it as a sunrise based on this meeting. I am so glad that God allowed me to live long enough to be here. Thank you to the FDA.

DR. MCINNES: Thank you very much, Carol. Carol, would you entertain a couple of questions if we have. I

know Dr. Madhi is on the phone waiting, but I think this is such a comprehensive – yes, Dr. Spearman. Please.

DR. SPEARMAN: Carol, thank you for that great presentation and for your leadership in this field. Could you enlighten us a little bit about the functional versus non-functional antibodies that bind? Is it all epitope specificity or is it antibody subclass or are there other things we should be thinking about with correlates that will really be functional?

DR. BAKER: Not enough work has been done in this area because again this is – our main job was to do Phase I and Phase II trials and then industry would jump with open arms and pick up the vaccine and go forward.

What I can tell you is that you cannot guess. The isomers, Ia, Ib. Ib makes Ia antibodies that do not kill Ia. We know that from one paper. We know nothing about subclass. We only know as IgG. I cannot answer your subclass question. I think it needs to be looked at. This is the kind of thing that Pfizer and maybe five other companies will jump in, this is so exciting, and address. Given the structure, there is going to be cross-reactive binding antibodies and it needs to be looked at more carefully.

For type III, we have not discovered any except that I can tell you in the SPIN Study, the one I just

presented about colonization, it looks to me like three is a two-three cross. Whether it is functional or not, I do not know. Paul, the major answer is we do not know enough to answer your question except Ia and Ib.

DR. MCINNES: Thank you. Dr. Greenberg.

DR. GREENBERG: Thanks for the presentation. In the SPIN study, the more or less 40 percent efficacy against colonization. I think you said it was at 18 months or through 18 months. It must have been the primary. But is there indication that there was a higher efficacy in shorter periods after vaccination?

DR. BAKER: That probably has been looked at Dr. Greenberg, but I do not know because again this has not been published. I just wanted to give the final primary endpoint with a comment about rectal because I do not know the vaccine that had prevented acquisition of rectal colonization. I was scared to death you were going to say explain to me by what mechanism. No one is allowed to ask that question because I do not know any explanation, but I believe it is a valid observation.

DR. MCINNES: Carol, thank you again. That was wonderful. Dr. Shabir Madhi has very patiently been waiting. He is on the phone, I presume, in South Africa. We look forward to welcoming Dr. Madhi to address us on the

clinical and immunological epidemiology of Group B Strep in low and middle-income settings. Welcome, Dr. Madhi.

Agenda Item: Clinical and Immunological Epidemiology of GBS in Low-Middle Income Settings

DR. MADHI: Thank you very much. It is a pity that I can't be there in person. I just wanted to mention that in case I am breaking up, or if I can't be heard clearly, please feel free to interrupt me to let me know.

So just in terms of declarations, I wanted to declare that my institution has been receiving grant support from the Gates Foundation, the CDC, GSK/Novartis and Pfizer with regards to GBS work, as well as the advisory board of the Gates Foundation, BIOVAC and Pfizer also in relation GBS vaccine development and epidemiology.

So what I am going to do over the course of the next half an hour is really to touch on the clinical epidemiology of invasive GBS disease in low or middle income countries. Although Darcie has sort of already provided the framework, I am going to focus more to the experience in South Africa, as well as illustrate what our learnings from the systematic review that was undertaken in relation to the feasibility of bringing vaccine efficacy trials in low middle income countries, as well as what are the clinical endpoints and what the challenges might be in

terms of addressing some of those clinical endpoints with regard to vaccine efficacy.

And then, I am briefly just going to touch on our experience in terms of trying to establish a correlate of protection against invasive GBS, very much already under work, which Dr. Baker has already presented on. And then spend a fair amount of time addressing the whole issue of prevalence and dynamics of GBS recto-vaginal colonization in low and middle income settings. And the data that we have been able to generate and collaborate the findings that were presented from the study in the context of the dynamics of colonization during pregnancy, as well as the new mediators that might be influencing that.

Darcie presented this data in some detail already. This was a systematic review that was undertaken that was published in November of last year, which tried to basically establish the global burden of GBS disease across different age groups, as well as specifically in infants as well as in stillbirths. Actually, an important thing to appreciate from this is that although we have been able to now generate some estimates, these estimates are largely founded on a really limited data, especially when it comes to low-income countries. In some instances, that might actually be working against our estimates. So they might be conservative estimates, rather than a true reflection of

the burden of disease. I will come back to that a little bit later.

At the high level, and this was the data which has been presented, the estimates are that about one-fourth of all women that deliver globally are colonized with GBS. And invasive disease amongst pregnant women is estimated at about 33,000. Fifty-seven thousand stillbirths attributed to GBS, and these are stillbirths, which are probably culture-confirmed cases. And that fifty-seven thousand obviously needs to be interpreted in the context globally, approximately 2.6 million stillbirths occurring. So 57,000 is a fairly minor small amount of the global burden. But it might well be that there is some level of under estimation in terms of the contribution of GBS through the stillbirth, which might be influencing this estimate.

In addition to which, there are about 320,000 cases of invasive disease that are estimated to occur, 90 percent of which occurs in low-income countries. Those contributed actually about 90,000 infant deaths globally. And Stephanie has already mentioned neurodevelopmental disabilities that occur especially in those that survive from the meningitis.

And then must also suggest approximately about three and a half million preterm births have been attributed to GBS. And once again, I think that is really

based on fairly limited data, mainly from high-income countries in terms of the hospitalization. It is work that still needs to be dealt with in more detail, especially in low-income countries.

An important message obviously, and of all of these diseases, the only one that is amenable to prevention from intrapartum antibiotic prophylaxis, as we have heard, is the early onset disease where there is a potential for many of the other disease endpoints to be influenced by maternal GBS vaccination.

One of the major challenges, as I have already alluded to, is porosity of data, and especially the porosity of data from low-income countries. On the top of this slide, you basically see the few countries which actually contributed to data for incidence estimates. As it is quite evident, there is almost a complete absence of data from the majority of African countries. Even for those African countries where we do have data from, there is actually a limited number of studies that have been undertaken, except that for South Africa and less so for India.

But what they don’t obviously want to present is the prevalence of heterogeneity both within low and middle-income countries, as well as between high-income and low-income countries if what is presented. And specifically,

in terms of the low and middle-income countries, based on the data that was available from the published literature, we find a much higher incidence in Southern Africa. There are some studies from South Africa and Mozambique, lower incidence in West Africa in a study from Gambia, as well as low incidence in Kenya, which was sort of some lesser incidence that has been described in India. This is what the information that was available to us in terms of trying to get to those estimates, which I have made mention of earlier.

Now, I think the lens that we perhaps need to interpret this data in terms of my suggestion that there might be an under estimation of cases in the low-income setting is looking at an incidence of invasive disease between high-income countries and low-income countries, and specifically in terms of incidence among babies who are born to mothers that are colonized. This is again Dangor was the senior author when this was published.

In essence, what it basically shows that as Stephanie had mentioned earlier, roughly about 1 to 3 percent of babies born to mothers that are colonized were developing invasive disease. Now, looking at the data from Africa and counting the numbers from Kenya, and again they are obviously small in terms of the number of cases, but overall, we will define exactly .7 percent of babies that

are born to mothers that are colonized who develop early onset disease in Africa.

In contrast, those figures are about 1.34 percent in high-income countries. As you can see in some of the studies from the United States and all of this data from the US, before the implementation of intrapartum antibiotic prophylaxis, in some of the studies, the incidence was as high as 3 percent of babies being born to pregnant women that are colonized developing invasive disease. This really suggests to us that there might be some systematic under estimation of early onset disease in low and middle-income countries. That might be for a number of different reasons.

Perhaps one of the most important reasons for the possibility of under estimation goes back to an early slide which Stephanie has also made mention of. That was the experience of the diagnosis of early-onset disease in the United States before intrapartum antibiotic prophylaxis. In the United States, over 90 percent of the early onset disease was actually occurring on day 0 of life.

What you also see is data from South Africa over a 10-year period where we basically show that in South African countries, about 70 percent of all early onset disease is occurring on day 0 of life. Roughly about 90

percent by day one of life. So the majority of disease is occurring within the first three or four days out.

But what is also important in the South African context is almost all of the cases that I diagnosed on day 0 of life are actually based on the culture, which is done at the time of birth of the child. I think that is really important, especially in terms of our discussion about the possible acquisition of GBS with stillbirth, which I will come back to. So what this really tells us is that the acquisition of GBS in these sort of settings is more likely occurring in utero rather than during the course of the birth of the child.

So the likely reasons for the under-detection of early onset disease in low and middle income countries in my own mind probably first might well relate to differences in terms of the thresholds investigating for invasive disease. Especially because of the non-specificity of the science and symptoms. There might be a higher threshold for investigating in resource-limited settings. And as an example, in the United States, any mild respiratory distress might warrant the blood culture being done.

In addition to that, there are other challenges that we face in low and middle income countries. The majority of births don’t take place in hospitals. Even though they might occur in the child care centers, those

child care centers are usually primary health care centers. A big proportion of births in South Asia might actually be taking place at home.

The challenge that you face is that very few of these children that are born with respiratory distress, which might be the cause of GBS, would actually have a blood culture done before actually repeating antibiotics, which is what the WHO actually recommends. In addition to which, we obviously might be facing challenges and concerns of the actual taking of blood, the venipuncture techniques, as well as issues in terms of the laboratory methods.

I think all of these things put together possibly might indicate the reason for under estimation of early onset disease in the context of the percentage of children that are born to mothers that develop the disease. But it also might explain some of the heterogeneity that cuts across the different low and middle-income countries in the studies which I have shown.

Perhaps to say the point that these are data again from South Africa which basically shows the incidence of invasive disease in the different provinces. The red dots basically shows you the sight where I work at, which have really generated most of the data which I have been presenting on, where we have consistently shown an

incidence of between two and a half and three per thousand live births for the past 20 years.

But at the same time, using a national laboratory-based in a public sector, which about 80 percent of the population would make use, we find tremendous heterogeneity in terms of incidence estimates. Incidence estimates being highest in the Western Cape and Gauteng, which are the two best resource providences in South Africa and have the highest percentage of births taking place in hospitals.

We have neighboring North West and Limpopo provinces next to Gauteng, there is almost no invasive GBS diseases actually diagnosed. Obviously, that is not because of heterogeneity in the population, but merely an issue of case detection and the challenges with regard to case detection even within the same country.

One of the issues where they are giving their data is whether there are actually any temporal changes in terms of incidence of invasive GBS disease in low and middle-income countries. This is Kenya data over in Soweto again. It basically indicates that there really hasn’t been any change in the incidence of either overall or early or late onset disease between the year 2005 and 2014. And in fact, the first studies we actually did on invasive GBS

disease dates back to 1997. The incidence at that stage was almost identical.

This is data has been generated in the context of a setting which uses a risk-based strategy for prevention of early onset disease. Unfortunately, the logistics and the resource constraints, given in a country such as South Africa, makes it implausible that you would be able to do a screening-based approach in terms of prevention of early onset disease.

Looking at age group distribution of the late onset disease case, as I mentioned for the early onset disease, the median age was one day of age to zero days of age. The median age for late onset disease in South Africa is perhaps a bit earlier, a bit lower than it is in the US. It is actually about 15 days.

And by two months of age, it constitutes roughly about 90 percent of all of the late onset disease that is observed. But in essence, there is really one thing to protect at least until two months of age. We should be able to protect again with over 95 percent of all of the invasive disease overall.

It was also mentioned, and obviously this is especially important in a country such as South Africa, where about one-third of all pregnant women are HIV infected. The increased susceptibility of HIV-exposed

infants, even if they themselves are not infected by HIV or invasive disease. That was estimated to be roughly about 4.4 fold greater of late onset disease.

Again, this data largely informed from estimates from studies done in South Africa, as well as the more recent study done in Mozambique, but included among this, in fact, was the first study that demonstrated this, which actually came out from Belgium. One of the issues that we are faced with is that in the South African context where HIV-exposed children might be contributing to a disproportionate burden of the invasive disease. We obviously would need to know how well the vaccine works in that particular population.

The systematic review, which was presented, and I think Stephanie alluded to this, was also presented data on invasive disease in terms of serotyping. And again, there was a limited number of cases that were available from East Asia, as well as South America. But in essence, I think the story is very similar across different settings. We are more than 95 or 98 percent of all the invasive disease isolates in different regions, which is either five or the six serotypes that are currently being considered in the vaccine that is in clinical development.

As to whether there are changes, temporal changes, in terms of serotype distribution, again this is

the data from South Africa over a 10-year period. What we show is that there are some temporal fluctuations in terms of serotype, the proportion of disease caused by specific serotypes. In particular, those changes over time relate to serotype 3 and serotype 1A.

So as you can see is an example of what we have observed over this 10-year period is there was roughly about a 9 percent year on year increase in serotype 1A disease. And there was about the 7 and a half percent decrease in serotype 3 disease. This picture was fairly similar for earlier onset disease.

But again, it doesn't really take away from the bottom line, which is that it is the same serotype that has been considered for inclusion in a vaccine that is responsible for causing the majority of the disease. What we are currently busy with this sero is basically doing genome sequencing on the serotypes, specific and getting to the understanding to the possible reason for the fluctuation in terms of the relative contribution of the different serotypes to invasive disease.

The one point that also been discussed also in the context of the possibility of including it as part of a clinical endpoint for invasive disease is stillbirth. As I mentioned, in those systematic reviews, the conservative estimate was roughly about 57,000 stillbirths were possibly

attributed to invasive GBS disease. This again unfortunately was based on very limited data. There were three studies. As you can see, the count of number of cases of stillbirths associated with GBS was relatively few. The percentage of the cases where GBS was cited in range between 3 percent in Kenya to 17 percent in Mozambique.

But some of the issues, I think, which need to be dealt with right now is that there are differences in terms of the methods that are using the different studies for attributing GBS as a cause of the stillbirths. So as an example, in the South African study, these estimates are based purely from post-mortem blood culture, whereas the study from Kenya and Mozambique, the extended investigation to include lung culture. In fact, in Mozambique, they also extended that to include more accurate diagnostics. In all of the cases in Mozambique, they were actually based on the PCR concerns.

What we also need to appreciate to put into context is the incidence of GBS-associated stillbirths and compare that to incidence of early onset disease. Interestingly in Kenya, what they actually showed in a paper that was published two years ago, the estimate for GBS confirmed stillbirths was, in fact, similar, if not higher, than for earlier onset disease. Just for overlap

of the confidence intervals obviously, but the estimate was .9 per thousand births for stillbirths and .76 for early onset disease.

In South Africa, in this unpublished data, our estimates for GBS culture confirmed stillbirth is 1 per 1000 compared to 1.4 for early onset disease. So these estimates are fairly close to each other. I think in essence, based on the knowledge that 90 percent of early onset disease is pretty much occurring on day 0 of life, I think the GBS stillbirth really represents a continuum of disease through the early onset disease rather than being a completely separate entity.

I think Dr. Greenberg and others actually raised the question as to how much might we be under estimating the burden of GBS by focusing on the invasive disease. This is a thesis that was recently published, but not yet in the literature, which Stephanie was, in fact, part of the study team, which tried to interrogate this issue.

So in the study, what we did is we had physician-diagnosed bacterial infections. These were newborns that were less than three days of age, that were treated empirically by the attending physician for suspected sepsis. Then we had the category of them that followed clinical laboratory algorithm definition of protocol-defined sepsis. Lastly, we had the group that was actually

blood culture confirmed. So all of these children were investigated with blood culture.

What it basically shows us is that even compared to those with protocol-defined sepsis, which uses a fairly stringent definition of sepsis, only 5 percent of those cases would actually have a positive blood culture. This is not just for GBS. But only 5 percent of them would have a positive blood culture.

Importantly also is that the case fatality rate for the suspected sepsis is 9 percent, which is lower than the 13 percent for bacteremia sepsis. But in terms of the actual number of children that died from that particular syndrome, it far exceeds at 240 compared to the 8 for bacteremia sepsis. I think this is a part which really, we wouldn't be able to tease out in the absence of a vaccine probe to be able to understand the contribution of GBS to the spectrum where we are not getting culture-confirmed disease.

The next slide, so what we did in the same study, and this is exactly the same study, just represented in a different way, is we tried to see whether we could improve our detection of invasive GBS disease using molecular diagnostics, in particular TACMAN Array PCR. What we found is that the amount of healthy controls was the background positivity rate of 1.6 percent, indicating that it is not

100 percent specific measure. But actually, having a positive PCR for GBS was 4.5 for greater among the cases, sitting at 7 percent.

Putting this data together, and in a sense of this graph, you basically see the BGS component of it is that we have GBS was the most common bacteria identified among the bacteremia cases in the children less than 72 hours of age, of which there were 23. And of those 23, 19 were also PCR positive.

In addition, we had another that were PCR positive, but blood culture negative. So at the bottom of the slide, after adjusting for the positivity in the control, what we were able to show is that the incidence of GPS, our estimate at least, increased roughly by about 73 percent by using a combination of cultures relative here, diagnosed invasive disease compared to culture alone.

I am not going to spend too much time on correlate because obviously Carol has been the world leader in this, and she has done a marvelous job on this. Just to again highlight perhaps one or two issues around that.

We undertook a study, again these were cases that were retrospective enrolled that were within 24 hours of them being confirmed as being invasive GBS disease. We matched with them and draw models where basically the controls for those models that were colonized with the same

serotype. And we tried to again derive a correlate of protection.

And on the left-hand side is a study which Dr. Baker has presented earlier. As you can see from the graph, they looked remarkably similar in terms of the distribution of the curve. But where they differ is the access in terms of the actual concentrations. Our estimates are, in terms of the concentration of antibodies that are required to about the 90 percent reduced risk, it is about 6 to 10-fold greater than what was proposed by Dr. Baker.

But I guess the big issue, as Dr. Baker pointed out, is that a challenge that we face is that even though we use the same, she was kind enough to provide us with the reference for our assays, again the assays themselves are not necessarily that actually comparable. But I think the other issue that needs to be addressed in terms of the correlate discussion is whether the correlate should be established based on maternal or correlate antibodies or newborn blood.

The data that we presented in and the data that Dr. Baker has presented are largely based on maternal antibody. Obviously, we know that efficiency of transfer of polysaccharide antibody is not for entities for protein antibodies. We need to, I think, tease out the newborn

blood that needs to be used to derive the correlates, or whether we satisfy through the maternal blood or maternal measures.

And then there is the question as to whether there should be a single correlate for both early, as well as late, onset disease. In my own mind, I think that is the case. There is no need for different correlates, especially where the majority of the disease is occurring pretty much in the first month of life.

But then the other challenge, which we are going to face, is that I think most of the studies have indicated that we probably would have sufficient power to derive correlates for serotype 1A and serotype 3, but not necessarily so for some of the other serotypes. And then the issue arises obviously as to how are we going to bridge in terms of getting some sort of estimate for correlates for the other serotypes, if indeed there is a difference in terms of correlates between serotypes.

This is just to introduce a study that is currently under analysis. It is another study that we do correlate of protection. In this particular instance, we enrolled 35,000 mother-newborn pairs, and those that are prospective cohorts. It just gives you an idea of the number of cases that we have been able to accumulate, both

early, as well as late, onset disease in children that were born before 34 weeks of gestational age.

So we have 35,000 mother-newborn pairs. Roughly, we were able to obtain about 38 cases in children older than 34 weeks, which is the incidence of about 1000, which is very different from our data. That is a different discussion. But I think it is just really just to say some of the data that will be forthcoming within the course hopefully of the next year, as well as some of the challenges in terms of even trying to divide the correlate of protection with suitable number of cases. The retrospective cases again are basically infant, where we are only able to obtain the blood after we have actually diagnosed the case, of which we didn’t get cord blood available to us in those cases.

I am going to not touch on the issue of colonization. This again, from the systematic review. I think without going into detail, the summary of this is that generally studies from Africa show a much higher prevalence of colonization compared to studies from Asia in the immediate levels of colonization in Europe and America, except in the Caribbean where prevalence of colonization is as high, if not higher, than it is in Southern Africa. And again, the graph basically just illustrates the countries where these studies have been done, and a relative

heterogeneity in terms of the prevalence of colonization between different countries.

Again, without spending too much time on this because these are data that is obviously published, the serotype distribution in terms of colonizing isolates. And we see the dominance of serotype 1A and serotype 3. But in some places, you also have got a much greater representation of serotype 5 as an example in Southeast Asia, less in West Africa. But again, just to caution that some of the studies involve a very limited number of cases that were actually analyzed, as indicated in the parentheses.

A study that is currently underway in nine different countries, including three South Asian countries and five African countries, involved about 780 mother-newborn pairs to try to see whether differences which were identified in a systematic review might be related to study methodology. But the study is also designed to try to address some of the other reasons why there might be a disconnect between the prevalence of colonization and the reported incidence of invasive disease.

So whereas the prevalence of colonization only differs at death by a twofold margin between South Asia and Africa, the difference in terms of incidence of early onset disease is more than a 60-fold difference. There is

something else is happening, which we don't really ever put and in terms of what, explain the differences.

Anyway, in that particular study, which will be completed in the course of this year, what we have shown as an example is that in India, the prevalence of colonization is much higher than has been previously reported in the literature. I think it is about 20 percent. And this slide also just shows you the different serotypes that are involved in the different studies where we have completed the serotyping at this point.

What the study will also be doing is basically measuring maternal, as well as newborn capsular antibody measuring GBS bacteriuria in the mothers, measuring GBS surface and mucosal colonization in the newborn, as well as looking at the density of GBS colonization in the mothers, and whole genome sequencing of the GBS isolates. This is data which we are hoping would become publicly available over the course of the next 12 months.

The big issue, and I think there was a fair amount of skepticism around whether a vaccine in pregnant woman would be able to protect against colonization. Obviously, Dr. Baker presented the case as to why that might happen. But the reason for the skepticism is sort of summarized in this systematic review, where all of the studies, and most of the cross-sectional studies looked at

antibody concentration in women that were colonized at a point in time. These were cross-sectional studies.

And consistently what all the studies actually showed is that mothers that were colonized at the time of birth generally had much higher antibody concentration than mothers that were not colonized. This led to some level of skepticism if every antibody would actually be able to prevent colonization.

What we actually did is we actually did a longitudinal cohort study really to address the issue as to whether antibodies prevent acquisition, rather than just looking at the presence of colonization and antibody concentration. And in this study in pregnant women, we sampled women at four different time points, from 20 weeks of gestational age to 37 weeks of gestation age.

We included both rectal, as well as vaginal, swabs. In addition to which we basically measured the antibody concentrations to serotype type 1A, IB, 3 and 5. I am not going to go into the details because again they have been published. But I am just going to try to highlight some of the key issues.

The first issue was that these changes in terms of the prevalence of colonization during pregnancy, in fact, colonization seems to be slightly lower at the time of delivery between 8 percent compared to at 20 to 24 weeks

where it sat about 33 percent. But I think another striking message from this particular study is that 50 percent of women would be colonized at least once between 20 weeks and 37 weeks of gestational age. Also, 28 percent would be persistently colonized by the same serotype, and 39 percent actually cleared their colonization.

But in addition to that, perhaps where a vaccine is most likely to work is the prevention of acquisition. And what we see in this study is that roughly about 20 percent of women would actually require the serotype, including about 10 percent of serotype of 1A and 7 percent of serotype 3. In this particular setting where we worked, there is a high acquisition rate of GBS within a short period of time in pregnant women.

So what we were able to show in this study, and perhaps also just to focus on the OPA data rather than the antibody concentration, is that women that developed a new acquisition get much lower OPA titers than women that remain colonized throughout pregnancy for that particular serotype. And on the bottom, what we show is that protection against acquisition at a rate of greater than 1.32 was about 95 percent reduced of being colonized. If the mother OPA titer than greater than 1 in 52 for serotype 1A and about 80 percent less likely without being colonized with serotype three at a titer greater than 52 in the OPA

assays. There was no association between serotype antibody concentration of the OPA titer and clearance of colonization in this particular study.

This is the summary of what Dr. Baker presented. I think the data is a longitudinal cohort, natural immunity data. It really makes the case as to why a GBS is seen in a very likelihood would be able to actually prevent acquisition and even acquisition during pregnancy. The issue obviously would be the timing of the vaccine during pregnancy to maximize, to reduce exposure of the newborn to GBS at the time of delivery.

Another interesting study which was also published last year was the study from Gambia. In this particular study where they tried to define whether functional antibody derived by the newborn from the mother was able to actually protect the newborn from becoming colonized either in vaginal or the rectum. And again, the data has been published, so I am just going to summarize it.

In essence, what it basically illustrates that high-end, high-concentrations of functional antibodies was positively associated with reduced risk of the baby becoming colonized mucosa with serotypes 2, 3 and 5, as well as associated with clearance of serotype 1A, 2, 3 and 5 in a baby. So babies that acquired high-concentrations

of functional antibodies from the mother were less likely to actually develop mucosal colonization and, in fact, more likely to subsequently clear the colonization. Yet, they have already been colonized at the time of birth.

I think as a conclusion, I think the first point that I would like to highlight is that although there is a high burden, and a much higher burden of invasive GBS disease in low and middle-income countries, especially in Southern Africa, given the few countries from which data is available, and given the innate issues in terms of behavior and where deliveries occur, et cetera, there is probably very limited potential for a vaccine efficacy trial to be done with culture-confirmed disease as an endpoint. It is something that we could probably do in South Africa, but it would probably take us a huge amount of investment to actually get it done in multiple settings. I think it will become even more difficult if you go outside of your resource setting.

The next point is that I think both in high, as well as in low, income countries, there is a strong association between antibody derived from the mother in protection against invasive disease, both for early, as well as late, onset disease, and possibly also for stillbirths. As I mentioned, the vaccine efficacy against specific maternal colonization is for early onset disease,

as well as colonization of infants as a proxy for late onset disease might probably be a more pragmatic pathway in supporting corroborative evidence together with the correlate of protection, the vaccination of pregnant women is actually able to protect the infant or the newborn against invasive disease.

I think I have experienced both from pneumococcal conjugate vaccine, as well as a Hib conjugate vaccine, is even that vaccine has about 50 to 60 percent efficacy against colonization. Generally, it translates into a tremendous amount of indirect protection and possibly even direct protection. I think together with invasive disease, being able to show that the vaccine is able to impact on colonization would make a fairly strong case in my mind as to why the vaccine will likely actually protect the babies.

That being said, I think from a public health perspective, what would really be required to really fully understand the role of GBS in terms of stillbirths, in terms of its contribution to preterm birth, in terms of its contribution to non-culture confirmed disease, is a vaccine probe study. For that sort of a study to take place, it really does require a randomized control trial. That is something that you certainly should keep in the back of our minds, at least in terms of a phase IV study to actually

confirm that protection actually translates into vaccine efficacy in the long term.

At that point, I will pause.

DR. MCINNES: Dr. Madhi, thank you very much. That was a feat well accomplished. Thank you. I think we have one or two clarification questions from folks, and then we need to move on.

DR. EL SAHLY: This question pertains to the correlate of protections. Dr. Baker's data, the cutoff for serotype 3 antibody levels was .5. Am I right? It was associated with the decline in infant disease. But in your data, it was at three using the same methodology? Or are we speaking different methodologies here?

DR. MADHI: No. It uses the same reference sera, but it uses different methodologies. We have analyzed a Luminex assay. There might be a whole lot of issues that on the differences in the assay. As Dr. Baker mentioned, I don't think we can make much in terms of head-to-head comparisons of these measures until there are standardized assays by which we basically analyze different samples. I think it is more to do with the assay and not necessarily because of differences between the populations, which might be the case.

DR. MCINNES: Any other questions?

DR. SHANE: I have a question about the loss and gain of colonization. It was very interesting to see the long-term measurements of that. I was wondering what your thoughts were with regards to when a vaccination would be optimal based on some of the data about loss and gain of colonization?

DR. MADHI: I think the two big issues related to what are we trying to achieve by reducing colonization. As an example, if there is an association with GBS in preterm labor, for vaccination to actually impact upon that preterm labor would require vaccination at the relatively early stage of pregnancy. Or else it is not likely that you are going to impact on preterm births, at least the early preterm births.

An example of what we are trying to achieve by reducing colonization. If the focus is mainly on preventing, and again, the same thing holds true for prevention of invasive disease in preterm babies in that it is unlikely that the very preterm babies will be protected through maternal acquisition of antibodies. But they could be protected by actually reducing acquisition or GBS colonization in the pregnant woman, and consequently, reducing the exposure of the preterm babies through GBS.

In my own mind, I think what we are needing to do is try to target vaccination as early as possible in the

early third trimester, late second trimester at the latest. Of course, what the longitudinal studies also show is that the antibody really only protects against acquisition. As I mentioned, it doesn't actually clear existing colonization.

What it has shown is that the median time for colonization varies between the serotypes, but is roughly about seven to nine weeks in terms of the median duration of colonization.

DR. MCINNES: We have one question from Dr. Gilbert for you.

DR. GILBERT: So your talk and also Dr. Baker's talk before it was showing that both the binding antibodies and some functional assays are consistently inverse correlates of disease in the infants from a variety of clinical endpoints in infants. And there seems to be consistency in that monotonic pattern. Maybe the thresholds are different, but the pattern is always in the right direction, correlation and that consistency could be important for thinking about whether some of these assay responses could be reasonably likely to predict clinical benefit.

But my question is, is there literature showing examples where these assay readouts did not correlate

inversely with some disease endpoints? Or is it really pretty uniform and consistent in the literature?

DR. MADHI: So the systematic review which I referred to, in fact, also looked at invasive disease. There was a handful of studies which didn't find an association. But that being said, those studies unfortunately generally had a very limited number of cases for it to be taken seriously.

I think across the studies, which were probably adequately powered or had sufficient number of cases, the direction of association is in the same direction. That is in support of possibly being established.

DR. MCINNES: I think one final question from Dr. Levine.

DR. LEVINE: In one of your final slides, you were pessimistic about the possibility of a randomized control trial using culture-confirmed disease as an endpoint. I wonder if you could be a bit more specific because your group has done pioneering trials in your youth with Hib and with pneumococcal conjugate. What do you see as the hurdles that make this so much more difficult with respect to specifics? Is it the incidence? Is it the level of expected efficacy, et cetera?

DR. MADHI: So I think there is a limited number of places where such studies would be able to be done. One

of the main reasons for that, as I tried to point out in the data, was that for these studies to be successful in terms of case ascertainment, you really need to be investigating for the early onset disease at the time of birth, which effectively means that you need to have a presence in the health care centers. If a child comes out with strep, you need to investigate. I think that is the first challenge.

That being said, that sort of study could pretty much be done in my setting. But I think we face a lot of challenges. And part of my skepticism around this really relates to the experience as an example of involvement in the vaccine study in pregnant women. That is what is understandably a risk aversion on the part of the companies that have funded the studies with regard to the inclusion and exclusion criteria.

It becomes almost impossible to mitigate to a reasonable level to allow for high numbers of involvement. So as an example, in our vaccine studies, for every one patient that we are enrolling, we are needing to screen roughly about 10 pregnant women. Then there are other issues in terms, issues regarding of what inclusion/exclusion criteria we would pose on the study for a vaccine that is not yet licensed in pregnant woman. That would make it really difficult to actually enroll.

Even in a South African context, we are using a composite of early and late onset disease, as well as stillbirths. We would require a sample size of roughly about 50,000. Again, that is 50,000 in the first part would need to be among HIV uninfected women obviously. But I think it would be a challenge getting 50,000 women enrolled with all the inclusion/exclusion criteria constraints that are imposed with three IMB studies.

DR. MCINNES: Shabir, thank you very much. I know Serina has emailed you about your time availability a little bit later on. We are most appreciative of your presentation. Thank you.

So I am commending everybody in this room and those are on the webcast for their focus, commitment and grace. I beg you for a little bit more of it. We are going to have our final presentation. We particularly want to thank these last two speakers who have waited so patiently. Then we will just look at the time, adjust it, and with your permission, probably truncate lunch, and then come back in.

The final presentation before lunch is from Pfizer, Dr. Annaliesa Anderson and Dr. Judith Absalon, about the burden of group B strep disease and Pfizer’s group B strep vaccine. It is Dr. Anderson first.

Agenda Item: The Burden of GBS Disease and Pfizer's GBS Vaccine

DR. ANDERSON: Thank you. I am Annaliesa Anderson, an employee of Pfizer and the chief scientific officer for bacterial vaccines. I would like to thank the FDA for the opportunity to participate in this meeting today and look forward to receiving input from the panel regarding approaches to demonstrate effectiveness for GBS vaccines.

This morning, I will begin by sharing some information on the burden of Group B Streptococcal disease and the Pfizer GBS vaccine. And then Dr. Judy Absalon will review the potential clinical development pathways for this vaccine.

We will be sharing with you information on the maternal vaccine that Pfizer is developing to prevent GBS disease in infants. The vaccine is comprised of six polysaccharide serotypes, each individually conjugated to the carrier, CRM197. It is designed to be administered to pregnant women who will subsequently develop antibodies that can be transferred to their babies in utero for protection. No regulatory precedent is available for vaccine to be licensed in pregnant women. Pfizer is therefore looking for guidance.

GBS colonization is a well-established risk factor for GBS disease. Approximately 25 percent of women are colonized with GBS in their recto-vaginal area. This colonization can lead to several disease states for the mother and the baby. These include invasive maternal disease, stillbirths and preterm births, and invasive infant disease, which presents as pneumonia, sepsis or meningitis.

Doctors Everett and Schrag have already described to you the benefit of intrapartum antibiotic prophylaxis, or IAP for short, in reducing the cases of early onset disease in the US. This approach has reduced the rate of early onset disease nine-fold. However, the burden still persists. There has been no impact on late on set disease.

Additional shortcomings, including missed isolates, women being colonized after screening, and the high level of antibiotic exposure for up to a third of pregnant women and newborn babies with unknown consequence in child development and antimicrobial resistance. For these reasons, some high-income regions have been reluctant to introduce this approach into their health care systems. GBS disease also has a higher burden in regions that do not have the infrastructure to screen pregnant women and to administer IAP.

As Dr. Madhi mentioned earlier, this is exemplified by rates observed in South Africa, which is shown here. Taken together, a vaccine that could prevent invasive GBS infections could have a positive effect in reducing the disease burden.

GBS strains are coated with capsular polysaccharides, which define their serotype. And as has been described previously this morning, capsular polysaccharide antibodies are protective and therefore good candidates for prophylactic vaccines. We are developing a polysaccharide conjugate vaccine that represents the most prevalent serotype shown here.

Though there may be differences in the distribution of specific serotypes by region, as exemplified on the left in the US and South Africa, six serotypes caused the majority of infant invasive disease globally with serotypes 1A and 3 being the most prevalent. We have included these six polysaccharides individually conjugated to CRM197 in our vaccine, which we will refer to as GBS 6.

I would now like to show you some preclinical data we have generated with GBS 6 to demonstrate the mechanism of action for a maternal vaccine. In this study, female mice were vaccinated either with GBS 6 or a control vaccine, and then mated. The resulting pups were

challenged with serotype-specific GBS isolates and monitored for protection compared to pups born to immunized mice.

As you can see in the figure, a high survival rate is observed for the GBS 6 vaccinated pups shown in dark blue compared to the immunized pups shown in orange for each of the six serotypes included in our investigational vaccine. This model effectively mimics a proposed mechanism of action for the maternal vaccine, antibodies induced in the dam are transferred to the pup in utero and protecting the pup after birth.

I would now like to discuss this in relation to the mechanism of action of the vaccine and how preclinical and seroepidemiology studies are important for us to assess the potential effectiveness of our vaccine. A critical question for any vaccine development program is what are the concentrations of antibodies that the babies will need at birth to provide protection over a defined period of time?

One can appreciate the defined level of protection could be established for different serotypes. Then it could great enhance our understanding of what a vaccine would need to achieve in terms of immune responses. We have explored this using a passive maternal preclinical

animal model that can directly measure the amount of antibody that is required for protection.

Pregnant mice are infused with unvaccinated seropositive human sera, and then the pups are challenged with type-specific GBS strains. In this example, we have used sera-positive human sera with titers of between zero, one and two micrograms per mil. And observing increasing levels of survival for the pups that receive the higher levels of antibody.

This model provides the opportunity to assess the different serotypes and also compare vaccinated and unvaccinated sera from human clinical studies. This can provide supportive data for the development of protective antibody thresholds for the different serotypes.

As has been described this morning, several sera epidemiology studies have been conducted that clearly link the protective IGG antibody levels to protection of infants. Here I am showing three of these studies. They all identified antibody thresholds in the mother that reduced disease risk for the infant.

I am showing these three as they all have the same standardized reference serum in common that was developed by Dr. Baker and provide derived protective thresholds using the Bayesian calculation, as opposed to the Odds Ratio calculation that was shown earlier. The

studies by Dr. Baker and Fabbrini assessed thresholds for early onset disease. Dr. Dangor extended the assessment out to include infants up to one month of age.

Each study was large, ranging in size from 25,000 to 135,000 subjects. Even with these relatively large numbers, protective thresholds could only be identified definitively for two of the most prevalent disease-causing serotypes type 1A and 3 with some supportive data for type 5.

It is important to also note that the complexity associated with these large studies are a magnitude lower than the level of complexity that would be associated with the study that incorporated an investigational vaccine for the purpose of demonstrating vaccine efficacy. Looking within the study, one can see differences in the protective level of antibody that is needed. Specifically, in Dr. Baker's study, an estimated titer of 2 micrograms per mil reduced the risk of infection for type 1A disease by 51 percent. And in contrast for serotype 3, 1 microgram per mil had 100 percent probability of reducing the disease risk.

Current drawbacks for these studies include that they have been conducted independently by different groups. The samples, assays, regions and assessments are all different. Despite these limitations, these data do

provide an indication that antibody titers can be predictive of protection. However, they can't be linked to current investigational vaccines because they are not conducted using a standardized assay.

Such an assay is in development by an International Academic Industry Consortium led by Dr. Ladoray(phonetic) at St. George's Hospital in London and funded by the Maternal Immunization Group headed by Dr. Vandermolen at the Bill and Melinda Gates Foundation. Dr. Madhi, as he also discussed, is conducting a large seroepidemiology study in South Africa that may also be possible if assessed using a standardized assay to link the seroepidemiology data to vaccine-immune titers.

I will now provide a perspective of what a vaccine may need to achieve in relation to immune responses. Despite natural GBS exposure, GBS capsular polysaccharide titers are naturally low in the general population. These low levels of antibodies transferred to the baby over time as illustrated by the red line. And these may be too low to protect the baby as indicated in the gray area representing the minimum protective threshold titer.

Vaccination, in contrast, could raise the mother's antibody titers, resulting in high levels of protective antibody being transferred to the baby and

protecting the newborn for a long period of time, illustrated here in the green line. The work by Dr. Baker, Marty, Lador, Vandermolen and Clerkman will be instrumental to the field by providing a standardized assay and defining the minimum protective threshold titers that may be required for a maternal GBS vaccine.

I would now like to introduce Dr. Judy Absalon, who is a senior medical director within Pfizer, and who will describe the possible approaches to demonstrate efficacy of GBS 6 to support licensure of vaccine for the prevention of infant invasive GBS disease.

Agenda Item: Potential GBS Vaccine Clinical Development Pathways

DR. ABSALON: Thank you. I would like to thank the FDA and the advisory committee for the opportunity to share Pfizer’s thoughts on potential pathways for the clinical development of a GBS vaccine. We initiated our clinical development program for this vaccine in healthy, non-pregnant women and men in June of last year and are planning to begin the studies in pregnant women by the end of this year. There are different pathways that can be pursued to demonstrate effectiveness to support vaccine licensure in the later stages of clinical development, which I would like to discuss during this presentation.

Three pathways can be considered that include demonstration of vaccine effectiveness in a clinical efficacy trial where the study endpoint would be incidence of an infant-invasive GBS disease. The next is demonstration of vaccine effectiveness using an established immunologic correlate of protection. Here, the proportions of infants who achieve the protective antibody level would be measured. In both of these scenarios, vaccine licensure would be obtained via the traditional approval pathway.

A third option would be to demonstrate vaccine effectiveness using a combined approach, where the initial licensure would be obtained using a surrogate of protection via the accelerated approval pathway. The endpoint would be the proportion of infants achieving antibody levels that are predictive of protection. However, per the regulation, a clinical disease endpoint study would need to be completed post-licensure to confirm the initial results.

I would now like to speak to each of these pathways in a bit more detail. Let’s start the discussion with the efficacy trial using a disease endpoint. This figure shows incidence of infant invasive GBS disease on the X axis and the number of evaluable pregnant women who would need to be enrolled on the Y axis.

Assuming a vaccine efficacy of 70 percent, with a typical assumption for a phase three clinical trial, a

study conducted in the US where incidence, and here we are using incidence that is a little bit older than what was discussed this morning, but where incidence is approximately 0.53 cases per thousand live births, would require a minimum enrollment of 200,000 pregnant women, which is not feasible.

What if, however, we were to adjust some of the parameters under which we conducted such a trial? For example, if we conducted this trial in a higher incidence region, could the efficacy trial size be reduced? In this figure, we have plotted the approximate number of pregnant women needed for enrollment in South Africa, which, as you have heard, has one of the highest incidences of invasive GBS disease in infants. We have used 2.5 cases per thousand live births. In this scenario, at least 40,000 pregnant women would need to be enrolled.

While this number is fewer than what would be required in the United States, the sample size remains quite large and is likely an underestimate, as other countries with lower GBS incidence would need to be included. It is likely that even in South Africa, disease incidence in the clinical trial might be lower than what we find from the published literature.

We could further decrease the sample size by reducing the lower bound of the 95 percent confidence

interval of the point estimate. For example, here, I am showing you the effect of reducing the lower bound to 0 percent from 20 percent. Ultimately, the parameters used to power clinical efficacy studies would be determined in consultation with regulatory agencies.

Another important point to note is that the study size is driven by the event rate. So if we increased that rate, the sample size could potentially be decreased. A composite disease endpoint, for example, might address this issue and potentially facilitate more rapid assessment of a GBS vaccine. Prevention of infant invasive GBS disease is the standard clinical trial endpoint.

A vaccine that impacts additional complications from GBS disease in infants, such as stillbirth or preterm, which we have heard quite a bit about this morning, could potentially contribute to the clinical trial event rate. For both stillbirth and preterm birth, data are limited on GBS-specific disease incidence. In addition, there are multi-factorial causes for both of these infant diseases, such as maternal hypertension, obstetric emergencies, and in the case of preterm birth, data are not conclusive regarding whether a GBS vaccine is the definitive causative agent in some of these outcomes.

Finally, a confirmatory diagnosis may be difficult, particularly for stillbirth where autopsy is

likely the most specific method and is unlikely to be accepted by many mothers in a large clinical trial setting. The inclusion therefore of either stillbirth or pre-term birth, as a composite endpoint, are not appropriate at this time and my dilute the ability to detect the vaccine effect due to the lack of GBS specificity.

What if we considered the addition of an endpoint, such as vaccine impact on maternal GBS disease? There is currently no regulatory precedent for different populations being considered in a single composite endpoint. And while this endpoint might be of value in an efficacy trial, the burden of maternal invasive GBS disease is not well described globally, and is less so in regions where rates of infant disease are highest, and where we would expect maternal disease to be high, as well.

Finally, if evaluated as a composite endpoint, impact on the trial would be contingent on the incidence of maternal invasive disease and the relationship to disease in the infant. More information would therefore be needed before this disease endpoint could be considered.

We have established that a vaccine clinical efficacy trial would be quite large. It is critical to understand also that these trials would be very complex. Let’s assume that approximately 50,000 mothers would need to be enrolled in a clinical efficacy trial. I have used

this estimate because it accounts for inclusions of countries with both moderate to high disease incidence rates. And again, as I have previously mentioned, the fact that incidence in clinical trials are often lower than the published data.

The estimate does not account for changes in standard of care for the prevention of GBS in pregnant women that might occur in the future. For example, if microbiological screening for GBS and widespread use of IAP are instituted, this would dramatically increase the sample size needed in the clinical efficacy trial.

So getting back to the complexity, the complexity comes from the fact that before the end of the study, the sample size would double with the delivery of the infants. Using assumptions based on recent ongoing maternal immunization studies, a trial of this size could take more than eight years to enroll if we used approximately 100 experienced sites in moderate and high-incidence regions.

The study would take an additional two or so years to complete, assuming infant follow-up is restricted to one year. This is an unprecedented timeframe for completion of a vaccine study. It is Pfizer’s assessment that a vaccine developed along this pathway would not be available for at least 12 years from study start.

If an efficacy trial is too large or may be too lengthy to conduct, another approach to consider is the demonstration of vaccine effectiveness using an established immunologic correlate of protection. This approach has been used with vaccines to prevent disease from other encapsulated bacteria.

Correlates of protection for haemophilus influenzae B, Neisseria meningitidis and streptococcus pneumoniae were determined from natural history seroepidemiology data followed by vaccine clinical trials. In the cases of Neisseria meningitidis and strep pneumoniae, the initial data were then used to support the development of correlate of protection for subsequent sero-groups and serotypes, respectively, without the need for additional clinical disease endpoint studies.

Could such an approach be used for Group B Strep? In principle, if a correlate was established for Group B Strep based on natural history data, this correlate could be used as an endpoint in an efficacy trial. As Dr. Anderson has previously mentioned, sera epidemiological data are suggestive immunologic threshold that could confer protection. However, validation of a correlate is difficult without efficacy data.

The third option is a combined pathway that could reasonably predict efficacy using a surrogate of protection

for initial licensure, which could subsequently confirmed in a clinical disease endpoint study. As previously discussed, a clinical efficacy trial is the basis for initial licensure as represented here using the traditional approval pathway.

As you heard from Dr. Baker, establishment of a correlate of protection is an alternative approach that would eliminate the need to conduct a clinical endpoint efficacy study. However, validation of a correlate in the absence of efficacy data, as I just mentioned, is unprecedented and is expected to take a significant amount of time.

The third and likely most feasible pathway uses a surrogate of protection to assess vaccine effectiveness as the basis for initial licensure, using accelerated approval pathway which is shown here. The surrogate would be developed by taking advantage of the ongoing work on assay development and standardization, the ongoing and future work from sera epidemiologic studies, as we heard from Dr. Madhi, as well as data from preclinical models previously discussed by Dr. Anderson.

Results from pre-licensure clinical trials using a surrogate, which would use an immunologic endpoint and assess safety in a minimum of 3000 vaccinated pregnant women would be confirmed in disease endpoint studies post-

licensure. The confirmatory effectiveness study might either be a controlled clinical trial or an observational effectiveness study, which are both shown on the slide. This approach would make a GBS vaccine available to those in need sooner.

In order to support an accelerated approval pathway to licensure, there are a number of areas that require further consideration. As discussed previously, there are ongoing studies in the academic community that are attempting to define protective antibody levels using standard assays. This work will need to be completed and shared prior to development of a surrogate.

In addition, we will need to determine whether different thresholds are required for early versus late onset disease, as well as assess the need for protective thresholds for each serotype, or whether thresholds for the more prevalent serotypes would be sufficient. We anticipate that resolution of these outstanding questions could be attained in the next few years.

In summary, I think it is agreed that there is an important unmet medical need for a vaccine to prevent GBS disease in infants. We have a mechanism of action for immune protection that is well established. Despite the high burden of disease, the relatively low global incidence

rate means that a clinical disease endpoint study alone will take many years and may not be practical.

While additional approaches can be considered, more data are needed to support an immunological threshold, whether a correlate or a surrogate. Pfizer is interested in working with the FDA to develop approaches that could bring us safe and effective vaccine to licensure to meet this unmet medical need. Thank you.

DR. MCINNES: Thank you very much. Are there any clarification questions from the committee?

DR. KOTLOFF: In order to consider the third option, the combined option, I would kind of need to have a sense of what type of effectiveness study we are thinking about, what the feasibility is, what the duration of time it would take to do that, et cetera.

DR. ABSALON: Thank you for the question. That would be something that we would have to -- there are a number of different options for a post-licensure effectiveness study, for example. And so those would be discussions we would need to have in consultation with the regulators.

DR. MCINNES: Sheldon, I believe you have a question.

MR. TOUBMAN: I have a question about the feasibility of the disease endpoints study. There is a

little bit of a difference there as far as the size needed. You had just said 40 to 50,000. Dr. Madhi said 50,000. In the briefing documents from the FDA, they say a study size of 25,000 to 33,000 had been proposed based on estimated incidence of early infant GBS disease in South Africa, 2.7 per 1000 live births.

My first question is why is there this discrepancy on the size needed? The second question is that sounds like a feasible study in terms of what is commonly done. Tell me why it is not, if it is unusual. It sounds like it is something. What I have seen of other studies, those are reasonable numbers.

My third question, I apologize, is why do you say, okay, eight years? That is obviously a very long time. Then the last question related to that is are there options for reducing that period of time, so that we could get something tested and fully vetted sooner?

DR. MCINNES: I am going to start with the last question first because I think it pertains to your time estimate, right, the eight years. Do you have a comment on how you might truncate that?

DR. ABSALON: I think there were two questions around how we came up with that estimate. The first part is we looked at an ongoing maternal immunization trial. I think it was referenced earlier by others. And that trial,

while a different disease, is taking quite some time to enroll. In fact, we used a higher potential enrollment rate. We used 100 sites as a benchmark that we would need. If you assume approximately 500 pregnant women could be enrolled in a month, with 100 sites, that actually comes out to 8.3 years to enroll. Our current studies would follow infants out to a year.

If you think about when we would enroll moms, which is in the third trimester, it is about 18 months, so maybe a little less than two years. So it is going to take 9 to 10 years to complete the study. Then we would have to compile the data, file a submission, ask the regulators to review it, and thus it would take a couple more years to actually have the vaccine available if we were successful.

DR. MCINNES: Is there any comment regarding the number estimated in the briefing document versus what Dr. Madhi put on the table?

DR. SUN: I think I am going to let Dr. Everett provide the assumptions by which we came up with those numbers.

DR. EVERETT: So the numbers were drawn from the literature. And my understanding based upon the article that they were from was that the following assumptions were used. A vaccine efficacy of 75 percent, a power of 90 percent, that 75 to 85 percent of disease is caused by

vaccine serotypes. That 70 to 80 percent of subjects were eligible. I believe those calculations were based on an assumption that the lower bound of the 95 percent confidence interval of vaccine efficacy would be zero.

I presented those just to kind of show the range of possibilities that would be thinking about as far as sample sizes. As I said in my presentation, those assumptions would need to be discussed.

DR. MCINNES: So I think you probed a little bit about the doabilty, feasibility of the conduct of such. My interpretation, from what he said, was it was largely around operational issues. It is not the cases aren't there. It is just operation will be very challenging for medically-attended births. All the procedures going correctly, the diagnoses going correctly, that resources that would be required at multiple sites. That was my interpretation of what he said.

DR. MADHI: That is what -- I am on the call. You pretty much summarized what the key constraints are in terms of being able to do such a study.

DR. MCINNES: Thank you. Mike, you have a question?

DR. LEVINE: It is related to this question of feasibility. Obviously, the tension is wanting to get a vaccine for this health burden out as quickly as possible.

But also, nothing takes the place of having real efficacy data. Even one trial goes such a long way.

In relation to South Africa, you folks did the influenza immunization where you had limited time period for enrollment. You did a great job. From what you said earlier, the main constraints were in a pre-licensure trial, all the exclusion criteria, which understandably makes sense from a company's point of view.

And the other one you mentioned was having to have access to births where there is somebody who can make a clinical diagnosis and say this newborn needs a blood culture. But you have incidence data. In Soweto, you know what the incidence is where there is a clinical suspicion, and you get a blood culture. So the real constraint in your environment would be these exclusion criteria.

My question for Pfizer then is if this were some sort of post-licensure effectiveness trial that were somehow controlled, how much would that change the exclusion criteria for entry into it would be a licensed vaccine presumably given in a place like South Africa at the same time that tetanus toxoid is given? What would be your exclusions post-licensure?

DR. ABSALON: Thank you. I am not sure I can go through what our exclusion would be specifically. Certainly in an effectiveness real-world field trial, they

would be probably less stringent than what we would do in a randomized placebo-controlled trial pre-licensure. But again, these are things that we would have to discuss, develop, gain agreement. But I think the point may be that the question is I think less rigorous than a prelicensure clinical trial efficacy study because the vaccine would have been licensed.

DR. MCINNES: Thank you very much. I appreciate it. What a wonderful morning. With the permission of the committee, I would like to propose. It is about four minutes before noon. I would like to suggest that we now stop, and everybody can go and find something to eat and stretch their legs. We have just a small number who are signed up for the open public hearing portion.

I would like to please start very promptly at 12:45 pm, which will still keep us on tract. Is everybody all right with that? Fine, thank you very much. Please be at your seats 12:45.

(Luncheon recess)

AFTERNOON SESSION

Agenda Item: Open Public Hearing

DR. MCINNES: Good afternoon everybody. Welcome to the Open Public Hearing Session. Please note the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing Session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if it's known its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. We have I believe one person signed up, two people signed up. Dr. Keith

Klugman, please come to the podium. You have no more than five minutes, and the light system will be used Dr. Klugman.

DR. KLUGMAN: Thank you very much Dr. McInnes, a great pleasure to be here. I am Keith Klugman, I head up the Pneumonia Program of the Bill and Melinda Gates Foundation. I have no personal conflicts of interest at all. The Gates Foundation is embarking on a program to fund manufacturers to reduce GBS vaccines, and I'll allude to specific funding as I make my presentation.

The Gates Foundation as you all are aware is essentially a private charity with a focus on reducing the burden of mortality and morbidity of children in developing countries. And although initially the program of the foundation was focused entirely on pneumonia, recognizing that a large number of children still dying in developing countries die very early on in life.

We are now focused on trying to prevent neonatal sepsis, and it's in that context that we are interested in preventing GBS disease. The foundation has been responsible so far for funding the meta analysis, which was used to define the burden of disease presentations that were made so far, and in particular we are intrigued by the role of GBS in still births. This is a large burden of mortality,

equal in fact to all neonatal mortality, which has not been addressed to date by vaccines.

Secondly then, we have looked very carefully at the possibility of conducting large clinical trials in high burden areas, and have come to the same conclusion that was presented this morning. So that is that even though in a country like South Africa, and I would say in parentheses that the research program led very adequately today by Dr. Madhi was started by myself many years ago. And in that setting unfortunately a burden of disease of around 2.7 per thousand is not in fact the burden of disease likely to be achieved in a clinical trial.

In fact the data presented by Dr. Madhi on 35,000 children who were prospectively collected in the last year, they were only able to prospectively take specimens from 35 children. So that was a rate of one per thousand, which would translate into a trial size of around 100,000. In the light thereof, we have been very interested in the possibility of a correlate of protection, and in that regard we are funding the assay, which was mentioned by a few people, to try and come up with a standardized assay.

Thirdly then, aside from the burden of disease and the assay, we are also supporting the opportunity to expand the correlate of protection by prospectively helping to recruit additional patients into that study in southern

Africa. What I would like to say finally is that we envisage countries not being persuaded by a correlate alone to actually introduce vaccine into developing countries.

So we very much see the path forward that if the FDA were prepared to give an accelerated license to a manufacturing, that the way forward would in fact be for randomized trials post licensure to be performed in developing countries using the vaccine as a probe, and we would envisage, I can't promise this, but we would certainly look at supporting a number of such studies, both in Africa and in Asia.

Asia is an enigma for GBS, like pneumococcus and Hib before there's been very little evidence of burden of invasive disease, but having a probe of a vaccine I think would be highly likely to show whether or not there is a burden of disease.

So effectively I just want to say that in summary that the Gates Foundation believes that GBS is a major cause of neonatal sepsis that is potentially preventable and that an accelerated pathway to vaccine licensure could allow subsequently post-licensure probe studies to be supported in a number of developing countries.

DR. MCINNES: Thank you very much Dr. Klugman. Are there any questions from the committee for clarification from Dr. Klugman?

DR. KLUGMAN: Perhaps I should add, because I don't think I did specifically mention, that we are then funding both Pfizer in their pre-clinical work, and we are funding a South African manufacturer Biovac to make a tetanus based conjugate. And we have funded MinervaX who are trying to make a protein vaccine, at least in some of their correlate work. And we are also in discussion with other potential biotechs looking at alternative approaches to this vaccine.

DR. MCINNES: Thank you very much. Are there other members of the public who would wish to make a statement? Can you please stand and go to the podium? Welcome.

DR. MEHRING-LE DOARE: My name is Cathy Mehring-Le Doare, I'm a clinical senior lecturer at Imperial College London, and I'm leading the serological assay, standardization consortium that you've heard about at this morning. I just wanted to talk to the panel very briefly about the UK perspective.

Professor Paul Heath, who is online, and I are working on several studies at the moment to try to answer some of the questions surrounding serocorrelates of protection. Because if you've heard from Dr. Schrag the UK has a particular concern with an increasing burden of early onset and late onset disease.

We have two studies currently ongoing, looking at serocorrelates of protection based on the serosurveillance undertaken countrywide in 2014, where we have 800 cases of early and late onset disease, and we are retrieving the newborn blood spot cards of those cases and comparing them to Guthrie cards collected at 2014 and also to a prospective cohort of healthy controls, to try and establish whether Guthrie cards would be a useful method of measuring antibody against group B streptococcal disease.

The second study we have that has recently been funded by the NIHR is a feasibility study looking at collecting maternal and cord serum from initially a cohort of 5000 women who would be randomized to either culture based screening or current standard of care in the UK, which is risk factor based screening to assess natural antibody in the context of GBS colonization.

If this feasibility study, which is due to start recruitment in June of this year and report its results in December as successful, this will then be embedded in a UK countrywide study of approximately 600,000 UK women where we will be able to collect in a proportion of those women maternal and cord samples in a cluster randomized control trial of universal versus swap based screening to assess antibody in colonization and disease. This is just a quick summary of the UK’s efforts.

DR. MCINNES: Thank you very much. I wonder if it would be possible for you to summarize such a large undertaking by the assay standardization effort. Can you just give us some of the guiding principles?

DR. MEHRING-LE DOARE: Certainly. So, we are a consortium comprised of Pfizer, GSK, MinervaX, academic partners in South Africa, Professor Madhi's group, and then within the UK who have previously worked on pneumococcal serocorrelates, such as David Goldblatt the idea being to develop standard reagents in terms of capsular polysaccharide for use in their ligand binding assays, and reference serum for use in both the ligand binding assays and opsonophagocytosis killing assays, using standard protocols which we will all then be able to adopt, or we will all be able to use the standard reagents to bridge between different studies to try and standardize the output of any future serocorrelate studies.

DR. MCINNES: Any questions on the committee on the standardization effort? Karen?

DR. KOTLOFF: I am struggling a little bit with how colonization might be used as correlative, if that were being considered. I think the comment that Shabir made that antibody will prevent acquisition of new colonization, but will not eradicate existing colonization. So when you're looking to correlate antibody levels with colonization, do

you have the ability to distinguish those events and see if there's a differential effect?

DR. MEHRING-LE DOARE: I think the studies would be slightly different because we're not using those studies to assess antibody and positive or negative colonization, but because colonization demonstrates exposure to GBS we will then have a population who have been exposed to GBS and who we can measure their antibody concentrations when the babies are healthy, compared to babies exposed who then go on to have disease.

DR. MCINNES: Thank you very much. I have a sense that you did actually sign up to speak, and somehow we lost you. And so we're very pleased we found you again. So thank you very much for your contribution. Is there anybody else who wishes to make comment from the public? I don't see any more hands raised, so we should close the open public hearing. 1:00 PM, we're good.

So I think the agenda now suggests that it's time for us to move into the discussion, the committee discussion period. And I have very good instructions here to ask all members to contribute. Before we lead off, I would like to have the questions put back up please, that would be helpful to keep us focused.

I also want to encourage people that these are the questions that are being put to us, not other

questions. And we are not here to tell the FDA what regulatory path they should follow, that is not what we're being asked to do here. So we should stick to these and take each of the topics, and we can certainly discuss guiding principles, conceptual issues, but it's not our job to design the regulatory pathway for the FDA. Arnold, please take us away.

Agenda Item: Committee Discussion

DR. MONTO: I just want to jump in because the word effectiveness is being used here. And I think correctly we heard from Keith Klugman that randomized trials, even though I am a proponent of observational studies, and that's mostly what we're doing right now, still they do not have the persuasive value, especially when correlates are still up in the air a little bit, of using a randomized design.

And I would hope that we could consider effectiveness and efficacy studies in terms of the mixed design that we heard, accelerated approval and then some kind of a clinical approach thereafter. I would also hope that we could consider as we discuss this the effect of following colonization, and the ethical issues about whether such colonization would need to be treated or not, and its effect on the trial.

DR. MCINNES: Arnold, I think where you are going with this, many debates we've had of efficacy versus effectiveness, trials and trial design, my sense is that the word effectiveness is being used in a kind of catch-all way, and I will ask Marion for confirmation of them.

DR. GRUBER: That is correct, Pam. So regarding question one, we use the term effectiveness deliberately, and not efficacy. And because, well we randomized pre-licensure clinical studies with clinical disease endpoint. That's usually what we mean or have in mind when FDA talks about demonstrating vaccine efficacy.

But here we have put additional considerations on the table, we were also talking about composite endpoints, we're looking at immunologic endpoints, colonization. So this is why we're using the term effectiveness versus efficacy.

But we realize that this is sort of like an FDA dictionary if you want, and there are other regions and other entities that even define these terms differently. I don't think we need to be getting hung up on these terms. I think our point, one was really do you discuss the strengths and limitations of doing studies with a clinical disease endpoint. And then B, immunological endpoints, and C, colonization. And I think the terms to be used here, efficacy versus effectiveness is secondary to this.

DR. MONTO: I think that is very helpful. The problem of course is that certain terms in certain disciplines convey certain characteristics. I think often what we do now is use the term VE so that we don't have to say efficacy or effectiveness, to try to get around this problem in terminology. But often it's efficacy/effectiveness. As long as we've noted this, we're moving in the right direction.

DR. MCINNES: So if we go to question one to guide us through here, there is sort of a presupposition about that laboratory confirmed early or late onset disease is accepted, and then what else can be added to that. I think the acknowledgment of the feasibility challenges of studies that utilize those, while these are somewhat purist and not subject to much debate, this is potentially a challenge.

But moving on, what additional clinical disease endpoints, unconfirmed and confirmed fetal or infant endpoints as well as maternal endpoints can be considered to demonstrate vaccine effectiveness. So aspects that were raised during the discussion included group B strep related still births. Maternal disease was brought up as a possibility. Pre-term birth with maternal group B strep bacteria. And then neonatal encephalopathy.

And I wonder if it might be helpful for us, and there may be others that people would like to add. But it

might be helpful for us to pick them and walk through them, with the guiding principle discussion in mind. So if we took group B strep related still birth as an additional endpoint, could we start with that as a discussion?

DR. HEINE: I think that is a very difficult endpoint to use for a study such as this. One, we could really get into how do you determine if that's a group B strep still birth. If you're going to say okay well I'm going to go in to do an autopsy and get an organ that otherwise should be sterile, I would argue that if you have a still birth and you induce her for 36 hours and she has high colony counts group B strep, that may be just a product of the labor and not a mechanism of the still birth at all.

There are many arguments around trying to, do I think group B strep causes still birth, yes I do, but I think it's a very difficult thing to ascertain, and I think doing a study where these studies would be done, I think it would be near impossible to identify and really document group B strep still-birth.

DR. KOTLOFF: So, there is a procedure that's ongoing in South Africa and other countries called MITS, the Minimally Invasive Tissue Sampling, I just wanted to put that on the table, where with permission postmortem infants are sampled with needle biopsies in multiple organs

and blood. That being said, I think it's subject to contamination effects.

DR. HEINE: I will give you an example. Somebody ruptured membranes and had a prolapsed cord for five days, and then you induce, and okay, you get group B strep out of whatever organ you minimally invade, and well she prolapsed, so labor puts so much into it, and the issue of group B strep transmission at the time of just a prolonged labor could account for that.

DR. GREENBERG: And further to the discussion about still births, as pointed out it would be difficult to identify those that are truly group B strep, and then I think if you look at it from the other aspect of unconfirmed, then I think it's a challenge because of the relatively few that are truly caused by group B strep, that it's not as if you would expect even in a fairly large trial to see a reduction in overall unconfirmed still births. So both confirmed and unconfirmed I think would be --

DR. MCINNES: Is problematic for you. Dr. Bok?

DR. BOK: I just have a clarifying question because I don't remember hearing it. Is this intended to be administered for pertussis, third trimester, 30-something week?

DR. MCINNES: Could you repeat the question please?

DR. BOK: Is this vaccine going to be administered like for pertussis, in the third trimester, late weeks for active transfer? I just want to clarify when do those --

DR. MCINNES: I did not hear anything other than third trimester. So you could be early third trimester, and I think Dr. Baker brought that up. So Dr. Baker is clarifying that 27 weeks begins when the pertussis can be administered.

DR. BOK: But this vaccine would be administered there too, at that range?

DR. MCINNES: I did not hear a particular number, but every context was presented in the same vein. Is that a correct statement? Are there any comments here or thoughts about confirmed or unconfirmed still birth? Dr. Madhi is on the phone and would like to talk about this. Welcome back.

DR. MADHI: I just want to make a point on, like I mentioned there are variabilities between the dozen studies that have been delegated the role of GBS in still birth, and I do agree with the comment that we’re not looking at all cause still birth, because that would be too nonspecific as an outcome. So what we’re looking at is GBS associated stillbirths. So Karen mentioned that the program that’s currently under way is minimally invasive tissue

sampling, and a great extent that actually mitigates against the unacceptability of doing autopsies and what it really involves is taking immediate post-delivery sampling of the blood, or it could also be of the lungs.

So the cases we've been describing from South Africa as an example, all of the still births are investigated almost within a few hours of delivery. And in general, in South Africa at least, the timing in terms of the still birth is completely -- the timing of the diagnosis of the still birth in relation to delivery is usually less than 24 hours as well.

So what I'm saying is that these cases are being diagnosed based on blood culture positivity and not any other organ system, which certainly could be subject to contamination. I think blood culture contamination for GBS, provided that you are purely diligent in terms of ensuring sterility when doing the sampling, is probably less likely to be the cause of contamination, and probably purely indicative of invasive disease.

And as I mentioned, for me I think the turning point in terms of association of GBS still births is really what we see with early onset disease in South Africa, where 90 percent of our diagnosed cases, if not more, actually diagnose based on a blood sample that's taken at the time of birth.

And what it really tells us is there is a spectrum of invasive fetal disease from GBS, some of the children end born with invasive disease, unfortunately others actually demise before they're born. But in terms of the pathogenesis for both cases the early onset disease, the majority of the early onset disease is related to still births, and infections actually occurring in utero, probably during labor rather than during passage of the baby.

DR. MCINNES: Are there any comments to that?

DR. HEINE: Although again I agree that group B strep is a cause, I think you just hit the nail on the head, that labor is what produced it. So if you have a still birth who then goes through labor, was it the still birth or was it the labor? If I really wanted to prove it, what I could do is if you had a still birth before you did an induction you do an invasive procedure of whatever tissue you wanted to get. But I imagine as part of a trial you wouldn't want to do invasive procedures to try to get sample, because that would be very difficult to do. So controlling for the effects of labor is the real problem.

DR. MCINNES: So, this would fall under the limitations of that particular end point is what you are bringing up. And I think obviously for people who do want to propose it as a particular clinical additive endpoint,

understanding exactly what was going to be done when it was going to be done would be critical to whether you could move it from a limitation up into the strengths. Did I say that correctly for you? Are there any other conversations or comments, questions people would like to raise about still birth as an additional clinical disease endpoint?

DR. SCHRAG: I guess I would just add that maybe one thing I agree with is I think laboratory confirmed early and late onset disease are probably the only things everyone in the room just 100 percent feels comfortable with, so we're venturing into the territory of accepting somewhat less specificity.

But the stillbirth endpoint I feel a bit more comfortable with than some of the others we may discuss, so I just want to put that out there. And while there may be some that get a false positive result, I think we're not seeing from the studies that have come out of South Africa and Kenya, the two that I'm the most familiar with.

We're not seeing certainly nearly the rates of positive results that would suggest it's just maternal colonization that you're picking up, because you would expect to find it much more frequently, and we're seeing these rates that are somewhat similar to the invasive early onset disease rates, which make some sense. And so there may be some mis-classification going on there, but I don't

see it from the data. The degree of concern is what we're hearing right now, and I just wanted to add that as context.

DR. MCINNES: Any other comment on this?

DR. HEINE: Just to add back, the colonization of skin, stomach, when we look at colonization we're invading deep spaces, so that may take a little while longer during the labor process for you to see deep space involvement. So again I just think the labor process, you just have to be concerned what contribution that made.

DR. LEVINE: I have been sitting here grappling for a couple of hours now with the burden numbers, and we've heard somewhere between one to four live births would have culture confirmed clinical GBS disease, and right now a number of countries in the past few months have just been affirmed or validated by WHO as having reached the definition of neonatal tetanus elimination, which to me means control, which brings down the incidence to below one per thousand.

In other words, the goal of that program, which is the grandmother of what we want to latch onto that's working so well in the developing world, is where this disease is starting. So that's one thing that's -- This is only essentially the first week of life, the early disease.

So if you multiple that by 52, you're actually up to a credible pattern that would be similar to certain other capsular invasive diseases that occur throughout infancy. It's a narrow window that makes that number seem small, but in fact I think it's very high. But for neonatal tetanus there's also the problem of non-specificity. There's no culture, there's no definitive microbiological assay to say this fatal case with seizures and with spasms was really neonatal tetanus.

So I just bring that out, and yes there appears to be success even in validation using the combination of seroprevalence and population of women of child bearing age, various other measures of immunization coverage and he endpoints, the clinical reports of that disease. So I don't think that lack of specificity is a huge problem if you consider this a study looking at prevention of that broad, broad syndrome, which may be important, but it doesn't make me personally happy, I'd like something a little bit tighter.

DR. MCINNES: Any other comments at this point, questions? All right, so the still birth piece I think we've talked about, we've laid out the possible strengths of using it, and then limitations that would have to be expressed technique-wise, criteria-wise, very carefully in order to be assed for its liability. So another one that

has been raised is pre-term birth, and in some contexts it was added to maternal GBS bacteria. So are there any comments about preterm birth being used as an additional clinical disease endpoint?

DR. HEINE: Because they're multifactorial. I don't mind using it, but they're going to have to rethink about when they give the vaccine if you're going to try to reduce preterm birth. Because yes, preterm birth happens in the third trimester more commonly, but the ones you really worry about are the ones that happen between 23 and 28 weeks, and if you're going to give it at 28 weeks you overlook that whole group.

So likely you'll want to give your vaccine probably even in the first trimester. What I need to know is how long the response is sustained and the maternal response, because you want transmission cross in the third trimester that's high, but if I'm really going to make a prematurity impact I'm going to have to give it earlier if we think that's an etiology.

DR. LEVINE: I think that make sense in the first world. In this big randomized trial we did of maternal immunization of flu vaccine versus Menactra, in West Africa a woman does not seek antenatal care until deep into the second trimester. This is cultural. And although it's very strong in Mali, we have heard this is true in many other

sub-Saharan African countries or regions, including in East Africa. And so that would be very difficult.

And the other thing is relating to prematurity, birth weight may be a better measure in terms of cutoffs, because again in an effectiveness trial in certain parts of the world, very difficult to put an age on the infant at time of birth. Infants just in birth weight are much lighter even at full term birth.

DR. MCINNES: Anybody else wish to comment on pre-term birth?

DR. HEINE: It would be a secondary outcome of mine, and I would hope that I would see a signal if I gave it at 28 weeks, that saw a signal that I had a reduction in less than 37 weeks, and then I'd take it to first world, because I agree that it's just not something that I'd use as my primary outcome.

DR. MCINNES: What about maternal disease? That was discussed. What are people's thoughts about that?

DR. HEINE: So, Group B strep is a leading etiologic agent of most maternal infections that, I'm not relating this to the newborn, but Chorioamnionitis and amniotic infection, whatever name you give it, up to a third have group B strep that grow out. Then you're going to go on to endometritis which is post-delivery wound infections, pyelonephritis.

And one of the things that we all in the infection world and OB have noticed since we've done group B strep interpartum prophylaxis, we have seen decreased rates of endometritis and chorio in labor. And I think that is definitely an outcome, that grouping of maternal infections. Now what I included in my primary, the Holy Grail here is the decreased neonatal sepsis, but I certainly would look at the grouping of labor related infections in the mother.

DR. EL SAHLY: I would second that, I mean it can be more easily ascertained with relatively acceptable invasive means.

DR. GREENBERG: I think it is an important area to focus on, it might be the secondary outcomes, but it's important I think to study because both of the burden of disease, and for the mothers. And because obviously there's got to be attention to that because of the design of studies, because it's of the mother and not the infant. But I would strongly support evaluating that.

DR. EL SAHLY: Would it be secondary or part of the composite? Statistically does it make a difference in the sample size?

DR. JANES: A comment along those lines, that I think in order for it to have value in terms of decreasing the size of the study, you would want to consider it in

conjunction with the infant endpoints, and doing so would thus require one to wrestle with the relative importance of the events that occur to the mother and infant, which is obviously a difficult issue to wrestle with.

DR. HEINE: Although not common, it's certainly more common than neonatal sepsis. So if I had a three to five percent chorio in labor rate, and so you have a third of that, I would need far fewer patients to show benefit, and I would worry that you would stop at just showing benefit in there, and does it weigh enough to immunize every pregnant woman across the world, when I could treat the chorio with antibiotic. I think that's what you're getting at. I'd probably do it as a secondary, not as part of the primary.

DR. KOTLOFF: This point may be obvious to everyone, but I just want to mention it. And that is if this is a randomized trial, then even these nonspecific effects may come out just because of the randomization. But I think with the still births there is some caution even with that, because it's possible that if you just have decreased maternal colonization, it could look like you have less GBS associated still births, when in fact you may just be measuring decreased maternal colonization. So I think that's another concern there, because you have a still birth, the group B strep gets into the organs as the

child goes through labor as having died, and it could still be contamination.

DR. SCHRAG: I guess I understand the point you're saying, but I think if really there were a decrease in colonization that could also be a real mechanism for decreasing GBS associated still births, which really has the same pathophysiology as early onset disease, and we know that reducing colonization reduces early onset disease. So we're stuck with that, and I don't know that I would use that as a reason to say that still birth results would be suspect, particularly if it's concomitant with really a reduction in the exposure.

DR. SHANE: So I think one other comment that might be helpful, and I'm not sure how to operationalize this, but I do think it would be important to know both fetal or infant and maternal outcomes together, meaning keeping those paired, because if you look at just the mother or just the infant, you may not really get a true understanding of the association. So therefore as best as we can keeping maternal and infant outcomes group together.

DR. MCINNES: Any more comments on this? We can loop back again if something comes up.

DR. GILBERT: Just a thought, kind of what we refer to as the easily acceptable endpoints, the invasive disease, early and late in the infants, assuming those are

only valuable in the live births, there's an issue with how does the analysis account for the still births.

Because if one is comparing disease rates between vaccine recipients that are live birth and placebo recipients that are live birth, that's not a randomized comparison. There could be post-randomization selection bias if the vaccine had an effect on still birth. So it's just a comment that we can't totally consider the EOD and LOD in isolation from the death of the infant.

DR. MCINNES: So I am going to put the fourth one on my list on the table for discussion, and that was the neonatal encephalopathy. Which nobody really talked about, except got mentioned a few times. Are there any comments about that as a contributing clinical disease endpoint?

DR. HEINE: I would expand that. What was exciting to me was the South African experience with suspected neonatal sepsis, expanding the diagnostic, using PCR. I would love to see that. Because that raised your overall rate, almost doubled it, and if you're able to use that technology. Because notice how suspected by strict criteria was so much higher than GBS proven sepsis.

So if you could expand your positivity rate, that does make a randomized trial, whether still feasible or not, may make it more doable. So instead of encephalitis, I

think expanding your diagnosis of suspected neonatal sepsis and coming up with a clinical criteria for that.

DR. MCINNES: Dr. Greenberg?

DR. GREENBERG: I agree completely. One of the concept I think to keep in mind is that whether it be encephalopathy or all neonatal sepsis, which they both have the limitation of specificity, but I think what many of us are recognizing more and more often is that a disease can be uncovered through these vaccine trials, and that if the mothers in this case are randomized that one can be surprised by these secondary outcomes, they seem to be reduced at a greater proportion than one would expect just from the laboratory confirmation.

And that doesn’t mean that it’s wrong, in fact it can mean that you’re uncovering disease that is underlying that you would not have found if you hadn’t been doing a clinical endpoint clinical trial.

DR. MONTO: I agree. I think we need to keep a separation between all neonatal sepsis and using new techniques or techniques that haven’t been used in the past such as PCR, which to me confirm that you’re dealing with GBS. Because the other question will be whether you want to use all neonatal sepsis as an outcome.

And the other thing is that we’re being asked to discuss this in the context of endpoints for a clinical

trial, and I think you discover all sorts of things during a clinical trial, especially in an area that you really haven't got as much natural history incidence data as you would like, but they are not outcomes in the clinical trials, and I think we need carefully to distinguish these, because some of the endpoints such as still births may turn out to be an interest, but to my mind shouldn't be used as an outcome.

DR. SCHRAG: Just to kind of second that, about the dangers of picking some of these. And I am a little unclear from some of the discussion, my read of that first question is looking for something to add to early and late onset, to have more power. Which means that it's all going to be a part of the primary endpoint.

And I would express definite concern around things like clinical sepsis being in that category, because I think Shabir showed, and I know from the work I've done in South Asia as well, this is an extremely common, high incidence entity.

In South Asia it was like 80 or 90 per 1000 live births, and we've seen what the incidence of group B strep is. And even with pneumococcal conjugate vaccines using a less specific definition like pneumonia made it very difficult in some trials to be able to find the kind of

vaccine advocacy that was really important to know for invasive disease.

So while I think they are important, I would make a big distinction and say it's dangerous to start to lump these things in with a primary endpoint, and I think there could be consideration potentially of PCR positive from a sterile site, but we have to remember what Shabir showed that we also can get that positivity in a healthy baby. And so somehow that needs to be noted and would need to be taken into account, that we are introducing some lack of specificity there.

DR. MCINNES: Are there any other clinical disease endpoints that people would like to put on the table for discussion, either a secondary endpoint or additive endpoints, which is now a new term for talking about this afternoon in the context of GBS? Mike?

DR. LEVINE: I was just going to ask if everybody is speaking about the same specific definition when we talk about neonatal sepsis. Do we mean physiological sepsis, as in intensivist would define it in an older kid or adult, versus just bacteremia? One of the syndromes that was mentioned in ABC was bacteremia, no focus.

To me a syndrome is really a clinical picture, and it wasn't clear to me if this means -- it wasn't clear what the drivers were to collect the blood culture. A

question arises if one just did a couple hundred blood cultures on newborns within the first day or two, what percentage would have a positive blood culture. When we are talking about sepsis, does this mean objective evidence of physiologic derangement, or is this a purely grab basket clinical term like it was four decades ago?

DR. MCINNESS: Carol, I wonder if we might call on you for your response to this question?

DR. BAKER: I don’t think there are enough mothers and fathers in this room. Most of you have had children, and most of your children when they were born were healthy. We don’t draw blood cultures from healthy people. Remember that. Bacteremia without a focus in a neonate means from ABC surveillance, bless them, that there’s a good reason to collect a blood culture. And in the fact majority the clinical syndrome is like sepsis, adult people would say septicemia, according to clinical criteria, without a focus.

So they may have a lung focus, they may have meningitis if they look, but some babies with mother has bad Chorioamnionitis. Maybe term and look healthy, but because it’s such a risk factor for the baby who’s term to develop sepsis in the first 24-48 hours, a blood culture is done.

So I think the terminology is confusing. Bacteremia means that GBS and a neonatal pathogen is collected from the blood stream. Most of those babies have clinical sepsis. Does that help at all? The other thing about efficacy is this is one vaccine, maybe one dose given to the mother to prevent disease in two people, three if you count the fetus different than the newborn.

DR. LEVINE: Carol, it is my understanding that intensivists across the world have gotten together and have defined sepsis.

DR. BAKER: Not for newborns.

DR. LEVINE: That’s my question. So this is not, when we see neonatal sepsis we’re talking about a purely clinical baby, it’s like 50 years ago being in a newborn nursery, it’s not with the modern criteria.

DR. BAKER: Modern criteria, using all the modern things you would use for adults, and even older children, have not been consensuses for the neonate. I think we’ll be moving in that direction. But it’s different than the adult situation. And the same with the mother. I mean I agree, using maternal disease even though we can’t detect bloodstream infection very often, it makes sense if you’re immunizing a person to prevent disease in her offspring to look at disease in the mother however defined as well as in the infant.

And I just want to say we need to see published more of the stillborn data. Because you know how I as a house officer discovered that prematures didn't have Hyaline membrane disease in the 1960s or early 1970s, because we didn't work them up, we thought they all had Hyaline membrane disease. When they did I did an immediate heart puncture, and pure group B strep grew from a substantial portion.

Now of course we evaluate these preterm with any breathing. But the sepsis is very nonspecific, and we evaluate probably I would say at least eight to ten babies for every baby that will actually have a positive blood culture. So you can't tell because it's so nonspecific. With clinical criteria, whatever sepsis is, we could consider it, but right now if you say sepsis it's like I like blue, you like green, they're very close colors, it's very nonspecific now, so you're going to have a lot of noise.

DR. MCINNES: Dr. Greenberg?

DR. GREENBERG: Just to clarify my point, I was thinking of the physiologic. So if a study was designed with criteria for definition of clinical sepsis in a newborn, that's the scenario I was thinking of when I said if there is a reduction of those clinically ill infants that then go on to a blood culture, and even if the blood

culture is negative, if there was a reduction of those cases that would show benefit of the vaccine in a randomized study, and I did not mean to have that in the primary analysis, I meant that to be secondary or exploratory, because it shouldn't detract from the primary analysis of laboratory confirmed.

And then as Dr. Baker has raised, that classification of infants whose mother has Chorioamnionitis, and then the child looks healthy, it doesn't matter, he's brought into some sort of a staffed up area or ICU, and has a blood culture drawn before the antibiotics are started, but never gets clinically ill? That's a separate kettle of fish. I think there are multiple categories of disease here. So it is different.

DR. MCINNES: Let me ask the FDA whether we have covered adequately for you this first question, or whether you have any follow-up that perhaps we could reflect on.

DR. GRUBER: We appreciate the discussion. We know this is very difficult. We've had a lot of internal debates over this, and I think some of this, we feel a little bit reassured and we heard other interesting comments and comments made here. So thank you for that.

DR. MCINNES: That doesn't mean we can't talk about it if somebody gets an idea a little bit later on,

but I just would like to get this moved along here. Now, we will move to immunological endpoints.

The impression is functional and ligand binding antibody levels. Could they be used to demonstrate vaccine effectiveness? If so, please discuss their strengths and limitations. So now we move on to the correlates, the serological correlates, the concept that we understand the mechanism of protection, we know how to measure it, we just don't all measure it the same way.

The challenges that are always vested in this. For those of you who didn't live the hemophilus, the meningococcus, the pneumococcus wars, this was a fundamental underpinning of every one of those activities, and it went on for a long time, and there were wonderful friendships that formed, and there were wonderful friendships that were ruptured.

This is just the way it is until we all agree on how we're going to do things and what reagents are going to be used, and how we're going to interpret things. So it's not new to this field at all. A lot of progress has been done, and I was personally delighted to hear about the standardization effort, as you can't get anywhere without such an undertaking. And it is not for the faint of heart, and don't expect a medal, because there has not yet been one forthcoming for previous activities.

So let’s move to the question, could they be used to demonstrate effectiveness? And then it’s a look at both the role of the functional assay as well as what really is a higher throughput workhorse assay for binding. Who would like to talk about this? Does anybody have any feelings about this?

DR. EL SAHLY: I would like to begin by saying that while the data point to the higher the better, generally speaking, the cutoffs from the data in South Africa versus the data in the US versus the data in Italy I think was the third study, are not uniform, and some of it has to do with the assay, either the reagents or the methods or both.

And we just heard very encouraging news that large studies are underway looking at standardization of these assays and correlating them in mother-infant pairs looking at specific disease endpoints as I understand it. So until we have those data showing a reasonable cutoff, and that can be used in different populations, and that has been correlated to a particular endpoint of interest, it’s hard to say beyond the general feeling, yes higher is better, but we just don’t know what to ask from the vaccine manufacturer to demonstrate.

DR. MCINNES: Preliminary vote of confidence ideally in the idea of this. Would anybody like to add to this?

DR. SPEARMAN: I would like to give you my impression from the morning's discussion that this is really a great way to go, but we need a lot more data, basically adding to what Hana has said. That to understand the level of which assay is really going to be associated with protection, it didn't sound like we're really there, but it's very promising, and I think that's where a lot of effort needs to be.

DR. EL SAHLY: I think one of the commentators from the collaboration mentioned that as early as December of this year we'll start having some of these data, did I get that right?

DR. MCINNES: I heard not for another year or so from the large study.

DR. LEVINE: I'll summarize what I think I heard today in my comments on that number two. If one had a correlate of protection, a particular antibody assay or assays, one could if one had confidence of course use that to draw conclusions about how this vaccine would work. So to have an immunologic correlate of protection you need protection.

What I heard today was epidemiologic studies, and Carol's, one of her many beautiful studies where she immunized and showed an impact on colonization, which is a biological activity due to the vaccine. in the case control, what one saw from several different sources was that kids or mothers of kids who developed early onset GBS disease had significantly lower titers of antibody, anti-capsular antibody than matched kids who didn't develop disease.

The only question or problem with that is there you're using an antibody as a marker, taking the mother who somehow saw the whole bug, you're picking out one particular antibody against a capsule, and it's possible that there was transfer of other antibodies that could play a role. I think that that can be tweezed out easily.

Pamela mentioned Hib, you go way back to Fothergill and Wright and you have overlapping inverse curves, there is bactericidal activity in the first couple of months of life, it disappears in the infancy when kids have the highest incidence of Hib, and then it builds up again. And later one showed that most of that antibody was anti-PRP, anti-capsule, but you could absorb that with purified PRP. You put all that together and you're on your way.

And first generation vaccine, that was a vaccine, non-conjugated PRP that actually gave us the cutoffs we still use today, one microgram per mil for long-term protection of anti-capsular, and 0.15 at a particular point in time, I haven't heard that total package today, but I've heard enough encouraging that this is a way to go, and going back to other vaccines, conjugate vaccines, one should be able to do similar studies to tweeze this out.

And the analogy then to Carol's protection against colonization would be Ron Dagan's studies with pneumococcus where there were multiple studies showing that if you can prevent acquisition that those vaccines went on to be very powerful protective vaccine.

DR. MONTO: To go a little further, from Mike's comments, the issue to me is also the question of types, because we're heard data almost exclusively for 1A and three. There seem to be some differences. So we really need broadening of information. We also need to remember that we need more antibody for late onset than we do for early onset, because of the timeframe. And we've got to be able to prevent both. That would certainly be the ideal. So we need to be able to look at the half-life as well when we make these decisions.

DR. MCINNES: So just to expand a little bit, I think what you're saying may be different for different

serotypes. The question always comes up about isotype and subclass, but in fact we were just thinking about that in the context of Hib, all the work that was done on avidity and all that now, it was IGG, and it was a very good measure of protection. It was not necessarily the only mechanism of protection, and I think this comes again, it may not be the only mechanism of protection, but it surely is apparently a very important mechanism of protection. So I think those - trying to understand avidity and understanding the role of - all of that I think is terribly important, but I'm not sure that it's a deal breaker, in fact I know it's not a deal breaker in terms of thinking about an immunologic endpoint for group B strep. And clearly your point is well taken.

I think we should also remember from those old lessons that that one microgram per milliliter, if we go back to that one-page paper from the Helenas in Finland was actually never intended on an individual basis, it didn't predict on an individual basis. You would get breakthrough disease in some children at that level. As a community, as a herd, as a group, it worked, and the efficacy data showed that, and in fact on an individual basis for some you could go much lower than that, and that's where the 0.15 came from.

So I think we don’t want to fall into that same trap again with group B strep. I think it may be as a group the mean that you need, and you need to have your confidence intervals around that, but I think it’s not intended on an individual basis. You will always have children who have some immunologic mechanism where one milliliter is not going to be enough for them.

DR. LEVINE: There are some other data that came from John Robins and Rachel Schneerson who followed individuals, this goes way back, individuals with Bruton's hypogammaglobulinemia who had to have exogenous immunoglobulin to stay alive, and they thoughtfully looked at the point at which empirically and clinically it had been found you had to give the immunoglobulin, and they looked at antibody levels there, and their cutoff of what was protective was as I recall 0.06, which one can argue is not 0.15. But it’s only half of it, it’s in the same ballpark.

I think if we could get to a situation where we are with Hib and weren’t with Hib, with a cutoff of if you have 0.15 you’re protected today. If you have one microgram per mil you’re protected through young childhood. I think that’s a great place to be if we could get that far. It would be a bit further than we are now, but that would be good.

DR. GREENBERG: I am challenged by this question. If there's a surrogate, which I probably think is more the case here, where there's an antibody level of that's the one thing that you're measuring, is anti-capsular antibody. There might be other factors, but if it's a surrogate for protection I think that's adequate. But it is true that then it has to be correlated to protection.

And traditionally that's done in large studies like with Hib and others where it's not so hard to study 20,000-30,000 children, or people. But as we heard today that's going to be a huge challenge for this vaccine for maternal immunization. So if we're going to progress the science and have vaccine that would be available to protect mothers and children, we probably have to meet somewhere in the middle.

So if the estimates are correct that it's an eight year study, I don't think any of us want to wait 10 to 12 years for that to be conducted, filed, and approved. But that's really going to be the ultimate of knowing whether or not a surrogate is truly indicative of that protection. So there can be and there have been studies in the animal model that provide some important information, and then here's the epidemiologic natural history data that are being collected now in the UK.

Those are critical, and I think they inform how the randomized clinical trial would be conducted. Whether that's pre-licensure or post-licensure, that's the FDA's purview. But I think if it's going to be perhaps post-licensure, then one has to be confident enough of all of the data, animal and epidemiologic data to at least have an estimate and have a vaccine that induces antibody that is either at or well above that, and then one can proceed.

And not only there are going to be differences in serotype, but then of course there are going to be differences in what the surrogate level is, or correlate for all the different things we've been talking about this afternoon. True, clinical, neonatal sepsis from GBS versus colonization of the mother or the infant, versus some of the other endpoints that we've discussed. It could be different for each of those. But if the primary is to reduce sepsis, and it is, then hopefully at least focus in that area.

DR. MCINNES: Thank you David. Dr. Kotloff?

DR. KOTLOFF: I agree very much with the discussion that using observational studies to try to understand correlates of protection is very powerful. But I think there are some examples where that correlate doesn't necessarily correlate with protective efficacy from a vaccine. And so I think a lot of us are giving our opinions

about acceptable endpoints with the requirement that there would be a clinical trial.

And if we're talking about a post-licensure clinical trial, and I've heard a randomized clinical trial mentioned a couple times, where I keep getting stumped is what would be done that would allow that to be feasible when a pre-licensure trial is not feasible. And so I think that we're making these recommendations assuming that something would be developed that's feasible, but none of that has been put on the table yet.

DR. MCINNES: So the one area that was the feasibility of the trial, following a licensure status of some description appeared to be easier in terms of inclusion and exclusion criteria, acceptability in the population and the authorities. Is Shabir still on the phone? Shabir, I think it was you who brought this up.

DR. MADHI: Exactly as you mentioned, I think it's really a loosening of the criteria for inclusion in the study. In this study, we are wanting licensure for efficacy trials. I think what is going to happen and what is very much sort of in a sense constrained involvement into vaccine trials which is currently involved in pregnant women is the inclusion/exclusion criteria, including things such as the timing of vaccine and the staging of gestational age, which you don't get confirmation

experiment in middle income countries, and as Mike had mentioned many of these women actually present at the relatively late stage, perhaps too late for accurate gestational age staging.

So I think what makes it more feasible, being done post licensure, is that there would be a loosening of the criteria for inclusion into the study, which would allow you to enroll many more women over a shorter period of time.

DR. KOTLOFF: The part of it that I was wondering about was the impediment that you discussed about getting culture confirmation when so many children are born with this infection, but they're born in primary health centers, community health centers, places where you can't get culture confirmation. So do you think that will also be something that's difficult to overcome?

DR. MADHI: Unfortunately, that part of it will remain. I think if babies are not being born in hospital with adequate laboratory services you are going to always be constrained in terms of the case detection. But I think what that lends itself to at the same time is the possibility of the use of PCR in terms of detecting those cases that we had a culture who might be inhibited because of preceding antibiotic therapy, but obviously this is something that still needs to be investigated in terms of

what the use of PCR would be in that context. But you are correct that in terms of case detection, even if it's done in more pragmatic manner in terms of enrollment, your constraint would be timely investigation of the suspected cases.

DR. MCINNES: Sheldon, I think you would like to have a comment or ask a question?

MR. TOUBMAN: It concerns the question of the meaning of feasibility. I actually understood feasibility to have two aspects, one of which was not stated. The first which was stated was the long duration that will be required due to the full clinical study. Eight years and then four years more is unacceptable, I think everybody agrees on that.

The other aspect of feasibility though not stated is cost. And I'm wondering whether it has accelerated approval using some compromised endpoint, that would address the long time period issue, because obviously we go forward right away, and then post licensure you require the full study, which will take maybe that long period of time, that's okay. But the second piece of course unstated is the cost to the company.

And although we were asked not to address the question of the FDA's regulatory model here, it was raised by the speaker in the public hearing, the gentleman from

the Gates Foundation, Dr. Monto raised it as well, that this group could suggest that whatever compromised endpoint is used or endpoints are used, that there should be a full robust randomized study post-licensure as a condition. Thank you.

DR. MCINNES: I think it is important at this point, even though I really didn't want to go here, is to just articulate the criteria for expedited approval that a clinical endpoint has to be done, could you just say that?

DR. GRUBER: That is a challenging question. If you go by the letter of the law or the regulation, it says if you do an accelerated approval based an endpoint that is reasonably likely to predict benefit -- let's assume in this case it's an immunological endpoint of some sort, let's say functional antibody -- then we could approve this product, but the company is then required to confirm, or it says to verify the clinical benefit of this product by conducting adequate and controlled studies.

Now, we have had the same internal discussions that you brought up, Karen. And that is if I have to do some study post licensure, why is it less difficult than doing it pre-licensure. But I think there are some differences, and I think the approval status in and of itself could really impact, the use of the vaccine, distribution of the vaccine. But the other thing, and I

think this is what you want me to address, it's a little bit how would these studies look like.

And I want to bring this up, and I think this is challenging perhaps also to FDA colleagues, but in 2015 we had an advisory committee here on maternal immunization, and that was for vaccines that were already licensed, such as influenza and Tdap vaccines that are recommended for us in pregnant women.

And if a vaccine manufacturer were to develop or would like a specific indication for use of these vaccines to protect the young infant from disease, flu disease or pertussis, then how could this be done and demonstrated, because randomized controlled pre-licensure studies cannot be done, because the vaccine is licensed and recommended for use in pregnancy.

So there we approached the committee and said could observational studies be used to confirm the clinical benefit. Let's say we would give such a vaccine an accelerated approval, let's say influenza vaccine to protect the newborn infant from flu disease for instance.

Then the committee actually said that observational studies, post-licensure studies to confirm, to verify the benefit, should be considered, and it's on the table, realizing challenges around conducting these studies, and these are observational data, they come with

certain concerns, but it was sort of agreed upon that this could be a way forward.

And in my opinion, and I have to clarify this, there are discussions ongoing not only in the Office of Vaccines. There are at the center level and at the agency level about the use of these real world evidence data to inform prescription drug labeling. And a final decision has not been made, but I see what we're discussing here today under the umbrella of these types of discussions.

DR. HEINE: I applaud that, because I'll use group B strep as its own example. We do not have a randomized trial showing that antibiotics reduce neonatal sepsis in the newborn. What we do is we have antibiotics reduce colonization, and we extrapolated that it reduced sepsis, and we followed them, we did population-based studies after that and showed a reduction. But we never did the randomized trial to show it in large populations that it reduced the risk of sepsis. It's its own example. If you got approval here and you want to this well-defined population and you showed a reduction, I think that would be reasonable.

DR. MCINNES: Thank you, Dr. Heine. Dr. Baker, would you like to comment?

DR. BAKER: I would, but Dr. Schrag will do a better job.

DR. SCHRAG: I think Carol just wants to make the point, and I agree with her, that there actually were randomized trials for group B strep using a disease endpoint, one of them was the one I talked about that was stopped early because of overwhelming efficacy. That was using a disease endpoint, but there were also observational studies that contributed.

DR. HEINE: Who was the randomized trial?

DR. SCHRAG: Boyer and Gotoff.

PARTICIPANT New England Journal of Medicine June 1985.

DR. HEINE: Wasn’t that colonization?

DR. SCHRAG: No, that was disease. It was using colonization as an indication for IAP, but that was not the endpoint. The endpoint was invasive disease.

DR. MONTO: The difference between the situation here and with influenza vaccine is the randomized trials for the clinical endpoint are already done, and this is adding another indication. Again, this is from somebody who does observational studies. I think the problem that we have is there is a climate out there in the world which is not yet ready to accept licensure on the basis of observational studies for the clinical endpoints.

My mind would be changed I think if we were further along in terms of the immunologic correlates. If we

were, and they were very convincing, this might change my mind. But right now sitting where we are, I think there really would be a requirement for at least some kind of a mixed design. We're getting very good at designing novel study designs, but there's got to be some, you can't be an open label study.

DR. LEVINE: A few comments on this very rich discussion. One is that the Gates Foundation did support three large randomized control trials of maternal immunization with flu vaccines, in three very different populations. We did one in Mali, and unquestionably, even though we're working in a very vulnerable population, pregnant women, it is a world of difference to do a post-licensure trial. It's much easier in terms of the rigor of the GCP paperwork.

We called pre-licensure, randomized the level of the individual if you could do it, placebo controlled trial, the gold standard. And I think it is for efficacy, but there are some instances where post licensure trials have been done where I think they unquestionably show the impact of the vaccine.

But they do it in a real world situation, and I'll give two examples which lead into kind of a crazy question or comment. One was in the early days of Gavi, with Hib vaccine having been routine in the USA, this fund

became available to get Hib conjugate to the poorest populations in the world. We got Hib conjugate vaccine in Mali, and the Ministry of Health introduced it in three steps.

The first step in the Capital City of Bamako, using the surveillance, the bacteriologic invasive disease surveillance that was in the One Children's Hospital as a measure, that showed this huge burden where nobody had ever heard of Hib, it was a major cause of hospitalization and death.

They introduced the vaccine, and in the same surveillance system over three years, not as a study, but as a passive surveillance showed an 88 percent drop in culture confirmed invasive Hib from the day the first kid got the first dose in this EPI normal delivery. Now, is that ecologic? It could have been.

But we did serosurveys before the first doses were given, and 18 months and 30 months after the first dose, and found that in the six to seven-month-old infants, the age of highest age specific incidence of invasive Hib, instead of having zero out of 200 at the baseline having a titer of one microgram per mil, when you go back at 18 months it was 72 percent, and at 30 months it was 82 percent, a mirror image in seropositivity.

But we also had in Mali very high incidence of invasive pneumo disease in the same age group, in the same clinical syndrome, no clinician could tell the difference, transmitted the same way, and when we look at invasive pneumococcal disease, no change whatsoever. You put that package together, how can you argue that this was not hid with specific antibody creating this public health impact.

The second example post licensure, we were getting ready to do a randomized at the level of the individual trial of Hib conjugate PRPT in Chili, when the FDA licensed PRPT on the basis of serological non-inferiority for anti-capsular antibody.

And we had a large number of doses, and what we ended up doing was a randomly allocated by health center among the 70-odd health centers, and they either introduced the Hib or they didn’t. And over 30 months of surveillance there was a 90 percent effectiveness. It was open, but this is a hard endpoint.

So I give all this background to say if there was some other pathogen in parallel with the group B strep that you could use the way we use pneumo to do sero surveys before, to show the full in NGBS and to show no change in the other, I don’t know of another bug, but this is not my area of expertise.

But thinking of is it possible that industry and the FDA could get together where everybody agrees that we really have to know that this first vaccine truly has an impact, could one if industry were willing to do it, could they manufacture two vaccines, one having 1A, 1B, and one other, and the other conjugate having three plus a couple of others, get them licensed, do a randomized trial post-licensure with those two vaccines, each serving as a control for the other, like has been done for both live Shigella and conjugate Shigella vaccines where everybody gets benefit. I'm sure my friends are cringing now, I don't mean to do it, I'm just thinking off the top of my head.

But if at the same time a large safety trial is done with the full six ready to go by a serological bridge, one would have actual hard data where each of the group is serving as the control for the other. And then one would be able with the whole package to license the six valent, purely theoretical, I apologize.

DR. MCINNES: Thank you.

DR. GRUBER: I want to make a comment. Maybe bringing us back perhaps to question number two. What I'm hearing is that immunological endpoints could be a way forward, but what I'm also sensing is there are differences in opinion in terms of the rigor or the type of study that should then be conducted to verify the clinical benefit.

And I think this is where of course more discussions would be necessary, but what I'm hearing if that the FDA in discussions with vaccine manufacturers should consider looking at immunological endpoints as markers.

But what I also wanted to say, and I don't want to prolong the discussion on post licensure studies, but the point that I wanted to make is that observational studies or real-world evidence studies are not all equal, and one could certainly define the criteria by which we would find them acceptable to verify clinical benefits. So that's all I wanted to say.

DR. MCINNES: I think we collectively agree that what you heard is I think what we all heard.

DR. MONTO: I think what set me off was I think I heard the word open label at some point.

DR. MCINNES: I think you said it.

DR. MONTO: I think I heard it when the word effectiveness was used in the industry presentation. I may have been wrong. But I agree totally with Mike, there are multiple ways to look at this. There has to be some kind of randomization, group randomization, or other ways that we could be confident that this is not ecologic.

DR. MCINNES: I think that is a guiding principle. I don't even want to tell them how to do it, I think we need to have convincing data, and I think there is support

for immunologic endpoints with all the provisos that we put on the table. We think we understand the mechanism, we think we know what it is, it's not the only thing that contributes, but it's probably enough.

We need to be well characterized, it needs to be matched to a functional antibody assay so that we are sure it's not just finding antibodies that do not have function, and we have some stories of that in the Group B Strep literature. And then I think it's plausible to then be followed up with a clinical study that is rigorously conducted and thoughtfully negotiated between those parties. Is there anybody who wants to add anything to that.

DR. MADHI: I think the main point I want to make is that in terms of the Phase IV integration I do agree that doing observational and ecological study would certainly be able to determine the effectiveness against culture confirming base of disease. I think where it becomes more difficult is the nonspecific endpoints, which I think are equally important if not more important. And I think if we're truly trying to establish the role of GBS, be it for preterm labor, or be it for the non-culture confirmed sepsis, for those particular endpoints you need to require a randomized control trial.

So it really speaks to the issue of the ethics of being able to do a randomized controlled trial in the context of a licensed vaccine. I think as Mike has pointed that the influenza vaccine trials that were conducted in pregnant women in Nepal, Bali, and South Africa were done in the scenarios of it being recommended for pregnant women in high income countries.

And certainly our own ethics regulatory report, Perspectives, wonders why that the courts didn't form part of standard of care, and unlikely to form part of standard of care in the absence of data which shows impact on severe disease, it was unlikely that the vaccine was ever going to be introduced into the public immunization program. On that basis, they agreed for placebo controlling the mice trial. And I think for GBS, at least from a Gavi perspective, they're going to require much more than simply invasive disease as an endpoint, because I think in the broader scheme of things, despite being relatively high, it's fairly modest in term of its contribution to mortality, than just looking at culture confirmed disease and the need for a vaccine probe, essentially.

DR. MCINNES: Peter?

DR. GILBERT: So, I agree with what others have said, that the markers that have been measured, because they're consistent universal correlates of disease that

they’re highly promising to be able to reasonably predict benefit. So I would just add two comments. One is that the Phase IV study I guess would need to store samples on just about everyone in the study to try to validate the surrogate endpoint directly. I think David made the comment too that eventually getting some more validation of the surrogate endpoint would be important.

The second comment is that, so now there is a very welcome effort on standardized assays and running those in observational studies I assume and being able to study correlates of risk in those contexts, I think it would be worth considering more multivariate statistical analysis where you have multiple immune responses measured, and then also the prognostic factors measured, and then basically use machine learning to build the best predictive models that could be rich combinations of the markets, and used pretty flexibly in non-parametric learning, because there may be some discoveries. It might not be a threshold from one assay that is really what predicts best, it might be some nonlinear combination, and be good to let the data teach us that.

DR. MCINNES: Any other comments on this point number two?

DR. SCHRAG: I would make one comment from the CDC standpoint, just to say that our division at CDC has kind

of what Marion was saying that we have decided that immunological endpoints look like they could be a way forward, and so we are actively trying to figure out with the US active surveillance that we do if there is a way we can contribute to evidence base.

DR. MCINNES: Thank you. Let me ask the question, have we massaged this one sufficiently now, FDA, anything else?

DR. GRUBER: I think we are good.

DR. MCINNES: So, number three, could colonization be used to demonstrate vaccine effectiveness? If so, please discuss its strengths and limitations. So let’s move on to the colonization discussion here. And I think we certainly got some preliminary look at a trial that was done, it was a randomized trial that had an impact potentially on colonization, and it had an impact on colonization, it had an impact therefore on potential efficacy.

Are we talking purely here about maternal colonization, or are we also going to infant colonization here? I just want to know what people think about that. Are we looking at this prior to pregnancy, are we looking at child bearing aged women here? What do people think about being able to demonstrate -- If the organism isn’t there, if it’s the black and white case, then it’s sort of easier

to talk about. That doesn't seem to be what happens, but let's start with something. David?

DR. GREENBERG: I had the same question, either maternal or infant. Maybe others can correct me, I'm thinking of this as being another surrogate. So it's a clinical endpoint surrogate, but it would be an indication of effect of the vaccine and hopefully reduction of disease. So I think in that sense I'd encourage it, I'm all for it. I don't see it replacing clinical effectiveness of sepsis.

DR. EL SAHLY: I would second that, especially note of the data that after introduction of the IAP in the Netherlands and the UK, which I think would have impacted or treated colonization, they saw an increase in the disease in those two countries, and in the African American subpopulation where they seem to have the same rate of decolonization or treatment inter-partum, but still have higher incidence of disease. So it would be data to be collected and analyzed in the bigger scheme of the clinical trial, but not necessarily a vaccine effectiveness endpoint.

DR. KOTLOFF: I guess two things. One is are we talking about maternal or infant colonization. I think what we're most familiar with is maternal colonization. So it seems like that's the easiest target. There's another

issue, something that Shabir mentioned that made me think, and that is that antibody acquisition would affect acquisition of new colonization, but it wouldn't eradicate existing colonization, and so it would seem that the endpoint would have to be acquisition of new colonization, which is more difficult to ascertain, but I thought that would be something that's worth discussing, whether we would have to parse those two things out.

DR. MCINNES: So Carol, can I ask you to address this again? So in terms of your and Sharon's trial, you had time, right, time to colonization or serotype specific colonization was your endpoint, correct?

DR. BAKER: That is correct. The primary endpoint was time to acquisition of vaginal. The rectal data were sort of exploratory, ad hoc, not the gold standard kind of thing, because we kind of looked at the data and noticed it. Let me make some things clear. Intrapartum Chemoprophylaxis or IAP, it is prophylaxis, it is not treatment, it does not eradicate colonization.

We have tried to do that in mothers using parental antibiotics, including bicillin, historically, long-term oral treatment. You cannot eradicate this commensal from the GI tract. You can decrease the number of organisms. That's why we use high doses of ampicillin or penicillin to immediately reduce the number of organisms

that the baby is exposed to. So it's prophylaxis, it's not treatment.

But all kinds, that was the very first thing people tried to do, was get rid of maternal colonization back in the 1970 and early '80s. So we are transiently decreasing the inoculum, and then immediately when the mother goes home, she goes home colonized, the organism is not gone. So our trial was 18 months, you had to be negative for 12 or 13 sampling points, vaginal or rectal colonization, you had to be negative every single time to be perfect, or time to first acquisition.

And the rectal part was an extreme surprise, I don't know of a vaccine that has had any effect on a GI commensal given parenterally, but Dr. Levine might be able to think of one. Our concept for vaginal delay in acquisition was vaginal fluid would have about 10 percent of serum IGG circulating. Nobody has studied IGA very well in group B strep, whether that perineural vaccine does that also we don't know. So there is a lot more to know about colonization.

Again, I think this could be something that could be considered intellectually, but think about the difficulty of sampling so frequently, Dr. Madhi's studies show you that the dynamics of acquiring and losing colonization due to GBS. So this might be a little piece of

a package, but adding it even as a secondary analysis I think might be difficult. I'm very positive for anything that could make things go forward. Does that answer your question?

DR. MCINNES: Thank you. I think certainly we are here to discuss group B strep. I want to, and I think it makes sense in that context, I just think in general for infectious diseases though, if you have an intervention that has an impact on colonization, colonization has to be on the table for consideration as an endpoint. I think it doesn't make a lot of sense here in terms of the data we're seeing, I don't think it's off the table, I think it should be studied and looked at, but it's not black and white. I mean the data you got were not black and white.

And then I think the question always comes around sampling error, which we've had lots of examples of. You could have multiple serotypes around, and are you picking the right colonies off the plate in order to go and type them, I think all of those are interesting issues, even though you developed a technique to try to --

DR. BAKER: Speaking of technique, these colonies, poor Sharon Hilliard, the PI and her lab techs, they probably all resigned since the study was done, this was a multiple colony pick from each swab. So the difficulty of

doing this for all the reasons that we heard would be quite an undertaking.

DR. MCINNES: It might have been easier with a multi-valent vaccine. It was particularly difficult because it was mono-valent.

DR. HEINE: What is the status of quantitative PCR as far as looking at level of colony counts? Because it may be that the vaccine may not eradicate, but it may take you from high colony count to very low colony count. We know that high colony count correlates with transmission.

DR. BAKER: We already knew that by routine microbiology. I don’t know of studies that have looked with PCR. I would suspect that PCR, because all it does is detect DNA --

DR. HEINE: That may be easier to where you’re doing these studies to get the sample.

DR. BAKER: It depends on whether you’re in Africa and have a $50,000-$100,000 machine or not.

DR. MCINNES: Any other comments on colonization? Shabir, you’re free to weigh in if you’d like to.

DR. MADHI: I can hear what Carol is saying and I can hear that she sounds a bit cautious about it. I think in term of if you’re not going to be measuring early onset disease as a pathway to licensure, I think we need to have

something, a reasonable proxy, or that we are actually going to be impacting on early onset disease.

And obviously we know that colonization is the major risk factor for early onset disease. And given the study that we did, the longitudinal cohort study, it basically requires a sample size of about 600 women who had an acquisition rate of 20 percent between 20 weeks of gestational age and 57 weeks of gestational age. And that was sampling at four time points.

So I think it’s something that is much more pragmatic in terms of numbers, and I think that we would be able to actually show vaccine efficacy, even if the vaccine efficacy is only 40 to 50 percent, I think that itself is telling in terms of the reduced risk of exposure and consequently the reduced risk of early onset disease in babies of mothers who are vaccinated.

In terms of the other issues that were raised, so currently we’re using the Fluidigm assay which is sort of a PCR assay basically to address the issues of multiple colonization, using sort of a quantitative measure of quantitative quantity of colonization or density of colonization. So that’s work that’s currently underway, and it would include all of those nine different countries which I referred to earlier. But I think that showing some

impact on colonization would be an invaluable adjunct to the correlate in terms of making a case for licensure.

DR. MCINNES: Any other comments?

DR. SUN: I just want to follow up on one of the points brought up, whether this was maternal colonization versus the newborn colonization, whether any consideration should be given to the effect of a vaccine on newborn colonization.

DR. MCINNES: Even though we asked the question we've been talking largely around vaginal and rectal colonization. Any comment about neonatal colonization?

DR. SCHRAG: I would just add a little complexity I think in thinking about the newborn colonization is the timing and then what it means in terms of the disease that could be prevented, because if you swab a newborn right at birth they might not be colonized, it might just be surface contamination from passing through the birth canal. But if you are interested in early onset disease, you can't wait a couple of days to see if the bacteria has really established, and early onset disease is the high burden disease in countries that haven't done widespread IAP.

So I think it's tricky because you could be looking at just surface contamination, and Shabir could comment more, but some data I've seen is kind of the more samples you take from the newborn right at that time of

birth, it seems like if you have colonized mother you are almost guaranteed to find some evidence of the bacteria, particularly if you add in PCR to the mid. So it's tricky to get more meat. For late onset disease you could say that you're going to wait a couple of days and if colonization establishes maybe that is a risk for late onset disease. That's just something from an immunologic context.

DR. MCINNES: I think we are at the bewitching hour. On reflection about all the challenges that this brings to mind, I think we agree, there's no disagreement that this is an important disease in infants, and it certainly merits our full and collective attention to fully engage in intervention development to get licensure through whatever creative means needs to be, and to get full dissemination into clinical care in order to impact this disease in infants.

So it was done for other pathogens, they were not easy either, and I want everybody to just keep positive about this. It is in fact our new imperative in neonatal and young infant disease, and it's one that we have to strap in for and work together to make this happen. I want to thank everybody for their contributions to the meeting today, and not easy discussions but most appreciated. Yes, Dr. Gruber?

DR. GRUBER: I just want to also add my sincere thanks on behalf of the Office of Vaccines and the FDA for this very thoughtful discussion and the comments, I think you gave us a lot of good insight, and I am hopeful that this field would move forward. I also want to really thank our speaker, Shabir and Carol because they're really informed with their contribution and the work done in this discussion, so thank you so much to you.

And Pam, you were thanked this morning for your contributions to the VRBPAC and again on behalf of the FDA thank you for all that you have done, you came here for years and years to serve, I think long before I ever had a VRBPAC meeting attendance. Thank you, thank you for your efforts here, for your work and your help, and on a personal note I will really miss you, not only on the VRBPAC but I know we have been colleagues for I don't know, 25 years, when you were a program officer at DMID and I was a primary reviewer in the Office of Vaccines, and guess what we discussed, group B strep vaccines. So thank you again Pam.

DR. MCINNES: So we are moving to topic two, and it is an open session that leads off. I know those of you who came for group B strep are definitely going to stay for the site visit report, no, that's a joke. Those who are here for the site visit report, we just wait a few minutes

for those who are leaving, and then we will have the open session, and then we will have a closed session. So we will take a ten minute break.

(Break)

Agenda Item: TOPIC II: Presentation of the Laboratory of Respiratory Viral Diseases (LPRVD) Division of Viral Products (DVP), Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER)

DR. MCINNES: Good afternoon. I would like to call the meeting to order for this topic II of this VRBPAC meeting, which is a presentation of the Laboratory of Respiratory Viral Diseases, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research.

We'll move to the conflict of interest statement. This will have an open session and a closed session.

Agenda Item: Conflict of Interest Statement

MS. HUNTER-THOMAS: Thank you, Dr. McInnes. Good afternoon, everyone. The Food and Drug Administration is convening today, May 17, 2018, for the 152nd meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

I will proceed to read the conflict of interest statement for topic II. Dr. Pamela McInnes is serving as the chair for the topic II session, as well. The following information on the status of this advisory committee's compliance with federal conflict of interest laws, including but not limited to 18 US code Section 208 of the Federal Food, Drug, and Cosmetic act is being provided to participants at this meeting, and to the public.

The conflict of interest statement will be available for public viewing at the registration table outside. Under topic II, during the open session the committee will hear an overview of the research program in the Laboratory of Pediatric and Respiratory Viral Diseases, LPRVD Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research.

Topic II is determined to be a non-particular matter and there are no affected firms determined to be a non-particular matter and there are no affected firms identified for this topic and no prescreening of the members and consultants was conducted. Based on this agenda topic, it has been determined that the overview presentations on the research programs do not pose actual or an appearance of conflicts of interest.

Following this open session in accordance with 21 CFR Section 14.27 implementing 5 USC 552b(c)(6), the Center for Biologics Evaluation and Research is authorized to hold a closed session of the Vaccines and Related Biological Products Advisory Committee meeting on May 17, 2018, between 4:10 p.m. and 4:45 p.m. The purpose of this closed session meeting is to review matters of which the disclosure would constitute an unwarranted invasion of personal privacy of permanent CBER staff with regards to their personnel actions and or staffing decisions.

Dr. David Greenberg is serving as the industrial representative. He is employed by Sanofi Pasteur. It is to be noted that the industry representatives are not special government employees and are not voting members of the committee. Hence, they do not participate in the closed session and do not have voting privileges.

Mr. Sheldon Toubman is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are the voting members of the committee. Hence, they do participate in the closed sessions and do have voting privileges.

This concludes my reading of the conflict of interest statement for the public record regarding topic II of this meeting. Thank you.

DR. MCINNES: Thank you, Serina. So the first presentation is an overview of research and the site visit process within CBER, and this is Dr. Carolyn Wilson, who is the associate director for research for CBER at the FDA.

Agenda Item: Overview of Research and Site Visit Process

DR. WILSON: Thank you. I want to start by thanking Drs. Kathryn Edwards and Hana El Sahly who co-chaired this particular site visit that we will be talking about later this afternoon, and also to mention that Dr. El Sahly was very generous and offered her time yesterday in a second site visit, which is quite appreciated, and I am giving fair warning to the other members of the VRBPAC that we will likely at some point count on your expertise and time to help oversee site visits in the future for the office of vaccines, and we're really appreciative of the work that's being done by these site visit teams.

So as was mentioned, I'm going to try to give a quick overview. So I know that this group is well aware that the center regulates vaccines, but you may not realize that also within the office of vaccines are a very complex set of allergenic products which represents actually over 1,200 different extracts that are used both for diagnosis and treatment of disease, therapeutic probiotics including things like phage therapies, fecal transplantation, as well

as blood, blood components, blood derivatives, and certain devices that are used not only in the blood industry but also, for example, selecting cells for cell therapies. We also regulate gene therapies, tissues, and xenotransplantation products.

The complexity of the biologic products that we regulate, as well as some of the devices, and combined with the fact that most of these products cannot be terminally sterilized or subject to things like inactivation procedures to remove or inactivate infectious agents, and the complexity of the types of products that we regulate, we feel that it's very important that we have a robust intramural research program to augment the regulatory oversight of these product areas.

This is a graphic that developed now quite a number of years ago, and I apologize for those of you who may have seen this a million times by now, but I find that it is instructive, and really what it's saying is that everything starts with a public health issue that drives, for example, the development of a novel product to address that need, but those novel products often pose a challenge from the perspective of a regulator trying to evaluate whether or not it's ready to go into humans, whether it's safe, whether it's effective. Perhaps there's no good

animal model, or we don't understand the mechanism of protection in the case of a vaccine, for example.

So that's where regulatory science helps through a combination of discovery research and targeted development of new tools to fill in the gaps in the science and help provide a better framework for informing our regulatory policy, to help advise sponsors better and our decision making. From that we have improved data from our sponsors that help us be in a better position to make benefit/risk decisions about the safety and efficacy of these products, and at the end of the day, we share the goal of everybody to have a positive impact on that public health need and have a safe and effective product licensed, but it doesn't stop there because as you know, in particular in the vaccine world, that really for our entire product portfolio, the post-market surveillance is critical to ensure ongoing safety and efficacy of these products.

So we view our regulation of biologics to be collaborative so that research is one of several different dimensions of fulfilling our regulatory mission, and our research scientists are what are called researcher reviewers, which means that they not only have their own research program or participate in a research program, but they also all the same duties as full time reviewers, meaning they're reviewing submissions, they may be going

out on inspections, they're writing guidance documents, they're participating in advisory committees and workshops, and this ability to transcend both worlds, both as a regulator and as a member of a scientific community, allows us to integrate our research and review, making sure that we're addressing the most important issues.

So again, the benefits of the research program are to prepare for the future in terms of both innovative products, as well as public health challenges, to develop tools and data that are available to all stakeholders and support developmental product classes, recruit and retain highly-trained scientists with the necessary expertise to inform our review processes, and to fill gaps to inform policy development and regulatory decision making.

To do this we have a variety of scientific expertise within the center, a variety of applied technologies that help with analyzing the types of products we regulate as well, as you would imagine, a diversity of microbiology, immunology, biochemistry, molecular biology, cell developmental biology; most recently tissue engineering and microphysiological systems has been added to our staffing, and of course epidemiology and biostatistics, and also in the last five to six years we've developed a bioinformatics core.

In addition, we have core facilities supporting flow cytometry, confocal and electron microscopy, a variety of different biotechnology needs, and the bioinformatics, as I mentioned. We also have a state of the art vivarium that allows for imaging using a variety of modalities, animal procedure rooms that allow for use of agents at both BSL2 and BSL3, and a transgenic derivation facility.

I want to mention because especially this body, the VRBPAC, has on several occasions suggested to us the need for more mentoring of some of our PIs. Because we're a fairly small center we felt that a formal mentoring process that is being done in some of the larger organizations might be challenging. So what we've developed instead is an informal CBER peer mentoring group which is a monthly meeting open to all PIs, but we have always at least one or more senior PIs who volunteer to be present each month to facilitate the discussions, and we've received really positive feedback from the individuals who meet in these meetings, both in terms of the assistance and guidance that they've received there, but also importantly, this group has become a little bit of a brainstorming group to help provide suggestions back to upper management about things that could be approved or addressed, which is really helpful.

We don't do all this work by ourselves. As any scientists, we need to collaborate, and we collaborate extensively within the United States, globally, and the types of collaborations are in a variety of different sectors, primarily academia, or other government agencies, but we also do collaborate with industry and nonprofit organizations, as well.

So our research management processes really involve the development of CBER regulatory science and research goals and, you'll hear shortly, also development of office goals and objectives. We also have developed and implemented a research impact framework for evaluation of the research, and then we do evaluation of the research program by leadership and something called the Regulatory Science Council, and then by peers through a combination of internal and external review.

So our research goals currently for the center are to advance the scientific basis for regulation of biologics, tissues, and blood, by developing and evaluating technology reagents and standards to inform CMC, developing and assessing non-clinical models and methods predictive of clinical performance, improving clinical evaluation pre- and post-licensure, and importantly preparing for future regulatory and public health challenges, and of course the

group that you'll be hearing more about shortly is very much in the thick of that with influenza preparedness.

The research impact framework really identifies portfolio and project level review elements, and so of course we want to make sure that the work we are doing is aligning with our center and office goals and objectives, that the work is building up expertise to allow us to address our review needs, and that we also have agility within the research program to address unexpected and urgent public health needs.

We want to make sure our research is addressing those scientific gaps and questions that are unique to our regulatory mission, but always at the bottom, at the foundation of all of this is to make sure that the work we do has strong scientific merit and the PI is continuing to have acceptable levels of productivity.

So as I mentioned, we do internal review of our research program, and some of this was going on before FY17, but this is what we've implemented starting in FY17 as a formal review process, and one of those is internal peer review of 25 percent of each research program, of all research programs, and any new project proposals are reviewed on an annual basis. That means that every research program would undergo internal peer review once every four years, but annually all programs are reviewed by

the management chain of supervisor, division, and office, and then there's a portfolio review by the Regulatory Science Council where we're taking each year a review of each of the four offices that engage in research. So again each office has a portfolio level review once every four years, and again we're applying the research impact framework to that.

I'm not going to go through this but I just have this list to remind me that we use an online research reporting database, and we collect a number of important details and information that allow us to manage the programs at both the program level as well as the project level, and it includes things like experimental approach, progress and plans and anticipated results, but also various administrative or compliance-related things like IBC, RHISC, ACUC, and so on.

So, in addition to this internal peer review that we're doing every four years, we also have external review by site visits, and that's where we bring in outside experts to review in a very thorough way our programs, and that's what you'll be hearing about today, which is a draft report of that site visit process. In addition to coming here as one stop to get reviewed and finalized and approved, there's also one more stop which is an internal

additional peer review committee for promotion and evaluation of researcher reviewers.

And so this diagram is intended to help you decipher the complexity of our career pathways, and so the top row is senior staff fellow, and that is for a principal investigator. The idea is that this is an individual who is an independent scientist who receives resources to support his program from the office or division, and then there's a staff fellow or visiting associate, which is a support scientist. In both cases these individuals have up to seven years, and during that time they go through at least one or more site visits, as well as the CBER review.

In addition, at any point in this process and certainly at the end of it, there may be an open competition, and these individuals can apply for those positions, and, if they are deemed to have appropriate credentials, may be chosen for conversion to permanent status.

In rare cases, we have individuals who become permanent staff scientists and over time their scientific capabilities really mature under the mentorship of the PI, and there may be an opportunity to recognize that through providing them an opportunity to go into what we call an acting PI track, where then that dotted line is essentially going back to going through a site visit and a CPERR to

confirm that this individual should be in PI status rather than a staff scientist. In the event that it turns out that this individual really isn't going to make it as a principal investigator, they can always return back to their staff scientist position.

So again, to come back to what you're doing here today, you're looking at a draft report that the site visit team developed, and we're asking you to look at it and either accept the report as written, you have the liberty to add amendments to the report or you can reject the report and send it back to the site visit team, but once it has been approved by the full advisory committee, then that final report is very useful, and again, it becomes part of a larger package that goes for internal peer review. The PIs take the recommendations very seriously to improve their own research program, and of course, management takes your recommendations into serious consideration as well.

So I want to again thank the site visit team and your attention to looking at this report this afternoon. I'm happy to answer any questions.

DR. MCINNES: Any questions for Dr. Wilson? Thank you, Carolyn. So we move on to the next topic which is the overview of DVP, which is the Division of Viral Products from Jerry Weir.

Agenda Item: Overview of DVP

DR. WEIR: So I am going to give a brief overview of the Division of Viral Products. The Laboratory of Pediatric Respiratory Viral Diseases is one of seven laboratories in the Division of Viral Products. You did not get an overview of the Office of Vaccines, but the Division of Viral Products is one of three divisions in the Office of Vaccines, one of two divisions that have a laboratory component.

The respiratory viral diseases is headed by Dr. Zhiping Ye as the chief, and this laboratory's focus both in review and research is almost exclusively in the area of respiratory viruses.

The mission and function of the Division of Viral Products can be summarized simply as we regulate viral vaccines and related biological products, ensuring their safety and efficacy for human use. We also try to facilitate the development, evaluation, and licensure of new viral vaccines that positively impact the public health.

The staff in the division in this laboratory have several major responsibilities. We're involved all aspects of premarketing activities, including the review of investigational and new drugs and biologic license applications, and any other premarketing activities. The staff is involved in all post-marketing activities, such as

BLA supplement review, lot release review. The staff participates both in pre- and post-licensure manufacturing inspections, and we have a very heavy consultation role with other public health agencies, in particular the WHO.

Last, but not least, the staff is responsible for conducting research related to the development, manufacturing, evaluation, and testing of viral vaccines.

The role of research in the Division of Viral Products is summarized on this slide. Our research and laboratory activities are designed to complement the regulatory mission. They're designed to address issues related to regulated viral vaccines, but they're also designed to anticipate and address issues related to the development and evaluation of new viral vaccine products. Sometimes these issues are very general and apply to many products, for example, cell substrate issues. Sometimes they're very specific for a product, and I gave the example of correlates of protections necessary for our efficacy evaluation.

The next two slides give a snapshot of the division of FY17. Our fiscal year runs from October 1 to September 30. In FY17, the division had about 75 fulltime equivalents. These are government employees. But the division staff is supplemented by about 40 contractors. Most of these are on our ORISE program. Probably most of

them are postdoctoral fellows, but there are quite a few that are post-bac students. Post-bac contractors are only involved in research; they're not part of the regulatory program. In FY17, the division budget had a basic operating budget of a little less than $6 million. We had additional targeted FDA support of about $0.5 million, and we had external DVP support of about $2.8 million.

The FY18 budget is not completely final yet, but we're pretty far along in the fiscal year, and it looks like the budget will be somewhat similar to last year. The division of staff in the laboratories, you can see on this slide, respiratory viral diseases is actually one of the larger laboratories. Right now we have two principal investigators, Zhiping Ye and Judy Beeler, but we are recruiting for a third one, and when we had the site visit in January I mentioned that the recruitment was underway, and actually the status now is that we have brought candidates in and we're in the process of interviewing a final four candidates, and we hope that we will be able to find someone for the third PI position in this laboratory.

So, the site visit evaluation that you're discussing today is designed to assess our progress, the progress of the individuals on the projects that they pursued since the previous site visit. There is a component of individual review, because certain staff are

in consideration for promotion, and as always, we value your input on the future directions that have been laid out by the different PIs and staff members.

And I'll stop there, if there are any questions.

DR. MCINNES: Any questions for Jerry? Thank you. That laid it out very nicely. We are going to move on now to an overview of the Laboratory of Respiratory Viral Diseases, Zhiping Ye.

Agenda Item: Overview of LRVD

DR. YE: Thank you very much. Carolyn and Jerry gave overview from CBER to divisions, and I just wanted to focus on the activity of the laboratory of respiratory disease. As Jerry said, this lab contains three initial -- contains three PIs: myself, Judy Beeler, and Maryna Eichelberger. She left OVRR to take a position in a different office in November last year. As Jerry said, we are looking for a new PI to replace this position.

Our regulatory review responsibilities are based upon the viruses. Here is an example and production, product review for the virus vaccines, which include influenza virus vaccines and other respiratory viruses, such as respiratory syncytial virus, parainfluenza viruses, human metapneumoviruses, measles, mumps, and rubella. And here I wanted to emphasize that my lab, and initially Maryna's lab, is focused on influenza viruses. In Judy's

lab they are focused on the rest of the viruses. I think this group carries on a lot of responsibility for the non-influenza respiratory viruses.

The whole lab includes the review responsibility, it includes the clinical and the preclinical review for the virus vaccines, and lot release, responsible for the vaccine lot release, and then the manufacturer inspections, because doing the inspection they do need to know, people know the facilities itself. Also they need to know from experts from a science point of view. We also participate and make presentation to the VRBPAC meeting, such as the one in strain selection.

This is a snapshot of the regulatory workload, and this represents the workload from August 2013 to 2018, and we have 10 scientists, and here for the regulatory, we are involved in reviewing the pre-INDs and INDs and amendments, BLAs, and BLA supplements. As you can imagine, that in Judy's lab it involve a lot of viruses, and those are usually involved in the phase I, phase II IND trials. The flu lab are involved in not only the INDs, we do have quite a few BLAs, because we have quite a few licensed influenza vaccines, so we have some review related to the BLA supplements.

There's other regulatory and public responsibilities of this lab, and we are involved in

preparation of potency reagents for testing of the candidate pandemic influenza vaccines, to standardize the vaccines. We're also involved in the seasonal, as well.

We participate in selection and recommendation of strain selection for seasonal influenza viruses, and CBER and our lab as well, too, is one of the WHO essential regulatory laboratories, and we participate in serological analysis of vaccine response in northern and southern hemisphere strain selection. To select the adequate viruses for vaccine production or for the update, the composition of the vaccine, we need to evaluate the serous response of the current vaccine to identify those circulating viruses needed to be used for replace vaccine production for next year. We are also participating in preparation of WHO guidelines on influenza and RSV viruses.

Here is the highlights of my group, which is influenza viruses molecular biology. The personnel, we have myself, and we have other staff: Hang Xie, Ewan Plant, Xing Li, Olga Zoueva, Hongquan Wan, and Jin Gao. And we are involved in, of course, as I said, influenza vaccines.

And the research areas involved in molecular and genetic approach to improving influenza vaccine candidates and vaccine potency reagents. And we're also involved in molecular mechanisms of influenza virus attenuation and

virus virulence. So, I think the reason we are doing this one is to make sure that the virus candidate for vaccine production is adequate for vaccine production, and also to make sure the viruses, especially those pandemic viruses, are attenuated and adequate for the vaccine production.

The last site visit was, as I said, in October 2013.

Here is the research update in my group. As I said, our group is involved in the support influenza vaccine production, and the research emphasizes how to support vaccine production. The first research area is evaluating antigenic and immune response of the influenza viruses to identify issues to maybe improvement over the strain selection, and this area was led by Hang Xie, another one of the personnel actions.

The second was is identify in the NA antigenic epitopes and studying antigenic drift and to help to improve the candidate vaccine viruses selection, and this work actually is continued from Dr. Maryna Eichelberger, and staff Hongquan Wan and Ms. Jin Gao, worked under Maryna, and this project and continue in that group right now.

We're also involved with develop and evaluate influenza candidate vaccine viruses, and the related potency reagents to have the potency reagents ready for a

pandemic situation, and because every year we need to have 150 million doses of the vaccine, we have to make sure that the viruses, the candidate viruses have higher yield so that you can achieve -- manufacturer can produce a vaccine to ensure that 150 million doses of the vaccine every year in the United States.

So we are working to make sure the viruses grow well and have a high yield, and this work is done by Ewan Plant and Xing Li. I think that a few persons I mentioned here are those persons who had personnel actions.

Here is Judy's lab, Antigenic Structure and Functions. They only have three staff, Judy herself, Lynne Crim, and Susette Audet, and as I said, the major regulatory responsibilities, RSV and other respiratory virus vaccines and measles virus vaccines, as well.

Areas of research related to the serological correlates of the infection and protection of RSV and measles viruses. I think since the studies are quite important, because for development of RSV, we need to -- especially to conduct clinical trial and to see if the positive or negative individuals, that really have a lot of impact on the design of the clinical trial and vaccine evaluation and approval.

The research update follows. The antigenic structure and function research on RSV and the project 1 is

the characterization of a human immunoglobin to be used as a reference standard for RSV utilizing assay, and as you can imagine that to conduct the clinical trial, you do need to have good standards so that you can measure the adequate antibody response in human. The project 2 is antibody profiling by immunoprecipitation of luciferase-targeted protein to detect anti-RSV IgG response. So this is also related to the assays and to measure the antibodies.

The next area is related to the measles viruses, and one of the projects is for the development of a high-throughput assay to measure the neutralizing antibody against the measles and using qPCR readout. Then the last, not least, the collaborative clinical studies to support measles elimination efforts.

These are all the projects in the current labs. Thank you.

DR. MCINNES: Thank you, Dr. Ye. Are there any questions for Dr. Ye? Yes, Dr. Levine.

DR. LEVINE: On your last slide from Judy Beeler's lab, I was looking through the report, and the ability to measure measles neutralizing antibodies in one day instead of a week or more with plaque reduction, that is spectacular. How far along are you on that? That's major.

DR. YE: This group really contributed to standardize the assay not only to give accurate but also

more time, more robust, in the study. As they said, to implement this, so they are working on the study with -- they said originally WHO or PATH come over to look at the assay, and I would like Susette Audet -- and she works on her staff -- to answer this question. This is Susette Audet, and the staff is in Judy's lab.

MS. AUDET: My name is Susette Audet in Dr. Judy Beeler's lab. In response to your question regarding the high throughput qPCR assay, we are quite far into that project. We have funding from -- we are collaborating with William Moss in Johns Hopkins, and we have funding through the Gates Foundation to hire someone to start this project. So we are, I would say, like 80 percent complete in this project, and it is going from the traditional plaque reduction neutralization assay, which I've done over 25 years, is a five-day assay. So this is going to be a 24-hour, and it seems to be as equally sensitive to the PRN assay.

DR. MCINNES: Thank you.

Zhiping, I have a question, just in terms of production of the potency reagents, you're only doing those now for pandemic, not for the seasonal strains?

DR. YE: We are involved in seasonal reagents preparation, too, but I think that that mainly ticked over in DBSQC of the office, but we are involved in that, but I

think my lab -- because for the pandemic vaccine viruses, unlike a seasonal, the pandemic viruses, you needed to have a different lab facility to prepare for the reagents.

DR. MCINNES: Thank you.

Yes, Dr. Greenberg?

DR. GREENBERG: Just a comment. I think I can speak for all of industry to thank you sincerely for all of the research and the work that you do, especially around the influenza vaccines and the work to improve strain selection, the candidate vaccine viruses. Obviously, we depend on yourself and your lab and CDC and others around strain selection, paying attention to neuraminidase, which really hasn't been an extensive area of research in the past. These are all critical areas for industry, and I want to thank you.

DR. JANES: One question; I noticed in the description of the two labs a difference in the terms of the numbers of support staff between the two labs, and I wondered if you could elaborate on that in light of the regulatory burden, and I don't know if that was an observation on the part of the committee and if there were any recommendations based on that.

DR. YE: Yes, I think so. I really appreciate Judy Beeler, really. She, this group, take a lot of responsibility in review and just take over this job not

too long ago, the thinking that -- talk to Judy too, if she has some review, she really needed to get help. I think we can help her to review by assigning some of the review within the group with such a -- my group or if new PIs come in. So we can share this responsibility to try to take off some of their burdens, as well.

Right now, this lab chief, I know try to learn and try to involve in some regulatory if I can help to her, but this, she is expert on the RSV for the R01, but I'm learning it and also try to help her from myself and also, as I said, if we can, we try to assign some review to other people, as well, to help her to lower the burdens.

DR. MCINNES: Thank you, Dr. Ye. This may come up in the closed session of the discussion. Any other questions?

Thank you very much, Dr. Ye, for your presentation.

Agenda Item: Open Public Hearing

I would like to ask if there is anybody who wishes to make a statement in the open public hearing section of this topic II.

(No response.)

Seeing none, I believe we are going to move to closed session, and then we need to be sure that the webcast is closed down and that all attendees other than

committee members and leadership and anybody who is not supposed to be here will leave the room, and then we will take a roll call to identify who is in the room.

So thank you very much, everybody who came to the open session.

(Whereupon, the Open meeting was adjourned at 3:40 p.m.)