FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)

151st Meeting of the

Vaccines and Related Biological Products Advisory

Committee (VRBPAC)

March 1, 2018

FDA White Oak Campus
Silver Spring, MD 20993

CONTENTS

PROCEEDINGS (8:15 a.m.)

Agenda Item: Call to Order and Opening Remarks

Introduction of Committee

DR. EDWARDS: Good morning. I am very pleased to be here, this first day of March, and to be chairing the 151st meeting of the Vaccines and Related Biologic Products Advisory Committee.

Before we begin, I think it would be very important for us to introduce ourselves. We have two new members of the committee, and so, Len, let's start with you. If you could give your name and just briefly what you do, and then we'll just go around the room.

DR. FRIEDLAND: Thank you very much. Good morning, everybody. Leonard Friedland, GSK Scientific Affairs and Public Health. I'm a pediatrician, vaccine researcher. It's nice to be sitting here at the table rather than up at that podium where I've been a few times, so this is a real pleasure, and I look forward to being part of the committee. Thank you.

DR. KATZ: Good morning. I'm Jackie Katz. I'm not officially part of the committee, but I'm from the Influenza Division, CDC, and I'll be telling you about the global surveillance of influenza viruses.

DR. SHANE: Good morning, I'm Andi Shane, and I'm a pediatric infectious disease physician at Emory University in Atlanta, and delighted to be here.

DR. OFFIT: I'm Paul Offit. I'm a professor of pediatrics in the Division of Infectious Diseases at Children's Hospital, Philadelphia, and the University of Pennsylvania School of Medicine.

DR. MONTO: Arnold Monto, School of Public Health, University of Michigan, and I'm back again.

DR. MCINNES: Good morning, I'm Pamela McInnes, Deputy Director for the National Center for Advancing Translational Sciences at the NIH.

DR. EL SAHLY: Good morning, Hana El Sahly, Baylor College of Medicine, clinical vaccine development and adult ID.

DR. EDWARDS: Kathy Edwards, Vanderbilt University, pediatric ID.

DR. BENNINK: I'm Jack Bennink. I'm at NIH and NIAID, in the Viral Immunology Section, influenza researcher.

DR. BOK: Good morning, I'm Karin Bok, representing the National Vaccine Program office at HHS.

DR. WIESEN: I'm Andy Wiesen. I'm a preventive medicine, internal medicine physician. I work for the

Assistant Secretary of Defense for Health Affairs in their Health Readiness Policy and Oversight office.

MR. TOUBMAN: I'm Sheldon Toubman. I'm the consumer rep, and in my day job I am an attorney at New Haven Legal Assistance Association, where I mostly advocate on behalf of Medicaid folks.

DR. WILSON: Carolyn Wilson, Associate Director for research at Center for Biologics.

DR. SLATER: Jay Slater, I'm the Director of the Division Bacterial, Parasitic and Allergenic Products.

DR. GRUBER: And my name is Marion Gruber, I'm the Director of the Office of Vaccines Research and Review at CBER, FDA.

DR. EDWARDS: Thank you. We're very, very happy that everyone is here. There also is an open web line, so we welcome those people that are watching as well. And certainly, want to welcome Dr. Shane and Dr. Offit to the committee. We're very excited that you're on the committee. Thank you.

Serina, could you read some housekeeping and conflict-of-interest statements?

Agenda Item: Conflict of Interest Statement

CAPT HUNTER-THOMAS: Sure. Good morning everyone. My name is Capt. Serina Hunter-Thomas, and it is my pleasure to serve as the designated federal officer for the

151st VRBPAC meeting. The Committee Management Specialist for this meeting is Ms. Rosanna Harvey, as well as Joyce Mercer Dickens, and the Committee Management Officer for this meeting is Ms. Jeannette Devine. Also, in the room from our office is our Division Director, Dr. Prabhakara Atreya, and Miss Asia Brown.

On behalf of the FDA and the Center for Biologics Evaluation and Research, and VRBPAC, we would like to welcome everyone to this meeting. Today's session has two topics. One that is partially closed to the public, and one that is open to the public in its entirety. The meeting topics are described in the Federal Registry notice that was published on February 13, 2018.

The press media representative for today's meeting is Mr. Paul Richards. Mr. Richards, if you are in the room, please stand so that everyone can identify you, and reach out to you as needed. Thank you. The transcriptionist for this meeting today is Mr. Chanda Chhay, representing CASET Associates. Thank you.

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

the public, and everyone will be in the room listening also via webcast. I will now proceed to read the conflict-of-interest statement for this meeting.

Good morning, everyone. The Food and Drug Administration is convening today, March 1, 2018, for the 151st meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all participants of the Committee are special government employees, SGEs, or regular federal government employees, RGEs, from other agencies that 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 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. This meeting will have two separate conflict of interest disclosure statements read at different times prior to each topic session that will occur during this meeting.

I will now proceed to read the conflict of interest statement for topic 1. Under topic 1, during the open session, the Committee will hear overview

presentations of the research programs of the Laboratory of Mucosal Pathogens and Cellular Immunology, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines, Research and Review, from the Center for Biologics Evaluation and Research. Topic 1 is 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. 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 the open session, in accordance with 21 CFR section 14.27, implementing 5 U.S.C. 552(b)(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 March 1, 2018, between 9:15 a.m. and 9:45 a.m. The purpose of this closed session meeting is to review matters and disclosure of which would constitute an unwarranted invasion of personal privacy of permanent CBER staff with regards to their personnel actions and or staffing decisions.

Dr. Leonard Friedland is serving as the alternate industry representative. He is employed by GlaxoSmithKline, and it is to be noted that the industry representatives are not special government employees and

are nonvoting members of the Committee. Hence, they do not participate in the closed sessions and do not have voting privileges.

Mr. Sheldon Toubman is serving as the consumer representative for this Committee, and 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.

The conflict of interest statement will be available for public viewing at the registration table outside, and this concludes my reading of the conflicts of interest statement for the public record regarding topic 1 for this meeting.

Thank you.

DR. EDWARDS: I am sorry, Holly, I skipped over you. Could you tell us who you are? I know you're on the phone bridge, Holly.

DR. JANES: Thank you, Kathryn. I am Holly Janes, I'm a biostatistician at the Fred Hutch Cancer Research Center in Seattle, and I apologize for not being there in person. Thank you.

DR. EDWARDS: Thank you. So we're well represented with statistical expertise, which we appreciate greatly.

So, we'll begin then the overview of the research and the site visit process. Carolyn Wilson will present this.

Agenda Item: Topic I: Presentation of Laboratory of Mucosal Pathogens and Cellular Immunology (LMPCI) Division of Bacterial, Parasitic and Allergenic Products (DBPAP), Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER)

Agenda Item: Overview of Research/Site Visit Process, CBER

DR. WILSON: Good morning and thank you. I realize this is a somewhat off-topic for the reason most of you are sitting around the table today, so we do appreciate the opportunity to have a little bit of a side topic, but this review, this process of doing external reviews of our research program is a really critical component of supporting our regulatory mission. And I just want to start by thanking Dr. Pam McInnes and Karen Kotloff, who were the co-chairs for this particular site visit, and just to give a heads-up to those of you who sit on VRBPAC, that there may be other opportunities to serve on site visits, and we really rely on the expertise of the members of the VRBPAC to help lead these site visit teams of our research programs.

So, with that, what we're going to do this morning is try to give you a little bit of an overview of the research program at the center, office, and division level, so you have a context for where LMPCI research fits into the broader scheme, and then Dr. Stibitz will give you a little bit more information about the research that goes on. And then as was noted earlier, we'll go into closed session where Dr. McInnes will discuss the details of the site visit reports. So, just a reminder that none of that should be discussed in open session.

Obviously, this Committee knows well that we regulate vaccines, allergenic products, certain types of therapeutic probiotics, because these are areas that you're probably familiar with as your roles on the VRBPAC. In addition, just to give you a broader scope, we also regulate cell and gene therapies, certain human tissues, xenotransplantation products, blood, blood components, blood derivatives, and certain related devices.

The complexity of the products that we regulate really requires that we have very robust science and scientific expertise to support our regulatory decisions and policymaking. And for that reason we have always had a strong intramural research program. And we view this as really a critical component of addressing regulatory needs and advancing product development.

And it really begins with a public health issue, which drives development of a novel product. These novel products, though, may pose regulatory challenges because we may not have sufficient science and knowledge to be able to support regulatory decision-making, such as understanding of mechanism of action to inform sponsors how to develop a potency assay, for example, not good enough understanding of a correlate of protection for a vaccine. Perhaps there's methods that need to be developed; animal models; or reference materials, in order to support evaluation of the product.

And so that's where regulatory science, through a combination of discovery science and targeted development of new tools, can really help to address some of these gaps and inform regulatory policy and decision-making. As we get better policy out to our stakeholders, then they're in a better position to generate the science that we need to make those benefit/risk decisions, so that hopefully, at the end of the day, we can license a product that's safe and effective and will have the desired positive effect on the public health, and it doesn't stop there, because, as you know, we need to continue with post-market surveillance.

And we take a collaborative approach to the regulation of biologics. Obviously, the data that sponsors

submit to the FDA is a critical component, but we do view our active research and surveillance and internal CBER and external discussions as also equally important.

It's worth noting that our research scientists are what are called researcher reviewers, which means that they not only have their own intramural research programs, but they also have duties similar to fulltime reviewers, meaning they are reviewing regulatory submissions, they may go out on inspections, they develop policy documents, they present here to advisory committees, and so on.

And because these individuals have firm footing in two very important communities, one, their external scientific professional community, where they may be seeing science evolving before it's come in to the agency, allowing us to be proactive in addressing potential scientific gaps, while also seeing things within the agency, which allows us to look across a portfolio of products, and perhaps address those most critical gaps that could really address a whole product class.

Again, our benefits of having research are to prepare for the future, innovative products, develop tools and data that are available to all stakeholders. We publish essentially all of the research that we do and often integrate what we can into guidance, either

informally, as well as formal guidance to sponsors to support development of products.

We obviously have highly trained scientists with necessary expertise to do the review, and we, again, are focusing on filling those gaps to inform policy development and regulatory decision-making.

Within the intramural program we have an array of scientific expertise. I won't read through this list, but it provides a nice, rich environment for cross-disciplinary research. But obviously we can't do everything by ourselves. We can't have all potential expertise within a fairly small center. I'll just say, also, that within the intramural program, we also have core facilities supported by the center, including flow cytometry, confocal and electron microscopy, traditional biotechnology support, including now next-gen sequencing, bioinformatics support for next-gen sequencing, and then a state-of-the-art vivarium, including a number of imaging tools, as well as BSL-2 and BSL-3 animal support and transgenic derivation.

We have developed a CBER peer mentoring group. This actually is in response, in part, to some of the advice we've received when we've brought site visits to advisory committees. In fact, the VRBPAC in the past has been very vocal on this issue. This has been going on now for two years. We're in the third year of doing this.

It's a monthly meeting, open to all PIs, but we identify at least one senior PI who's willing to lead the discussion and be present, and they've really found this to be very helpful. It's sort of a self-driven conversation about issues that are of importance to the PIs, and I think it's helped not just some of our younger recruits, but also even the more senior PIs have benefited from this discussion.

Obviously, we can't do everything by ourselves, so we collaborate extensively across the United States, internationally, and with a variety of different sectors, including a lot of interactions with academic investigators, as well as other government agencies, and industry and nonprofit.

So, to finish with the research management processes, we developed center-level regulatory science and research goals. You'll also hear from Jay about office-level goals and objectives. We developed a research impact framework, to allow both internal and external assessment to be made based on clear guiding principles, and we have a number of processes for evaluating our research program. We've stood up a governance council for research called the Regulatory Science Council, composed of leadership, as well as a number of mechanism for doing internal and external peer review.

Our research goals are to advance the scientific basis for regulation of biologics, human tissues, and blood, by developing and evaluating technology, reagents, and standards to inform and improve CMC. Goal two, developing and assessing nonclinical methods and models, predictive clinical performance. And goal three, improving clinical evaluation pre- and post-licensure through a variety of approaches, including big data, innovative designs, and statistical analysis and modeling approaches. And then, importantly, also preparing for future regulatory and public health challenges.

The research impact framework, we view as sort of on two different levels. One is to look at the portfolio level, and that's really looking at how our research is aligning with center and office priorities, objectives, and goals. Making sure that we have the appropriate expertise to support our review needs. And making sure that we also have the internal capability to address urgent public health needs.

And then we also have, in the framework, the more typical elements that are relevant to a review of individual projects and PIs, including how the specific research is addressing our regulatory mission, of course, the scientific merit, and the PI's historical productivity.

So, our internal review of research includes a peer review group that looks at 25 percent of all research programs every year, and if there's any new project proposals, those are looked at in the year they're proposed. All of the research is reviewed every year by the supervisor, division, and office levels, and that helps to inform resource allocation. And then the Regulatory Science Council does regulatory review. And again, the research impact framework is applied to all of that.

We have an online research reporting database, where we open that up once a year for three months to allow PIs to submit a variety of information at the program level, listed here, as well as at the project level, and that includes not just the scientific piece, but also how is this supporting our review needs and the expected outcomes and impacts. The work -- the projects are organized around specific aims. We also collect there a lot of administrative information, as well, to help us in the evaluation.

So, in addition to all of these annual things, there's also a cyclic peer review every four years, and that's what we're here to discuss today, which is an external site visit by peer reviews of the individual scientists under review.

The output of the site visit report that you'll be discussing in closed session later becomes part of a larger package that includes also information about the individual's regulatory work and performance, that goes to an internal peer review committee called the Promotion and Evaluation of Researcher Reviewers.

We have two career pathways for scientists, from temporary to permanent. The top track are for independent principal investigators. They start out in the service fellowship program. They're called senior staff fellows or visiting scientists, and they have up to seven years to go through this process.

They need to undergo at least one site visit, and then go through the CPIR review, and then there's an open competition, where they, as well as anybody else, can apply for a position, and if deemed qualified, they'll be hired as a permanent principal investigator.

The support scientist is in the bottom half of the slide, and those are, again, service fellows that come in as staff fellows or visiting associates, and similarly, they go through site visits, CPRR, and open competition before becoming a permanent staff member.

The site visit report that you receive today is a draft report that Dr. McInnes and her team prepared for your review. Today, in closed session, you have three

potential outcomes of your discussion. You can accept the report as written. You can amend the report. Or you can reject the report and send it back to the site visit team.

Once it's approved by the full advisory committee, the final report is really important to us. It's obviously used as part of that internal peer review package. The PIs take the scientific input from these experts very seriously, to improve their research programs, and then of course management takes into account the advice in terms of resource allocation decisions.

So, I'll just finish where I started, with a big thank you to the site visit reviewers, to Dr. McInnes, for her strong leadership of the site visit team, and today, to you for your deliberations. And I'll stop there and answer any questions.

DR. EDWARDS: Any questions? Okay. Would you introduce yourself, Dr. Wharton, please?

DR. WHARTON: I am Melinda Wharton, Center for Disease Control and Prevention.

DR. EDWARDS: So, our next speaker, to introduce an overview of the division of Bacterial, Parasitic, and Allergenic Products, is Dr. Jay Slater, the director of this division.

Dr. Slater.

Agenda Item: Overview of OVRR/DBPAP

DR. SLATER: Thank you very much. Good morning. Actually it's my job to bring you down two steps. Ultimately we're going to be talking about LMPCI. Dr. Wilson gave you background on CBER and CBER's research program. I'm going to bring you through the Office of Vaccines' research program, then the division, and then you'll be ready to hear from Dr. Stibitz about the lab.

OVRR, the Office and Vaccines Research and Review, regulates vaccines, obviously, but also allergenic products, live biotherapeutic products, including probiotics and fecal microbia for transplantation, and phage therapy as well. OVRR's mission is to protect and enhance the public health by assuring the availability of safe and effective vaccines, allergenic products, and related products, and the research program is specifically designed to complement and support the regulatory mission, by focusing on issues related to the development of safe and effective products.

OVRR's core activities -- obviously the main activity is the regulatory part, and that is to review, evaluate, and take appropriate action on INDs, BLAs, amendments, and supplements, for all of these products. We also develop policies and procedures for the premarket review of regulated products. But very importantly, and

what we're going to focus on today, conduct research related to the development, manufacture, and evaluation of vaccines and related products.

Here's our organizational chart. The Office of Vaccines is headed by Dr. Marion Gruber. Her Deputy is Dr. Phil Krause. There are three large divisions within the Office of Vaccines. One of them is the Division of Vaccines and Related Product Applications; that's on the right. In shorthand, we call that the clinical division. That's headed by Dr. Wellington Sun and Dr. Loris McVittie.

There are two research divisions. One of them, on the left, is the Division of Viral Products, headed by Dr. Jerry Weir and Dr. Robin Levis. And the division that we're going to be concerned about today, is headed by me, the Division of Bacterial, Parasitic, and Allergenic products, and my Deputy Director Dr. Drusilla Burns.

OVRR's research goals are to focus on the safety, the efficacy, and the availability of the products that we regulate. And in fact, one of the most newsworthy achievements, in terms of research, really had to do with the availability of menin-J vaccine in Africa several years back. But virtually all of the research projects within the division can be classified as belonging to one of these three research goals.

We like to think of research as particularly important in our part of the FDA. Obviously, research and science is what drives all of FDA's regulatory activities, but we think that there's something particular about vaccines that makes research especially important. There's a tremendous emphasis on safety for vaccines.

These are products that intended for mass use, often universal, the recipients are healthy individuals, often children, and therefore safety is of primary importance. It's also of primary importance because there's a high level of scrutiny by the public of our products. Regulatory decisions really have to be well-grounded in science, and obviously, there are increasing number of groups that are hostile to part of our portfolio, and we have to make sure that our regulatory decisions are absolutely bulletproof.

Keeping pace with technology is critically important. We have to have scientists that are actively involved in science today, to be able to keep pace with that technology, and our model, I think, serves that purpose.

Clearly, as well, we have to be able to respond quickly to public health threats. All of our scientists understand that their projects can be redirected, subverted, if you will, in view of important public health

threats, and certainly antibiotic resistance and C. diff are of primary importance.

We intend our research to be broad. We can't cover everything, and we don't really try to cover everything, but we really try to cover the ground as best we can. We intend it to be highly collaborative, as Dr. Wilson showed, not only within the agency but around the country and around the world. We think the investigator-initiated model is really the best, and we really cherish it, and you will see evidence of that in the report that you'll be reviewing in closed session.

We fully expect our research to be excellent. Our motivation is primarily the regulatory mission, but it is our expectation that our research scientists are members of the broader research community, that their work is recognized as excellent by that community, and by well-known experts in the field. And we expect our science to be flexible. Our scientists work on topics that allow for rapid adaptation in case of emerging threats.

And then finally -- this is my last slide on OVRR -- the researcher-reviewer model is really the core of our research program. It's our expectation that having researchers who are also reviewers and regulators concurrently is going to best integrate the best science into the work that we do.

Let me bring you down to the Division of Bacterial, Parasitic, and Allergenic Products. This is a division that has four labs within it, only one of which you'll be reviewing today. I'm the director. Drusilla Burns is my deputy. The lab that you'll be reviewing is to the lower right, and therefore I'll speak least about that. The three other labs are the Lab of Bacterial Polysaccharides, the Lab of Immunobiochemistry, in which I'm a principal investigator as well, and the Lab of Respiratory and Special Pathogens.

There's no really easy and obvious way to review the portfolios of our division in these labs, but this is an attempt that I've made to do that. If you look at what we do through the lens of the organisms and the products that we regulate, you'll that among the bacteria, we have, in the upper left, noninvasive toxin-producing bacteria -- anthrax, pertussis, botulinum, tetanus, diphtheria, and C. diff.

We have, as well, invasive organisms for which the protective responses seem to be predominantly through their polysaccharides. Obviously, H. flu and Neisseria meningitidis, and Strep pneumo. We have intracellular pathogens -- Francisella tularensis, Mycobacterium tuberculosis. And we have enteric pathogens -- campy, salmonella, shigella. We have parasites -- we focus on

malaria. And we have other and emerging products, Staph aureus, allergenic products, live biotherapeutic products, phage, and other microbiome-related products.

So one way to look at the different labs is to see which organisms they focus on. So, the Lab of Bacterial Polysaccharides focuses, obviously, on the invasive organisms for which the protective responses are the polysaccharides. One of the salmonella typhi vaccines is an injected vaccine and is largely a polysaccharide vaccine, and that is regulated by LBP as well.

If you go the Lab of Immunobiochemistry, that's my lab, we regulate allergenic products. That only makes up one entry in this table. It's a little deceptive, because there are over 1,000 allergenic products, and it's a very varied and rapidly evolving field. But that's the group of products that we regulate.

The Lab of Respiratory and Special Pathogens focuses on the toxin producers in the upper left. The Lab of Respiratory and Special Pathogens is often -- was also tasked, along with LMPCI, which we'll be looking at today, at looking at Staph aureus as an emerging pathogen, and that's a collaborative effort of the two labs.

And finally, the Lab of Mucosal Pathogens and Cellular Immunology, which has a broad and varied palette. One of the investigators focuses on C. diff, in the upper

left-hand corner. There's a major effort focusing on intracellular pathogens in the lower left corner. Obviously, the enteric pathogens in the upper right are a major area of focus.

You might not expect this lab to focus on malaria, but we do. And in the lower right, this lab is actively involved in the two-lab effort in preparing for Staph aureus vaccines but also focuses on the live biotherapeutic products, the phage and the microbiome-related products.

LMPCI is a very large lab. October 25 was an extremely busy day. The Committee heard from nine members of the lab during the course of the day. And I want to add my thanks to Dr. McInnes, and the rest of the Site Visit Committee. It was a lot of hard work, and we all appreciated what you put in on that day and after.

I'll be happy to take any questions.

DR. EDWARDS: I would like to introduce the next speaker, Dr. Scott Stibitz, who is the director of the Laboratory of Mucosal Pathogens and Cellular Immunology, and he will present an overview of LMPCI.

Agenda Item: Overview of LMPCI

DR. STIBITZ: Thank you very much. So, descending through the layers of organization, you've now arrived at your destination. This is the laboratory level. The

laboratory level is the level just above principal investigator.

And I think, at this point, it's reasonable to ask who are we? And I believe answers to that question have multiple levels. At the CBER level, as you've heard in the preceding presentations, I don't think I can improve on that, but just to reiterate, we're bench scientists who also regulate products under FDA jurisdiction.

And, very briefly, what do we mean by regulate? Human clinical trials are done under INDs, which we review. And of course, the ultimate goal is a licensure and an approved product, and we are part of the team that reviews those license applications. As Jay has pointed out, we are laboratory-based as well, and our role in the review of applications is generally based on, or focused on, the product, in terms of manufacturing, but also testing.

Who are we, at the lab level? I tend to think that LMPCI is in this regard like a typical micro-department. Because we're focused on infectious disease, we have both microbiologists and immunologists. LMPCI's research programs are varied, and they relate to the products that we regulate. Primarily to ensure that those products are safe and potent. In other words that they have the potential to be efficacious.

Dr. Wilson just briefly alluded to the issue of potency assays, but this is at the core of determining product potency and efficacy in a reliable fashion. And so I think when I get to the point where we're talking about some regulatory challenges, potency assays will come up again, but this is something we could spend a day talking about. I will now move on.

I think you've very clearly gotten the overall organization of our institution. I want to give you a little bit of lab history, briefly go through our regulatory portfolio, briefly discuss a couple of regulatory challenges, and then just close with some thoughts about our research programs.

As Dr. Slater pointed out, these are LMPCI staff who presented at our October 25 visit. The far-left bullets are the PIs. Dr. Cowley is an immunologist. She's working on methods to predict and improve efficacy of vaccines against bacterial pathogens.

Our newest PI is Dr. Paul Carlson. He's been here about three years now. I think he's working on vaccine development against gastrointestinal pathogens. At least that's what he thought. Since he's come here, his research has really branched out heavily into microbiome-related matters, and he's really a shining star in our laboratory.

For my laboratory, I had four staff scientists or staff fellows presenting -- Dr. Qing Chen, who works on Bordetella pertussis regulation; Dr. Dharmasena, who was evaluating Ty21a as an oral vaccine delivery platform; Dr. Oakley, who works in the field of malaria in terms of biomarkers and preclinical models; and Dr. Stephen Derrick, who was a TB researcher and has spent a lot of time looking at novel vaccination strategies for TB, both in terms of routes of administration, as well as adjuvants; and finally, last but not least, Dr. Karen Elkins, is looking at intercellular pathogens, biomarkers, and from her laboratory, we had Dr. Roberto De Pascalis. So, those are the people who were really addressed in the site visit book that I believe you have access to.

A little bit about LMPCI history. We are a fairly new lab. And we were formed by the merger of two existing labs. The oldest of those was the Laboratory of Mycobacterial Diseases and Cellular Immunology, which was created, I think, before I came 30 years ago, to consolidate review of TB vaccine files. But over the years, research projects were added to address additional regulatory responsibilities in the field of malaria.

The Laboratory of Enteric and Sexually Transmitted Diseases was created de novo in 1993, and one of its purposes was to review a large number of enteric

vaccines we were receiving, but we were also anticipating a spike in the number of STD vaccine applications.

And so, when those two labs -- when the lab chief for LMBCI, the mycobacterial lab, left, I took over as lab chief and we merged these two to form LMPCI. We've had the position that Dr. Morris left open, open for a while. We've had two job searches, and in the last one I think we were highly successful, so successful that we've actually recruited two new PIs. So we have one PI working on malaria, and one on TB. And I'm extremely excited about that.

Just very quickly, our regulatory portfolio in the area of vaccines, as Dr. Slater has outlined, we have TB vaccines. Historically, those have been subunit vaccines, purified proteins, although also some DNA vaccines, when that was all the rage. But more recently, a lot more thought about live attenuated TB vaccines.

Somewhat similarly, in the malaria field, historically those have been subunit or purified protein vaccines, but there's now a lot of activity on live attenuated, attenuated either through genetic alteration or by radiation.

And of course, over the years we've had all of the enteric vaccines. Our two licensed products in our portfolio are both live attenuated -- that's Vivotif for

typhoid and Vaxchora which was licensed last year for cholera. But we also have quite a number of subunit vaccines, and similarly the STD vaccines so far have been subunit vaccines.

But, in recent years we've expanded into the area of therapeutics. First, we were dragged in on probiotics, when people were doing trials with a lot of over-the-counter probiotics, but they met the definition of a drug, and so we had to regulate them, and that was extremely challenging. But more recently we've had sponsors interested in really developing live biotherapeutic products. We toss the term around pharmaceutical grade. But specifically developed for drug indications with attendant attention to CMC issues and also rationally chosen for their properties.

Fecal transplant hit us about five years ago. That's been interesting, so the product here is fecal material. And the kind of evolution of that product is, one way of looking at it is, into defined microbial consortia -- so, trying to understand what it is about fecal material that works to prevent C. difficile infection, and really plucking out the bacterial strains that are crucial and putting those in a more defined product.

And even more recently, we're dealing with bacteriophage therapy. The products that -- the overall product areas that we're looking at are defined products, like defined phage cocktails, but also we're now facing the concept of phage banks for treatment, so you could call this personalized medicine, you can call it the treatment center model, but the idea is that a given patient will be treated with a subset of perhaps thousands of different phage.

And I'll just give two challenges in the CMC regulatory area that I think illustrate the value of our research programs. In the area of live biotherapeutic products, the inherent problem in terms of microbial purity and safety is finding contaminants in a preparation of 10^9 to 10^10 bacteria, and so we've had a research project for a number of years, developing improved tests for microbial purity, by using phage lysins, which most people use to kill the bad bugs and we're using to kill the good bugs, to remove the product bacteria, so that we can see any contaminants in an unbiased and robust fashion.

And in terms of fecal microbiota for transplantation, you can probably imagine that designing a potency assay that is meaningful for FMT is extremely difficult, even though we have the ability to sequence huge

amounts of information. Unless you know how to interpret it, it's not of that much value.

And so, really the holy grail has been to try to determine what bacterial species are really crucial. And Dr. Carlson and Dr. Cowley are collaborating on a project which I'm incredibly excited about. They found that mice with a knockout of MAIT-cells, instead of being, as they had predicted -- because it's an immune defect, more susceptible to C. diff infection -- found out that they're resistant. And so what this means is they now have a reliable source of fecal material that works to prevent C. diff colonization and one that doesn't. And so with that tool they can start to pick apart a species that may actually be responsible.

And then finally, this is my closing slide. I just wanted, because I can't go through all our research programs in the time allotted, I wanted to provide some general thoughts, and these are from the point of view of someone who's worked here for 30-plus years and loves their job.

So, basically, I view our research programs, as all of those in CBER, as providing a cadre of scientists to perform regulatory review who are active in the research fields relevant to the products they regulate, and who are also free of conflict of interest. They allow us to speak

with scientific as well as regulatory authority. They also provide us with state-of-the-art, first-hand knowledge of the areas that we regulate.

They provide expertise to design tests, to assess safety, purity, and potency. And in that way, I think, lead to regulatory decisions that are based on problem solving, not just problem identifying. And finally -- this is a phrase that we use a lot -- they provide for sound scientific judgment that addresses the technical feasibility of the things that we request of sponsors, and therefore provide an ability to separate need-to-know, versus nice-to-know.

And I'll stop there. Thank you.

DR. EDWARDS: Thank you, Scott. Are there questions?

Yes, Paul.

DR. OFFIT: Just one quick question. I hadn't realized that the FDA regulated probiotics. Is that -- do you hold probiotics to an efficacy standard?

DR. STIBITZ: It's an area that spans different centers within the agency. It depends on whether the intended use is to treat a disease. So, CFSAN, the Center for Food Safety and Nutrition, regulates them as dietary supplements. But the claims that they can make are limited. If they want to -- if a clinician, for example,

wants to study even an over-the-counter probiotic to prevent, say, antibiotic-associated diarrhea, it's now legally a drug, and that's when we step in.

DR. EDWARDS: Any other questions?

Thank you very much. So we will now go into closed session.

(Break.)

Agenda Item: Topic II: Strain Selection for the Influenza Virus Vaccines for the 2018-2019 Influenza Season

DR. EDWARDS: We are going to begin Topic 2 of this meeting today: the strain selection for the influenza virus vaccines for the upcoming influenza season. We will begin first with Ms. Hunter-Thomas, reading the housekeeping and conflict of interest statement.

I guess since some of the people in the audience were not here when we introduced ourselves at the beginning then we will go around one more time and introduce ourselves.

Len, can you start please?

DR. FRIEDLAND: Good morning. Dr. Leonard Friedland, the Alternate Industry Representative, pediatrician, vaccine researcher.

DR. KATZ: Good morning. I am Jackie Katz from the Influenza Division, CDC.

DR. OFFIT: I am Paul Offit from Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine.

DR. MONTO: Arnold Monto, University of Michigan, School of Public Health.

DR. MCINNES: Pamela McInnes, Deputy Director of the National Center for Advancing Translational Sciences at the NIH.

DR. EL SAHLY: Hana El Sahly, Baylor College of Medicine.

DR. EDWARDS: Kathy Edwards, Vanderbilt University.

DR. BENNINK: Jack Bennink, NIH, NIAID, Viral Immunology Section.

DR. BOK: I’m Karin Bok, National Vaccine Program Office, HHS.

DR. WIESEN: Andy Wiesen., Office of the Secretary of Defense for Health Affairs, Health Readiness Policy and Oversight.

MR. TOUBMAN: Sheldon Toubman, Consumer Representative with New Haven Legal Assistance Association.

DR. WEIR: Jerry Weir, Division of Viral Products, CBER.

DR. GRUBER: Marion Gruber, Office of Vaccine, CBER.

DR. EDWARDS: Holly, would you introduce yourself too please on the phone?

DR. JANES: Holly Janes, a biostatistician at Fred Hutchinson Cancer Research Center.

DR. EDWARDS: Thank you very much. Serina, would you please read the conflict of interest and housekeeping statements?

Agenda Item: Conflict of Interest Statement

CAPT HUNTER-THOMAS: Yes. Also, I would first like to check if Dr. Lisa Grohskopf is on the line.

(No response)

Good morning everyone again. My name is Captain Serina Hunter-Thomas and it is my pleasure to serve as the designated federal officer for the 151st VRBPAC meeting. The Committee Management Specialist for this meeting is Ms. Rosanna Harvey along with Joyce Mercer-Dickens. The Committee Management Officer for this meeting is Ms. Jeanette Devine. We also have Dr. Prabhakara Atreya in the room and Ms. Asea Brown in the room.

On behalf of the FDA, the Center for Biologics Evaluation and Research and VRBPAC, we would like to welcome everyone to this meeting.

The Food and Drug Administration is convening today, March 1, 2018, for the 151st meeting of the Vaccines and Related Biological Products Advisory Committee under

the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all participants of the Committee are 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.

Under Topic II at this meeting, the entire meeting is conducted in the open session during which the Committee will discuss and make recommendations on the selection of strains to be included in the influenza virus vaccines for the 2018 to 2019 influenza season. This topic is determined to be a particular matter involving specific parties or PMISP.

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

208, their employers. These interests may include investments, consulting 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 conflict of interest. However, based on today's agenda, an all financial interest reported by members and consultants, no conflict of interest waivers were issued under 18 US Code 208.

Dr. Friedland is currently serving as the alternate industry representative for this meeting. Dr. Friedland is employed by GlaxoSmithKline. Industry representatives act 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 do not participate in the closed sessions 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 voting members of the Committee. Hence, they do participate in the closed sessions and do have voting privileges.

At this meeting, there may be 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 conflict of interest.

The FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms as products and if known its direct competitors. We would like to remind members, consultants and participants that if the discussions involve any other products of 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 final reading of the conflict of interest statement for the public record related to Topic II. Thank you.

DR. EDWARDS: Thank you very much. We will begin this very important meeting with a presentation and an introduction by Anissa Cheung, regulatory coordinator of the Division of Viral Products and the Office of Vaccines Research and Review at CBER.

Agenda Item: Introduction

MS. CHEUNG: Good morning everyone. I would like to introduce the topics of today's VRBPAC meeting is for the strain selections for influenza virus vaccines for the 2018 and 2019 season.

The purpose of today's VRBPAC's meeting discussion is to review influenza surveillance and epidemiology data, also antigenic characteristics of recent virus isolates, serological response to current vaccines, and the availability of the candidate vaccine strains and reagents.

After you review all those data and at the end of the discussions, the Committee will be asked to make recommendations for strains of influenza A, which includes H1N1 and H3N2 and B viruses to be included in the 2018 to 2019 influenza vaccines licensed for use in the United States.

You are going to hear several presentations. And the types of analyses that are used for vaccine strain selections include epidemiology of circulating strains. CDC will have a presentation on the surveillance data from the US as well as around the world.

You will also hear antigenic relationships among contemporary viruses and the candidate vaccine viruses. You will help a couple of talks from CDC and also DoD. And the methods and techniques that will be used to assess the antigenicity includes hemagglutination inhibition tests using post-infection ferret sera, also the hemagglutination inhibition tests using panels of sera from humans receiving recent inactivated influenza vaccines. You will also hear data from the virus neutralization tests, the antigenic cartography, phylogenetic analyses of the HA and NA genes. You will also hear vaccine effectiveness report.

As you may know, there are challenges for vaccine strain selection. First of all, the vaccine effectiveness depends on the match between the hemagglutinin of the vaccine strain and the circulating virus strain. Antigenic drift of hemagglutinin is continuous both for influenza A and B viruses, but the antibody of hemagglutinin correlated with vaccine efficacies.

Also, the timelines for influenza vaccine production are relatively fixed. Usually the strain

selection occurs in February or March, and it is necessary in order to have the vaccines for subsequent northern hemisphere season to be available.

Also, the time manufacturers have to begin productions of monovalent bulk of one of the strains before strain selection is being recommended. They have to do it at risk in order to make sure that the vaccines will be available for the coming season.

Also, the availability of the reference strains, which we also call the candidate vaccine viruses. The suitability of the vaccine strain for vaccine manufacturer is very critical too. The vaccine production depends on the growth properties of the strain and the strain have to grow well and have adequate HAUs for vaccine manufacturers.

In addition, strain-specific reagents are needed for potency determination for inactivated vaccines as well as the recombinant protein vaccines.

I would like to show you this table to illustrate a very tight production timeframe of the seasonal influenza vaccines starting from surveillance to the administrations of the vaccine to the general public. As you can see, after the selection of the strain, there are multiple steps, which increase the generation of the candidate vaccine virus, productions of the reference reagent, and also productions of the monovalent bulk as well as formulations

into the final vaccines. And those vaccines also have to be released by the agency. And those steps really takes time. It takes several months after the strain selections before it can be distributed to the market for general public use.

For the candidate vaccine virus that are used for the production of the inactivated influenza vaccines are traditionally egg isolated. And the antigenicity is characterized by the WHO collaborating centers.

Starting in August 2016, the use of MDCK cell isolated candidate vaccine virus was approved for the manufacture of Flucelvax monovalent bulk, which is a cell-based influenza vaccine. This cell derived candidate vaccine virus is manufacturer specific. The CVV is derived from two approved WHO collaboration centers. The antigenic analysis is performed as the same way that was performed for the egg isolated vaccine virus strain.

The working virus seeds are approved for quality as well as safety by the National Regulatory Authorities.

Due to the co-circulations of the two antigenically distinct lineages of influenza B viruses represented by B/Victoria lineage and B/Yamagata lineage, the quadrivalent influenza vaccines have been approved for several years. Currently, we have seven quadrivalent vaccines licensed in the US, but both trivalent and quadrivalent influenza vaccines are available. Based on the

2017 and 2018 data, about 75 percent of the influenza vaccines are marketed as quadrivalent.

The current process for selecting appropriate B strains for inclusion in the trivalent and quadrivalent vaccines is similar to what have been done for the trivalent vaccines. We will have WHO and VRBPAC review the data and make recommendations for each formulation for both the trivalent and quadrivalent.

I would like to have a quick recap of the previous recommendations of the influenza vaccine compositions for the 2017 and 2018. We had the VRBPAC meeting on March 2017 last year, and the VRBPAC recommends the following strain for the 2017 and 2018 influenza virus vaccines. For H1N1, it is an A/Michigan/45/2015 (H1N1)pdm09-like virus.

For H3N2, it is an A/Hong Kong/4801/2014 (H3N2)-like virus. For trivalent vaccines, the B strain recommended B/Brisbane/60/2008-like virus from the Victoria lineage. For quadrivalent vaccines include about three viruses as well as a B/Phuket/3073/2013-like virus, which is from Yamagata lineage.

VRBPAC also had another meeting held on October 2017 to give recommendations for the antigenic composition of influenza virus vaccines for the southern hemisphere 2018. The recommended strain A/Michigan/45/2015 (H1N1)

pandemic 09-like virus. For H3N2, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus. For trivalent vaccines, they recommend a B/Phuket/3073/2013-like virus from Yamagata lineage. For quadrivalent vaccines, contained about three viruses as well as B/Brisbane/60/2008-like virus, which is from Victoria lineage.

Right now, for this – actually, the WHO has a meeting, just a little bit a week ago, on February 22, 2018. They give recommendations for influenza virus composition for the northern hemisphere 2018 and 2019. And the following strains are being recommended. For the H1N1, an A/Michigan/45/2015 (H1N1)pdm09-like virus. There is no change from the 2017 and 2018 Northern Hemisphere recommendation. For H3N2, they recommend an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus. There is a change from A/Hong Kong/4801/2014 (H3N2)-like virus, but same as 2018 Southern Hemisphere recommendation.

For trivalent, the recommended B strain is a B/Colorado/06/2017-like virus, which is from a B/Victoria lineage. It is a change from the B/Brisbane/60/2008-like virus vaccine recommendation.

For quadrivalent vaccines, they recommended containing about three viruses as well as a B/Phuket/3073/2013-lke virus, which is from the

B/Yamagata). There is no change from the 2017-2018 recommendation.

As in previous years, national and regional control authorities have to approve the composition and formulations of vaccines used in each country.

Now, I would like to let you know that at the end of the discussion, the Committee will be asked to decide the influenza strains which need to be recommended for the antigenic composition of the 2018 and 2019 influenza virus vaccines in the US.

I would like to show you the options for the strain composition for the 2018 and 2019 trivalent influenza vaccines.

For influenza A, the H1N1 strain, you can either recommend an A/Michigan/45/2015 (H1N1)pdm09-like virus or recommend an alternative H1N1 candidate vaccine virus.

For influenza A (H3N2) subtype, you can either recommend an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus or recommend an alternative H3N2 candidate vaccine virus.

For influenza B, you have three choices. You can recommend a B/Colorado/06/2017-like virus, which is from B/Victoria lineage or you can recommend an alternative candidate vaccine virus from the B/Victoria lineage or you

can recommend a candidate vaccine virus from the B/Yamagata lineage.

The options for the quadrivalent vaccines for the second B strain also have three choices. Either recommends inclusion of a B/Phuket/3073/2013-like virus from Yamagata linear or recommend an alternative candidate vaccine virus from the Yamagata lineage, or recommend a candidate vaccine virus from the B/Victoria lineage.

Before I end my talk, I would like to freshen up the voting questions that the Committee will be asked to vote at the end of the meeting. Thank you.

DR. EDWARDS: Thank you. Are there any questions? Thank you very much.

Dr. Shane, I think we missed you. If you could introduce yourself that would be great.

DR. SHANE: Andy Shane. I am at Emory University and I represent pediatric infectious disease.

DR. EDWARDS: Thank you very much.

The next report will be from Dr. Lisa Grohskopf at the CDC. She will present information on US influenza surveillance and interim estimates of vaccine effectiveness for 2017 through 2018.

Agenda Item: US Surveillance

DR. GROHSKOPF: Thanks everyone. Good morning. I am going to move on to Slide 2. I am going to cover three

things. US surveillance. This is from the CDC FluView Systems and it will be current as of Week 7 of the calendar year, which is February 17 of 2018. And as summary of interim 2017 and 2018 influenza vaccine effectiveness estimates from the US Flu VE Network. And then finally, I have a very brief update from the Influenza Session at the most recent ACIP meeting, which occurred on February 21.

I am going to be starting with US surveillance. First with influenza positive test results reported to CDC. These come from both clinical laboratories and public health laboratories and are presented separately.

These are clinical laboratory results. In general, for the clinical laboratories, subtype and lineage determinations are not made. For the most part, these results are just reported as influenza A or influenza B. Colored bars, yellow for influenza A, and green for influenza B, represent the numbers of positive specimens. The different lines at the top black, the percent positive specimens for any virus, the middle line, yellow black dotted line, percent positive for flu A, and the bottom line, green and black, is percent positive for flu B.

Overall, you can see that A is in yellow have predominated the season. But in recent weeks, the proportion of influenza B viruses has increased. We also see that the percent of specimens positive for flu B is

increasing while the percent of A has started to decrease over the last several weeks.

These are similar results from the same system, but these come from the public health labs, which generally do perform typing and lineage determinations on specimens. We have more colors in this graph than in the last one.

H3N2 viruses in red had predominated the season. There is also still however some circulation of (H1N1)pdm09, which is shown by the orange, almost at the top of the bars.

With regard to influenza B viruses, the two shades of green at the bottom of each bar represent those for which we have lineage determinations and from this, we can see that we have mostly been seeing B-Yamagata lineage viruses among the Bs.

Next, we will cover some genetic and antigenic characterization results. This first slide summarizes genetic characterization results for specimens submitted to CDC. The pie chart on the left provides an overview of the relative proportions of each virus type and subtype reported by the public health laboratories. The sets of charts on the left and the gray box summarize the results for each type – subtype or lineage of the genetic testing for each type or subtype or lineage just for the subset of specimens that were submitted to CDC for genetic testing.

Starting in the upper left, phylogenetic analysis of the HA genes for 779 A(H3N2) viruses revealed some genetic diversity with multiple clades and sub-clades co-circulating. The HA genes of most circulating viruses belong to Clades 3C.2a, but we also had some sub-clades 3C.2a1 and 3C.3a.

In the upper right for (H1N1)pdm09, of 350 specimens all belong to Clade 6B.1.

In the lower left, of 68 B Victoria lineage viruses, all HA genes belong to genetic Clade V1A, which is the same clade as the vaccine reference virus B/Brisbane/60/2008. However, a number of viruses had a 6 nucleotide deletion encoding amino acids 162 and 163. These are the ones called V1A-2 delete or V1A-2Del in the HA.

In the lower right, phylogenetic analysis of 402 influenza B Yamagata lineage viruses indicated that all belong to Clade Y3.

Antigenic characterization of the flu virus submitted to CDC. This covers viruses submitted from October 1 to the present. For A(H1N1)pdm09, all 268 viruses antigenically characterized using ferret post-infection antisera were antigenically similar to the reference 6B.1 virus A/Michigan/45/2015-like, which is the H1N1 component of the 17-18 vaccine.

For A(H3N2), 364 of 371 or 98.1 percent were well inhibited by ferret antisera raised against A/Michigan/15/2014, a cell propagated A/Hong Kong/4801/2014-like reference virus representing the H3N2 component of the 2017-18 vaccine.

As of February 9, 2018, 64.4 percent of viruses tested were well-inhibited by ferret antiserum raised against the egg-propagate A/Hong Kong/4801/2014 reference virus.

This is now antigenic characterization for the B viruses. For B/Victoria, 23 of 51 or 45 percent reacted poorly with ferret antisera raised against cell propagated B/Brisbane/60/2008 reference virus, which represents a B component in both quadrivalent and trivalent influenza vaccines for the 2017-18 season and these viruses had the V1A-2Del HA.

For B/Yamagata lineage, all 260 were antigenically similar to the cell propagated B/Phuket/3073/2013 reference virus, representing a B component of the quadrivalent influenza vaccines for the current 2017-18 season.

This is a discussion of ILI activity. It is a summary of data from ILINet, which is a network of providers who report weekly to CDC, the percent of visits

that were for influenza-like illness so not lab-confirmed influenza illness, but influenza-like illness.

This chart depicts the percent of visits for the current season in the red line with the triangles as well as for selected other seasons. For Week 7, the percent of visits that were for ILI declined by about 1 percent from 7.4 percent, which was in the previous week, to 6.4 percent for Week 7. It is still, however, well above the national baseline, which is shown by the dotted line going horizontally across the graph and has been above baseline for 13 weeks as of Week 7.

This is a summary of laboratory-confirmed influenza associated hospitalization data for this season from FluSurv-NET, which is a population-based surveillance network for lab-confirmed influenza associated hospitalizations. These data are collected from 13 states and represent approximately 9 percent of the total US population. The data are cumulative. As the weeks go on and we have more hospitalizations on the X-axis, we would expect the lines to go up over the course of the season. On the Y-axis, we have the rate of hospitalizations per 100,000 population.

Since October 1, 2017, a total of 21,279 lab confirmed flu hospitalizations were reported to this

network, translating into a cumulative overall rate of 74.5 hospitalizations per 100,000 people in the United States.

The highest rate of hospitalizations is among those 65 years and older at 322.7 per 100,000, followed by those 50 through 64 years at 79.9 per 100,000 and youngest children ages 0 to 4 years at 52.6 per 100,000. During most seasons, adults 65 and older have the highest hospitalization rates usually followed by children 0 to 4 years.

These rates in general are higher than the end-of-season rates for the 2014-2015 season. For that season, overall hospitalization was 64.2 per 100,000. For people 65 and older were 308.8 per 100,000. The hospitalization rate for people 50 to 64 years for that season was 53.4 per 100,000 and for 0 through 4 years were 57.3 per 100,000.

Next is pediatric mortality. Pediatric deaths and association with lab confirmed influenza have been reportable since 2004. As of Week 7 for the current season, a total of 97 deaths have thus far been reported. Of these, 69 or 71 percent were associated with flu A and 27 or 28 percent with influenza B. And the last one – we have no information on type or subtype. That was not reported.

This is the map that appears in FluView each week during the season, summarizing weekly flu activity estimates as reported by state and territorial

epidemiologists. This information describes the distribution and spread of influenza activity and is not an index of disease severity. We can see here from the color of the map – most of the map is brown – that widespread activity was still being reported throughout much of the country. More specifically, Puerto Rico and 48 states were still reporting widespread activity for Week 7.

Just a summary of surveillance. Influenzas A(H3N2) viruses have predominated during the season; however, influenza B activity is increasing. ILI activity dropped from 7.4 percent in Week 6 to 6.4 percent in Week 7, but remains higher than peak activity observed in many past seasons and are the highest seen since 2009.

Final severity cannot be determined until the end of the season. But for adults, hospitalization rates and mortality could be similar to or exceed those seen during the 2014-2015 season.

The majority of circulating strains are similar to those contained in the 2017-2018 vaccine. The B/Victoria lineage viruses are the only viruses clearly showing drift, but – proportion or 1 percent of circulating viruses.

This is the beginning of the VE discussion. These are data from the US Flu VE Network, which were presented by Brendan Flannery at the ACIP meeting last week. I think a lot of folks are probably familiar with the general

methodology, but I will cover it briefly. This slide summarizes the sites. We have a total of five sites spread through the United States in Washington, Wisconsin, Michigan, Pennsylvania, and Texas.

Slide number 15 is an overview of methods. Enrollees are outpatients aged at least six months with acute respiratory illness and cough of less than or equal to seven days duration.

Dates of enrollment for this particular installment of the data are November 2, 2017 through February 3, 2018. The design of the test-negative case control design, which involves comparing vaccination odds among influenza RT-PCR positive cases and RT-PCR negative controls.

Vaccination status is defined as receipt of at least one dose of any 2017-2018 seasonal flu vaccine according to medical records, immunization registries, and/or self-report.

For analysis, VE is calculated as one minus the adjusted odds ratio times 100 percent. Adjustments made include study site, age, self-related general health status, race and/or Hispanic ethnicity, interval from onset to enrollment, and calendar time.

Slide Number 16 starts discussion of results. Total of 4562 were enrolled from November through February

3 at the five sites, 1712 specimens were RT-PCR positive, and 2850 were RT-PCR negative.

The chart at the bottom of the graph summarizes what was seen in terms of viruses. We see, not inconsistent with what we were seeing in the surveillance data, a predominance of the H3N2 virus is shown in red at just about two-thirds of the total. But we also have about 12 percent of A/H1N1 pdm09.

By week on the X-axis, the number enrolled and also the percent of positive specimens, the number enrolled and whether they were flu positive or flu negative is shown by the gray and yellow bars. You can see that after about Week 49 so approximately mid-December, we have a steady increase in the proportion of specimens that were positive, the number of positives. And that has continued pretty much through the end of the period. You can see the bars at the last section there. For Week 5, we are a little shorter. But I should just mentioned that that is probably not complete data because the Week 5 data includes only patients who had complete laboratory testing at that point. We really do not have complete information on everyone for Week 5. That should not be interpreted as a decline.

Slide Number 18, beginning of the VE estimates. This is interim-adjusted vaccine effectiveness against medically attended flu by age group for all flu, all A or B

for 2017-2018 as of February 3. Overall adjusted VE was 36 percent with a 95 percent confidence interval of 27 to 44 percent. When we break these results down by age group, we have statistically significant VE for those six months through eight years of age at 59 percent and for those 18 through 49 years of age at 33 percent.

We are going to begin to break these out a little bit by type and subtype. Unfortunately, when we do this, of course, we end up with wider confidence intervals because our sample size gets smaller. This first one is for H3N2, which was proportion-wise the most common type isolated.

Overall, VE for all ages is 25 percent. Confidence intervals are 13 to 36 percent. Here, for the H3N2s, we have statistically significant results only for the youngest age group, six months through eight years at 51 percent. We do not have statistically significant VE for the others.

And for the next slide, Slide 20, this is for A/H1N1 and for all B's, both subtypes. No lineage distinguishing for the B's. It is all B's.

For A/H1N1 pdm09, overall VE is 67 percent and statistically significant. We actually have statistically significant VE across the age groups except for those 60 and up. We have for 6 months through 17 years, 78 percent,

18 through 64, 51 percent, 65 and older, 34 percent and not statistically significant.

For influenza B overall for all age groups, 42 percent and statistically significant, 6 months through 17, 36 and statistically significant, 18 through 54, 50 and statistically significant, 65 and up, not statistically significant.

Summarize the VE interim results. Interim results for the 2017-2018 season through February 3 indicate vaccination reduced influenza medically attended illness by 36 percent. Twenty-five percent and significant VE against H3N2 for all ages. Fifty-one percent and statistically significant for children aged 6 months through 8 years. No other age groups had statistically significant VE estimates. Sixty-seven percent, 54 to 76 percent, VE for A(H1N1)pdm09 and 42 percent, 25 to 56 percent, VE against B, mostly B/Yamagata, which was not in the IIV3.

Final VE results will be shared at the end of the season. Final VE will be used once available to calculate averted burden in terms of cases, hospitalizations, and deaths. Despite the VE results not being particularly high, just a reminder that vaccination even when VE is not optimal averts thousands of hospitalization each year. During 2014-2015, 47,000 approximately influenza hospitalizations were estimated to have been averted.

I just want to acknowledge all the contributors to the VE Network.

Lastly, very brief summary of the ACIP meeting, the majority of which focused on the discussion of LAIV. Data presented very briefly were from MedImmune, who described the US Pediatric Shedding and Immunogenicity Study data.

We also had a discussion of two CDC analyses, one of combined US patient-level data analysis for the 13-14 through 15-16 seasons and the other is a systematic review and meta-analysis of published estimates of LAIV effectiveness in children.

After a fairly lengthy discussion of the data, the ACIP vote occurred and the language and summary that was approved states that for the 2018-2019 seasons, providers may administer any licensed, age-appropriate influenza vaccine including IIV, RIV, and LAIV. LAIV4 is an option for influenza vaccination for persons for whom it is otherwise appropriate.

I just want to thank team members who got these information together to present. That is all I have. I am happy to take questions.

DR. EDWARDS: Thank you, Lisa, for a very enlightening presentation.

Let me ask a quick question. It looks like that the majority of the B strains are Yamagata this year. Is that correct?

DR. GROHSKOPF: Yes.

DR. EDWARDS: Does it look like the B strains that are continuing to increase now are of that lineage as well?

DR. GROHSKOPF: As far as I know, that is correct. It has been pretty consistent just looking at the data on Slide 4, which was the public health lab data. It is always difficult to predict what is going to happen in the coming weeks. But those data for the B's have looked fairly consistent over the course of the season even when the overall B prevalence was lower, that relatively few Victoria's were present. Dr. Katz may have some additional comments on that.

DR. KATZ: Thanks Lisa. You are right. It is the B/Victoria's that are being very low throughout the season. We are not really seeing an upward trend at least at this point.

Hana.

DR. EL SAHLY: This is a question regarding the antigenic characterization of the H3N2 circulating ones. Are we still detecting this season the mutation and antigenic determinant site B with the T160K, I think is what it is called.

DR. KATZ: I will be talking about that in just a moment.

DR. EDWARDS: Any other questions of Lisa in terms of surveillance or VE?

DR. JANES: May I ask a question? Lisa, can you tell us what if anything is known about the generalizability of the genetic test results? I guess I am asking both in terms of the surveillance data and the VE distribution of genetic test results. On what basis is it determined that kinetic testing is done and what are the implications for generalizability?

DR. GROHSKOPF: I know a little bit about what is submitted for testing, but it might be better actually for Dr. Katz to respond to that.

DR. KATZ: Could you repeat the question?

DR. JANES: I am wondering about the generalizability of the genetic test result data. On what basis is it determined as a site level when the genetic testing is done and what can we best conclude about the generalizability of the genetic test result data?

DR. KATZ: The genetic testing is really done – CDC has set up three national reference public health labs that are national reference influenza centers. By region, the viruses from the public health laboratories are sent to one of these three national influenza reference centers.

There is one in California, one in Wisconsin, one in New York. They all use the CDC protocol and have been trained and have done proficiency testing. Then some samples also come to CDC.

All of the sites are testing in exactly the same manner. The viruses that are received come into the system through a process that we have called right sizing. We have gone to great lengths to get viruses that are representative of the regions, but also that equally represent the circulating viruses. We may over sample in the case of the B(Victoria) this year, but it is so that we can look for antigenic variation. We have calculated a certain threshold of viruses that we need to receive from each state or other site every two weeks. There is a very systematic process in which we sample the viruses and we determine the genetic characteristics.

Does that answer your question?

DR. JANES: Yes, thank you.

DR. BENNINK: Has there been any observed differences in the pathogenicity or something of the B deletion viruses?

DR. KATZ: Not that we have been able to detect.

DR. FRIEDLAND: Lisa, Len Friedland. Thank you for that overview. I am just wondering if you could comment if the database will have enough power at the end of the

season to report out on efficacy both by individual strain based on the type of vaccines that were given, also by age and by underlying comorbidities.

DR. GROHSKOPF: That is a good question. I think we always hope for that, but we really generally do not know until the end of the season.

DR. EDWARDS: Other questions? Thank you very much.

DR. GROHSKOPF: Thank you.

DR. EDWARDS: The next presentation will be the world surveillance and virus characterization by Jackie Katz. Jackie is the deputy director of the Influenza Division and also the director of the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza for the National Center for Immunization and Respiratory Diseases from the Centers for Disease Control and Prevention.

Agenda Item: World Surveillance/Virus Characterization

DR. KATZ: What I am going to talk to you about this morning is the representation of the data that was analyzed last week in Geneva at the Vaccine Consultation Meeting. The WHO Collaborating Centers together with over 140 national influenza centers, the essential regulatory laboratories and other specialized laboratories form the

basis of the Global Influenza Surveillance and Response System, which conducts year-round surveillance for influenza viruses.

Last week, the WHO Consultation reviewed all of the data provided by the collaborating centers, by the ERLS and selected national influenza centers and other specialists. The meeting was co-chaired by Kanta Subbarao and John McCauley. These are the rest of the advisors. Richard Webby from St. Jude is missing there. We had the 9 advisors and 30 observers that also contributed to the discussion.

Starting with the global circulation pattern of influenza viruses in the last several months since September 2017, you can see the increase here at the end of 2017 and the beginning of 2018. The orange color of the B influenza viruses and the multiple shades of blue are the influenza A viruses. It was quite a mixed season. There was H3N2, H1 and B's all co-circulating.

This is really demonstrated well here. You can see in the Northern Hemisphere in North America, influenza A and particularly H3N2 virus has predominated whereas in Europe and in the Middle East and Asia, it was more of a mixed season with in many cases, B appearing early, which is unusual and then having some H1 and other influenza A viruses coming in later. And then in other places,

particularly in the Middle East in the Indian subcontinent and parts of Asia, there was quite a bit of H1N1 activity. It was unusual that multiple influenza A and B viruses were circulating, but nevertheless, there was quite a lot of severe disease in many parts of the world.

This diverse season is reflected in the increasing number of samples that are brought in through the GISRS network. This figure shows the number of specimens processed each week. We are well over 100,000. You can see the black line that is 2017, which is higher than 2016 and higher again than 2015. The red is 2018. Each year the numbers of viruses are increasing. This also reflects the high level of activity globally in the last few months.

Many parts of the world contributed viruses for the review of genetic and antigenic analysis for the last six months since September. When broken down, the predominance was still influenza A shown in the blue color with about a third of the viruses being influenza B. And among the H1's, there was still more H3's that were evaluated in the system than H1's.

This represents the viruses that actually came into the collaborating centers and were evaluated antigenetically and genetically in the last three periods with the green being the timeframe since September. You can

see an increase in the B activity, also with H3, but not as high as in previous timeframes.

I will start with the characteristics of the H1N1 pdm09 viruses. This is just a heat map of the circulation of viruses or the activity level of viruses. It reflects – the shading of red indicates the more widespread, the outbreaks reported in that geographic region. Quite a lot of activity in Northern Africa, parts of Europe, and in Asia.

This is what we call our meta-tree. I hope you can see better than I can. I can hardly see these. But in general, there are just a few points to show you. Every little dot is a node. It is a virus. It is color coded by the region of the world. You can see the blue here is North America and green is Europe. You can see most of the viruses are coming from this region. The pink reflects the Middle East and Western Asia region.

But essentially, all these viruses we are seeing with very few exceptions, remain in the genetic subgroup 6B.1, which is demonstrated here. The vaccine virus for the 2017-2018 season is the Michigan 45 virus shown at the base of this tree. And all of the recent viruses have an accumulation of a few key amino acids. They are shown down here if you can see them. Changes at residue 74, 295, and particularly this 164 change. And what H1N1 viruses appear

to be doing at the moment is they are accumulating a few key changes and it just sweeps through almost all of the circulating viruses, suggesting that there is some selective advantage to do that.

In addition, we are seeing the introduction of a change at 183 sporadically popping up in different regions particularly in some viruses here from North America. And then there is another group here, particularly viruses circulating in Europe that have a change at 120.

Turning the neuraminidase, there is really not a whole lot to remark upon here. Again, they are all in the 6B.1 region. This is a smaller phylogenetic tree of the neuraminidase gene. And the viruses here, which are represented by their name are colored coded for the months of the year that they are isolated. You can see the oranges and pinks are the most recent December and January viruses.

All of the, again, of the most recent viruses have a substitution at 449D, but again that is not thought to be antigenically significant, but there is very limited data on that.

Turning now to the antigenic profile of these viruses and this is a complicated table. I will just walk you through how we do this. It is a hemagglutination inhibition table. We use selected reference viruses that

represent the different genetic groups that are currently circulating.

Across the top, we have ferret antisera that are raised to these viruses. Ferrets are infected, naturally infected with the virus. We are looking at a very strained specific antibody response that they produce.

Then we test across the top as our reference panel. And the corresponding homologous titer of the reference virus with its own sera is highlighted and underlined.

First of all, the top columns highlighted here in yellow are the antisera raised to the current Michigan 45 reference virus, both the virus propagated exclusively in cells and one propagated in eggs. We look at the antisera raised to the vaccine virus and look at how well it can inhibit circulating viruses. Here, in this table, we have viruses from the US, from Canada, Oceania, Asia, and a few from Africa.

You can see that without exception in this case that all of these viruses are well inhibited at titers that are generally within two-fold of the homologous titer whether it is the antisera raised egg or to cell.

If we raise antisera to more recent viruses, this is the – never mind. This is not the right table.

We have also seen with more antisera raised to more recent viruses that – and these are viruses that contain the substitutions I was talking about that we see exactly the same profile. We are not seeing when we look at ferret reference antisera, we are not seeing any antigenic variation at all for the majority of circulating viruses. There are rare exceptions and they have unique genetic changes that we know are associated with low inhibition in this case.

We also use panels of human pool sera routinely. Over here on the far right are pooled sera from humans that received – these are adults who received the 2017-2018 vaccine, which contained the Michigan 45. You can see the homologous titers to the Michigan viruses here in the order of 320 and 640. That is pretty much the same titer that we are seeing all the way down for all of these viruses, suggesting that the vaccine antibody is well inhibiting the majority of circulating viruses.

We can look at this in a different way and just visualize it using antigenic cartography from our colleagues at Cambridge University. And here, you can see the yellow dots represent viruses that have circulated in recent months. You can see this cloud around the Michigan 45 2015 vaccine like virus. This cloud really is not

moving, indicating that we are still seeing antigenic similarity with this vaccine virus.

This is the summary of all results of all the data from the different collaborating centers. First of all, we are comparing how well the circulating viruses reacted with serum raised against the Michigan 45 virus grown in cells. You can see overall that 99 percent of viruses were antigenic similarly with very few viruses being antigenically low.

If we compare also with antisera raised against the egg propagated Michigan 45, we get the same result. Ninety-eight percent viruses are antigenically similar.

The last thing we do for our antigenic characterization of the seasonal viruses is look at how well panels of human sera from individuals that are being vaccinated with the current vaccines are covering the circulating viruses. This is just a snapshot of the different sera that were tested by different collaborating centers and essential regulatory labs. Each group probably only tested several panels, but not all of them. But in combination, all of these panels were tested from these different populations and included pediatric samples, samples from younger adults and older adults and elderly.

This is a summary of all of that data put together. Here, we are comparing – these are the panels

from adults in blue, the older adults, the 65 and older age group, and then the children in the pale purple color.

Here, we are comparing the response of the panels of sera, the geometric mean titers, to the cell propagated Michigan 45 2015 as reference because the majority of our circulating viruses that we use to test are also grown in cells and that is the most appropriate comparator.

You can see that by and large each of the panels has geometric mean titers to different circulating viruses that are not significantly different from the reference virus, the Michigan 45 vaccine like virus. That can be seen here in summary for all of the viruses tested.

In summary for the (H1N1)pdm09 viruses, the activity overall globally was higher than in the 2016-2017 season. They were quite substantial outbreaks reported from Africa, Asia, the Middle East, and parts of Europe. And the vast majority of the HA gene sequenced belonged to the phylogenetic subclade 6B.1, which is what we have been seeing for the last couple of seasons with the addition of these three key substitutions in the HA and almost all of the viruses had these.

Almost all of the currently circulating viruses were antigenically similar to the reference vaccine viruses whether they were propagated in eggs or in cells. That is the Michigan 45 2015 vaccine virus. When we looked at human

sera post-vaccination panels, the geometric mean titers of these panels against the most recently circulating viruses tested were not significantly reduced compared with the cell propagated reference virus Michigan 45. That is an easy one.

Here comes H3N2. A little more complicated. There was quite a lot of H3N2 circulation in the Northern Hemisphere primarily this season, but also you can see some local to regional activity in many other parts of the world. And the intense widespread outbreak here in Australia really reflects the tail end of their Southern Hemisphere season, which went into October.

Again, this is a large mega-tree, as we call it. It is set out the same way. Each little dot is a virus. It is colored coded by the region of the world where the virus was obtained. Along here is the month of the year starting in September through January. Each bar represents a virus. You can see a heavy load of blue here, which represents the North America season. There still continues to be extensive genetic diversity in H3N2 viruses.

The WHO collaborating centers felt that in order to be able to communicate and talk about these viruses just amongst ourselves, we really needed to start coming up with a different nomenclature. This is identified here. Essentially, we still have the 3C.2a viruses and the 3C.2a1

viruses as well as a very small number of 3C.3a viruses still circulating. You will recall that these viruses are like the Switzerland vaccine virus from several years ago. They are still hanging on, but at low levels.

Shown in red is our current Hong Kong/4801/2014 vaccine virus. And the Singapore 2016 – I am not going to give its full name. It is just too long, which was recommended for the 2018 Southern Hemisphere season and now our 2018-2019 Northern Hemisphere season. It sits at the base of the 2A.1 viruses.

What we saw the majority of in the Northern Hemisphere were these viruses that we now refer to as 2A.2. They really took off and you will see in the next slides how they predominated.

In addition, the 2A viruses now also include the 2A.3 and 2A.4 genetic subclades. The 2A.4 was the group of viruses that were quite predominant in the Southern Hemisphere, but now appear to be dying out. There is some low level circulation of the 2A.3s.

Then the 2A.1 viruses are split into 2A.1a and then what is predominating mostly now is the 2A.1b and these are further divided into two groups based on changes that they have, which affect a glycosylation site at 135.

This is just shown a little more clearly I hope in this smaller tree, which was provided by the

collaborating center from Melbourne. This now defines what each of these genetics groups are. This is the 3C.2a4 group, the minor group that has really not circulated elsewhere. It was quite prevalent in Oceania and particularly Australia.

The 2A.3 group has substitutions at 121 and 144. And then the major group that we are seeing in North America and other parts of the world are these 2A.2 viruses and they have three key substitutions of 131K, 142K, and 261Q.

The 2A.1 viruses are – again, the Singapore virus is at the base of these 2A.1 viruses. These have evolved into the 2A.1a group and then the 2A.1b group, which have substitutions at 92, 311, and 62. And then a predominant sequence change at 135 and it is either changed to the N or the K, both of those affect glycosylation.

Something else interesting has happened with these viruses, particularly the ones that have predominated in North America and that is that they are actually re-assortants. Sometime we have traced it back to probably May or June of 2017. The viruses that have the HA of the 2A.2 viruses re-assorted on the backbone of viruses from the 2A.1 group. That means they have two genes, the hemagglutinin and the PB1 gene from this group. But they have the rest of their genes, including the neuraminidase

from these 2A.1a viruses. One might speculate that this has somehow created a quite fit virus because it is really predominated in the US.

While we saw these 2A.2 viruses last season, they were not re-assortants. There is actually another minor group down here that has yet another neuraminidase. This is quite an interesting observation that we are tracking closely.

How are these viruses circulating? Shown here in these pie charts is – this is all genetic data available in GISAID for this period. We have color coded the key genetic subgroups here. There are a few to focus on. The 2A.2 in this hot pink and the 2A.1b viruses in the red and the yellow in particular. You can see for North America – about 83 percent of the viruses circulating were of the 2A.2 group. We did see a smaller proportion of the 2A.1 viruses and the 1A.b viruses. But overwhelming, the 2A.2's took over. That was also seen with much smaller numbers in Central South American. In Europe, it was a little more diverse. They had more of the 2A.1b viruses with the substitutions at 135. But at this time, we believe the 2A.2's are increasing there.

Oceania. Again, this is the tail end of their Southern Hemisphere season. As I mentioned, they had a lot

of these 2A.4 viruses. They are starting to see some more 2A.2 viruses.

Asia interestingly enough is quite mixed. We are seeing increasing proportions of 2A.2. Over half of their viruses were the 2A.1b viruses.

Just to highlight. Since September, this is the proportion of the different 3C clades. You can see how the 2A.2 viruses have really dominated globally this season.

Here are antigenic characteristics of the H3N2 viruses. This is hemagglutination inhibition assay. Again, it is set up the same way as the previous table I showed you. Again, we have our reference viruses here and the corresponding ferret antisera across the top. Shown in blue are the antisera raised to Hong Kong/4801-like virus. This is a surrogate virus because we cannot actually use the cell propagated Hong Kong/4801-like virus in HI assays. This is something I have probably mentioned several times. An additional challenge of the H3N2 viruses in addition to their genetic diversity is that all of the 2A viruses have very poor ability to bind red blood cells. Roughly about 50 percent of the viruses cannot be assessed by the hemagglutination inhibition assay. In fact, a number of labs, including our own, use the Michigan 15 as a Hong Kong/4801-like virus.

If we look at circulating viruses and see how well the antisera 2 Michigan 15 cell propagated virus, the Hong Kong/4801-like virus, how well this antisera reacts, we see that in general we get pretty good coverage of circulating viruses. There are some low reactors down here at the bottom.

But when we look the same at antisera raised to the egg propagated Hong Kong/4801, this has a homologous titer of 640. We can see that many of the viruses reacting at titers that are eight-fold or more low compared to that homologous titer.

We also looked at other emerging 3C.2a viruses in this HI table. These are represented by these Brisbane viruses. We have a pair that is grown in eggs and cells and then another virus, which is egg grown. When we grow the virus in eggs, we are looking for a representative virus that can – where its antisera can cover the majority of circulating viruses. Since these viruses represent the 2A.2 group that is predominating, we are looking for a good candidate in this group. But we really did not find one. It is shown as an example here.

You can see if we just look first at the cell propagating – antisera rates of the cell propagated Brisbane 318 virus here, you can see that it does not really cover. It covers some viruses well in the middle

right here. In fact, these are viruses in the same genetic group. Overall, what we were seeing is although we could raise antisera to these viruses, they reacted best with their own genetic group and they did not cover all of the circulating genetic groups that we were seeing as well as we would like.

If we turn now to the Singapore viruses and these are shown in yellow, you can see we have here – this is the Singapore cell propagated virus with – it is very hard to see the homologous titer. It is a titer of 160 here. You can see when we compare with the circulating viruses that most of the viruses are well inhibited at titers that are similar or within four-fold of this homologous titer.

Even when we raise antisera to the egg propagated Singapore 2016 virus, the same is true. There is a titer of 640 and most of these viruses are reacting at titers that are within four-fold of that homologous titer.

Depicting visually using antigenic cartography, we can see that most of the circulating viruses since August of last year are clustering around the Singapore 2016 reference virus.

Because of the challenges we have with H3N2 viruses and testing them in hemagglutination inhibition assay, all of the collaborating centers are now also doing virus neutralization tests. And here, this is an example

from the collaborating center at CDC. The table is set up essentially the same way. You can see that antisera raised to the Hong Kong/4801-like virus cell propagated virus generally react well with the circulating virus. There is an exception down here. It is a 3C.3a virus and that is where we are seeing our antigenetically variant viruses. About half of the ones we detected at CDC fell into this genetic group. But this is an older genetic group and it is not circulating widely anymore.

However, if we raised antisera to the egg propagated Hong Kong/4801 as we saw in the HI and even more dramatically in virus neutralization assays, we see that the majority of viruses are not well inhibited by antisera raised to the propagated Hong Kong/4801.

Here is another example. This antisera raised to Wisconsin/19. That is another 2A.2 virus representing that emerging and predominating genetic group that we saw in North America. We raised antisera. It has a very high titer. While this antisera again well inhibited viruses within its own genetic group, the titers are viruses that fell into the 3C.2a1 groups were much lower, suggesting that as we saw for the HI, this group does not – it covers its own group very well, but it does not – antisera raised to this virus does not well inhibit all of the different genetic groups we are seeing.

In contrast, if we look at antisera raised to the Singapore 2016, you can see that it well inhibits the majority of viruses. This is also true for the egg propagated Singapore for antisera raised against it.

In summary, the data that was provided by the different collaborating centers is summarized here. If we look at antisera raised or we compare the circulating viruses to cell propagated Hong Kong/4801-like reference viruses, we are not seeing any antigenic drift. Ninety-one percent of these viruses are antigenetically similar to the Hong Kong strain. This is also true if we do virus neutralization assays with about 87 percent of the viruses being antigenically similar to cell propagated Hong Kong/4801.

However, if we compare the reactivity to egg propagated Hong Kong/4801 and this is by the hemagglutination inhibition assay, we can see that only 44 percent of the viruses are well inhibited by antisera to the egg propagated 4801 and a much higher proportion, 79 percent, are well inhibited with the antisera raised to egg propagated Singapore.

I should have mentioned that – I do not have it on this slide, but if we compared the viruses against cell propagated Singapore, 95 percent of the viruses would be antigenetically-like Singapore. The Singapore antisera

cover the majority of viruses well also, the cell propagated Singapore and also the egg propagated Singapore.

When we turn to virus neutralization assays, the proportions are a little lower, but we see the same trend. Only 33 percent of the viruses tested were well inhibited by the Hong Kong/4801-like egg propagated antisera, but 55 percent were well inhibited by the egg propagated Singapore reference virus antisera.

Turning to the human serology, this is set up the same way. It is a compilation of all the data from the testing labs. Again, we have the color coding of the older adults in children sera shown in these different panels and then across the bottom all the test viruses used. In this first figure, I am showing you the comparison of the geometric mean titers against all the tested circulating viruses with egg propagated Hong Kong/4801. In many cases, when we look at the cell propagated viruses, they are always showing quite a bit of reduction. This red line is a 50 percent reduction line and anything below that is considered to be significant.

However, if we look at the now comparing cell with cell because most of the circulating viruses are grown in cells. Here, we are comparing the reference Hong Kong/4801-like vaccine viruses, but the reference virus grown in cells and various cell propagated viruses. With

this one exception, which is a 3C.2a virus and again not circulating to any great extent at all, we can see that the majority of the viruses are still well inhibited by antisera from vaccinated individuals when we compare against the cell propagated virus, again suggesting that there has not been a lot of antigenic drift in the circulating viruses.

This is just shown in a different way. This is a neutralization assay from CDC, showing multiple panels. You can see again. If you just cast your eye at the dotted red line, you can see that the majority of the geometric mean titers are above that red line suggesting that there is no significant reduction compared with the response to the cell propagated reference virus Hong Kong/4801.

In summary for the H3N2 viruses, H3N2 did predominate in several countries and some countries in North America and particularly the US and Canada had severe epidemics due to H3N2. The majority of the H3N2 viruses are still falling within the 3C.2a clade with very few 3C.3a viruses detected. There were multiple genetic subclades circulating, which have been given a new nomenclature. In the Americas and increasingly elsewhere, the 2A.2 viruses were predominating.

Ferret antisera raised against cell propagated Hong Kong/4801-like virus or the Singapore 2016 virus well

inhibited the majority of viruses tested in the HI and virus neutralization assays. However, as we know, egg propagation introduces additional changes that affect antigenicity and this is particularly problematic for recent H3N2 viruses.

When we looked at how well antisera raised egg propagated Hong Kong/4801 virus inhibited these circulating viruses, we found that it was generally poor with 56 percent in the HI and 73 percent in the virus neutralization assays.

Ferret antisera produced against several other egg propagated viruses belonging to the different clades also pull the inhibited recently circulating H3N2 viruses. Amongst the CCs, we had multiple egg propagated viruses representing different genetic groups, but essentially none of them looked any better than Singapore and by and large they all looked much worse. However, ferret antisera raised against egg propagated Singapore well inhibited the majority of viruses tested.

In human serology studies, the post vaccination geometric mean titers against the representative cell culture propagated viruses were not significantly reduced when we compare to the cell propagated Hong Kong/4801-like virus.

Turning to influenza B viruses, there was quite a lot of variable B activity in different parts of the world. This pie chart down here really demonstrates the dominance of the B/Yamagata lineage. This is the Y3 clade of the B/Yamagata shown in blue. You can see that it is predominated in all regions. The orange and yellow are the B/Victoria lineage viruses.

We will talk about the B/Yamagata lineage viruses first. This is another large tree. Essentially, there is not a lot of genetic diversity happening. All of the viruses sequenced belong to the clade Y3. Most of them had the substitution of 252 and 173Q. That is that new emerging group. The current vaccine virus is the Phuket/3073 and it is down here at the base of this tree.

Apart from some sporadic introductions of changes, there is really not a lot of genetic diversity we are seeing in Yamagata. That is also true for the neuraminidase gene. There is an emerging group here. These are most recent viruses that have a couple of substitutions, but again it is not anything that we are too concerned about.

If we look at the hemagglutination inhibition antigenic characterization data, you can see highlighted in yellow here are antisera raised to the reference vaccine

viruses, the Phuket/3073 so antisera to the cell propagated and the egg propagated.

If we look at antisera raised to the cell propagated, we can see that all of the circulating viruses tested here are well inhibited by these antisera. By and large, we see a few more four-fold reductions, but that is also true for antisera raised to the egg propagated Phuket/3073. Antigenically, there is really nothing happening with these B/Yamagata viruses and that is demonstrated here, showing in yellow the most recent viruses from the last several months. You can see that they are still grouped around the Phuket/3073/2013 cell propagated reference virus.

And the summary from all of the collaborating centers is that overall over a thousand viruses were tested and 97 percent of them were similar to the Phuket/3073 cell propagated reference virus. And 96 percent of them were similar to the egg propagated Phuket reference virus.

If we looked with human serology and again this is a compilation of all of the data, this is in different color coding this time of older adults and children. You can see that antisera raised – so the geometric mean titers of these panels when compared to the reference Phuket cell propagated virus, you can see that there is no reduction in geometric mean titer.

For the B/Victoria lineage viruses, these have become a little more exciting. When I talked to you in October, I mentioned the emergence of B/Victoria deletion variants. These were seen quite a bit at the end of our season last year in the US sporadically in some other regions in Central America and in only one region in Europe. Fast forward through to the beginning of this year and we now see that these viruses are in quite a number. They have spread to several Central and South American countries. We see them throughout North America. And most notably, there are quite a number of European countries now reporting their detection.

In addition to a double deletion, there has also been independent emergence of a virus that has three amino acid deletions. The two amino acid deletion as Dr. Grohskopf mentioned earlier is at residues 162 and 163. These triple deletions have 162, 163, and 164 deleted. The virus is clearly looking for something somewhere to move to. We first saw these viruses in Hong Kong. We have now seen a few of them in China, but they are still at very low numbers whereas the circulation of the double deletions has increased globally particularly in the Northern hemisphere this season. This is shown here.

This is B/Victoria viruses now. You can see the darker orange represents the V1A so the regular

B/Brisbane/60-like viruses. The lighter yellow color is the double deletion virus and then in red is the triple deletion, which is still only seen in very small numbers in Asia, but you can see in North America, Central South America and Europe. Although the circulation of B/Victoria viruses has been very low. It is only at about 9 percent globally all B/Victoria. And B/Yamagata is at 90 percent. Nevertheless of the B/Victoria viruses that have been characterized, over half of them in Europe and North America and more than half in Central South America, over three-quarters, is this double deletion variant.

This is shown on this phylogenetic tree. These are all of the double deletion variant viruses. The Colorado virus is shown in here. The most recent viruses also have a substitution at 192 and 180 and then the double deletion.

Independently, there are the triple deletion viruses down here from Asia. And then there is one more virus of concern. This is a group that is still in very low numbers, but it has a substitution at 165 and 221. Antigenically, we are seeing some antigenic change here. There is a Kazakhstan virus that we have at CDC that represents this group. There have been a handful of viruses identified in Asia. This is one we are watching closely. But at this time, it is not circulating widely.

This is just showing the neuraminidase tree. The neuraminidase group is out in the same. These are the changes based on the HA.

Antigenically, there is quite a lot going on here. This shown in yellow over here is the antisera raised to cell propagated or egg propagated Brisbane/60. That is our reference vaccine virus here. You can see that a proportion of viruses are still well inhibited, but all of the viruses highlighted here in the green – these are all double deletion viruses. They are not well inhibited by particularly antisera raised to cell propagated Brisbane/60. However, if we raise antisera to these viruses and the Colorado/6 is a representative of this group then antisera raised to these viruses well inhibits these double deletion viruses.

We have a small group of triple deletion viruses. And these are represented here by the Hong Kong/286 virus. You can see that antisera raised to these viruses only really well inhibit their own genetic group. This is also true of viruses, which had this change at K165N represented by viruses from Kazakhstan. And again, you can see antisera raised to these viruses do not well inhibit the majority of circulating viruses. We have several distinct antigenic variants emerging here in the B/Victoria lineage. The most predominant and the most widespread at this time are the

double deletion variant viruses represented by the Colorado/6/2017 virus. That is the main reason that this virus was selected as the new vaccine candidate because it represented the majority of the antigenic variants that are circulating and spreading.

This just refers to the overall characteristics of the circulating viruses when compared with the cell propagated Brisbane/60. Still a majority are well inhibited by an increasing proportion. This is really dependent on the way were viruses were isolated. You can see 40 to 50 percent of the viruses that were seen in North America and tested by CDC or in Europe and tested by the CRIC are antigenically variant. They represent the double deletion variant viruses.

This just represents the same information, but now with reference to the egg propagated. Now, we are seeing 50 percent of the viruses are poorly inhibited by the Brisbane/60 egg propagated antisera.

If we look at the human serology and this was most notable with the pediatric sera from the US. This is an HI looking at the geometric mean titers of these different panels compared with a number of different viruses. And, again, because we are testing cell propagated viruses, we are comparing to the cell propagated Brisbane/60, which is set here at 100 percent. You can see

other more recent viruses that are Brisbane-like are not significantly reduced. But each of the antigenic variants and in particular the double deletion variant virus that I mentioned are all substantially reduced when we look at pediatric populations, suggesting that antibody being raised to the Brisbane/60 vaccine virus is not covering these newly emerging antigenic variants. As I said, it is most pronounced in the pediatric group, but there are some instances in the adults and older adults where we also see reduced titers to the double deletion variant.

In summary, both lineages co-circulated, but B/Yamagata vastly predominated the season globally. The B/Yamagata lineage viruses are still all genetically clade three. There is very little genetic diversity. There is no antigenic variability that we have detected. Either using ferret reference antisera or human post-vaccination sera.

For the B/Victoria viruses, the HA of all of the viruses do belong to the 1A. However, we are seeing an increasing number and geographic spread of the double deletion variant viruses and we are giving them the name 1A.1. You may see that in future WHO and FluView communications.

Although many recent circulating viruses were still well inhibited by ferret antisera raised against vaccine reference viruses such as the Brisbane/60 and the

Texas/2/2013, an increasing proportion of viruses particularly seen in the US and Europe were not well inhibited. And the majority of these belonged – had two deletions or three deletions in their HA.

However, ferret antisera raised against a representative of this two deletion virus group, the B/Colorado/6/2017 well inhibited viruses within this new emerging genetic group.

Post-vaccination geometric mean HI titers of pediatric sera were significantly reduced against most viruses with the HA deletions compared to HI titers against the reference B/Brisbane/60 virus.

Again, just reiterating the recommendations we heard earlier this morning. For the quadrivalent influenza, it is recommended an A/Michigan/45/2015 (H1N1)pdm09-like virus be used. For H3N2, the Singapore/INFIMH-16-0019/2016-like virus. For the B/Victoria lineage, a new virus is recommended, the B/Colorado/6/2017-like virus. And for the second B component in the quadrivalent vaccine, it is the B/Yamagata lineage, the B/Phuket/3073/2013.

For trivalent vaccines, the first three viruses. We selected to include the B/Victoria lineage virus largely because we felt that there had been extensive circulation of B/Yamagata. There has been extensive vaccination with both B/Yamagata and B/Victoria lineages in recent years.

And the Colorado/6 represented a very distinct antigenic variant, antigenically drifted virus. It was felt that it was important to include this in the trivalent vaccine so that populations and particularly children who might be receiving a trivalent vaccine in countries where only trivalent vaccines are used would have the opportunity to get primed and immunized against this new antigenically drifted virus.

I will just acknowledge all of the collaborating centers and the GISRS, including all of the national influenza centers that really contribute all of the viruses that we characterize and the collaboration center. University of Cambridge partners to antigenic characterization, the essential regulatory labs that are also part of this work and our US partners, the APHL and our colleagues at DoD.

In particular in the last couple of VCMs and particularly this season, we have been – the collaborating centers have been sharing their data, the genetic and antigenic data, with two forecasting fitness partners in Europe and in the US. They are using mathematical models to help us look at the viruses in a different way, look at the trajectories of their frequencies and they offer forecasting although they recognize that this is as challenging and as limited as the data that you have. But

nevertheless, it is a very useful addition to our process. And, of course, last but not least, all of my colleagues at the Influenza Division at CDC.

I will take questions. Thank you.

DR. EDWARDS: Thank you. In your usual excellent way, you have really given us an enormous amount of information. Questions?

DR. EL SAHLY: Thank you again for the wonderful presentation. Given that we were asked to make recommendations to include Colorado strain when it is a minor component of the circulation US and worldwide, do we know – and the Yamagata seems to have predominated now two or three years back to back. Do we know the degree of across neutralization when someone or ferret are immunized with the Victoria-like or the Colorado specifically against the Yamagata, which seems not to be changing much?

DR. KATZ: With respect to the Yamagata, the ferret antisera from ferrets infected, would that be Colorado 2016 virus or is it 2017 virus – it does not even cross react with viruses within the B/Victoria lineage. Although we do not routinely test against the B/Yamagata, we would expect it would not.

However, we have seen in panels of human sera that individuals that were vaccinated with B/Yamagata or B/Victoria do show cross reactivity. This is generally

older adults and adults. We are not seeing it in kids. We are seeing some cross reactivity there. We always see some cross reactivity, for example, if individuals received a trivalent vaccine with B/Victoria in it, there would be some cross reactivity against B/Yamagata because these individuals have probably experienced B/Yamagata in their lifetime through inflectional prior vaccination.

What we do not know yet because we have only just recommended the B/Colorado virus is in humans how well will it cover against B/Yamagata. We do not know that yet.

DR. EDWARDS: Jackie, do you have concern that the Singapore strain is going to cover the emerging H3N2 strains that we are seeing here in the US?

DR. KATZ: Yes. In fact, it does cover them very well. The majority of the viruses that we tested at CDC were that emerging 3C.2a2 group. And the Singapore virus covered those very well. In general, that is why we went with Singapore because – and again perhaps one reason that this virus does work well is that it is at the base of the tree. It is not at the tip of the tree where things are changing. It is a more conservative selection, but it is able to cover viruses that are emerging with different changes very well. The opposite is not true. If you select something at the tip of that tree and raise antisera to it

then it covers its own group. Great. It does not cover everything else very well.

DR. BENNINK: Has the ACIP ever recommended or strongly recommended that the youngest of children only get the quadrivalent?

DR. KATZ: Yes. I do not know if it is a recommendation, but QIV is used in children now in the United States.

DR. BENNINK: It is never the trivalent then?

DR. KATZ: Not in the US. In other countries, it is still trivalent I believe.

DR. GROHSKOPF: This is Lisa. I am still on if that is helpful. Currently, for the very youngest children, those age groups – what Jackie said is correct. Most of what is available is quad at this point particularly if you are talking about 6 months through 35 months. The vaccines that are licensed for that age group are only quad currently in the US. But there has never been a policy preference expressed by ACIP.

DR. EDWARDS: Thanks Lisa. Arnold and then Pam.

DR. MONTO: Two questions. First of all, in the Singapore strain that is recommended, what is the situation at the 160 site? Is this truly cell or is it still egg? And then the neuraminidase is the other issue.

DR. KATZ: Most of the cell propagated viruses – in the 3C.2a group, they have this -- when they are grown in eggs, they lose the glycosylation site at 158 to 160. That is one of the egg adaptations we see. If we passage repeatedly in cell culture, we also see it. If we do a limited passage in cells, which is what we use here in our tests, it retains the K160. It does look like what is in humans. In the vaccine, it is egg propagated. It is egg like.

DR. MONTO: How much have you looked at distribution and its early times, I know, of the neuraminidase variants in parts of the country? Because there seems to be some differences in the US in terms of both transmission, which is independent of vaccine effectiveness.

DR. KATZ: Are you talking about the re-assortment -- I believe over 90 percent of those 2A.2 viruses circulating globally and that would include in the US are that re-assortment. They have the 2A.1 neuraminidase.

DR. EDWARDS: Pam, did you have a question? Other questions? Thank you, Jackie.

The next presentation will be the Department of Defense, Vaccine Effectiveness Report. It will be presented by Angelia Cost, senior managing epidemiologist for the

Armed Forces Health Surveillance Branch, the Public Health Division of the Defense Health Agency.

Agenda Item: DoD Vaccine Effectiveness Report

DR. COST: Good afternoon. I am Angelia Cost and I will be presenting on DoD influenza vaccine effectiveness and strain circulation.

Just our disclaimer. The views presented in this slide set are not the official policy or position of the Department of Defense or US Government.

To give you an overview of our talk today, I will be presenting on the 2017-18 influenza season from our influenza surveillance networks. Included here will be surveillance data from our partners in North America, South America, Africa, Asia, and Europe. In addition, the surveillance data will also be presented on military recruits. I will be presenting a brief summary of phylogenetic analyses developed by the US Air Force School of Aerospace Medicine, which I will refer to as USAFSAM for the remainder of the presentation.

In addition, I will also be presenting three mid-year assessments of vaccine effectiveness within DoD populations developed by the Naval Health Research Center, USAFSAM, and the Armed Forces Health Surveillance Branch.

Our influenza surveillance program extends to over 400 locations in 30 different countries through the

work of DoD laboratories across the world. In addition to monitoring US personnel, our partners have relationships with foreign governments, including ministries of health, ministries of defense, and academic institutions, which provide disease surveillance data on local national populations.

Our laboratories have extensive characterization capabilities including cell culture, PCR and sequencing capabilities and on average, about 30,000 respiratory samples are collected and analyzed each year within our surveillance network.

This just shows you a graph or a map of the GEIS-supported influenza locations. The blue dots here indicate countries where GEIS has influenza surveillance. And the stars indicate core laboratory partners.

For the next few slides, I am going to be going over the strain circulation data that we have from different regions within the world. All of these will look similar with the MMWR week along the X-axis and the percentage of positive samples along the secondary Y-axis on the right. The number of specimens submitted along the primary Y-axis on the left hand side.

Three years' worth of data will be presented in these graphs, starting with week 40 of 2015 to the most

recent data for 2018. The different colors of the bars indicate the different influenza subtypes.

Military recruits are depicted here and they are a particularly vulnerable population within DoD, vulnerable for respiratory infections due to factors such as crowded living conditions and stressful work environments. They are actually a mixing of individuals from throughout the US that come together in these recruit settings.

Historically, up to 20 percent of recruit classes might be hospitalized for respiratory infection during the two months of their training. In addition, recruits are highly vaccinated populations. Essentially almost 100 percent of the recruits are immunized within the first few days of arriving at recruit training. Surveillance on them gives us information on what viruses might be evading current vaccines.

These data come from eight recruit training sites throughout the United States. So far, recruits have experience low levels of influenza infection. Influenza A(H3) has been the dominate subtype. But there has been no clear peak in the season's recruit data. Many of these cases come from clusters and newly arriving recruits where it has been less than two weeks since they were immunized such as the spike you see at the end here at week 6 for influenza B.

This graph represents surveillance data for military members and their dependents residing in the United States and select civilian populations along the US-Mexico border. Influenza A(H3) has been the dominant subtype with low levels of A(H1) and influenza B circulating.

This graph represents surveillance data for military members and their dependents residing in one of seven countries in Europe. Flu activity for this population has been relatively low with only 153 influenza positives from 726 samples tested for this current season. Nearly half the samples are influenza B and over half are a mix of influenza A subtypes H1N1 and H3N2.

The surveillance data here comes from select local national populations within Peru, Paraguay, Columbia, and Honduras. There has been relatively low flu activity and the predominant strain has also been A(H3N2) with a small mix of influenza B. These countries fall within the tropical regions so peaks are not expected as we have seen with other regions.

These data represent US military personnel and dependents stationed in Asia and select local national populations. Surveillance in Asia showed early dominance of influenza A (H1N1) starting around week 23, with a drop in H1N1 incidence and more A(H3N2) around week 40 to present.

The surveillance data in Africa come from foreign military and civilian populations in Kenya, Tanzania, Uganda, and Ghana. There are incomplete or missing data for Tanzania and Ghana for the 2015-16 season, which is why you will see a lower number of specimens for that time period.

Influenza A(H3N2) dominated starting around week 14 and then became mixed with A(H1). Now influenza B is in the mix with no obvious dominating strain. Ghana surveillance was different from the East African countries and then it had much more of the H1N1, accounting for 69 percent of the H1N1 cases presented here. These countries are also located in the tropics, so peaks are not expected as with other regions.

In summary, in North America, DoD surveillance has not shown as heavy of an influenza season as the national trends indicate but does show a heavy predominance of A(H3) like CDC has been showing.

Activity in Europe is minimal with influenza B dominating and a mix of the other influenza A viruses. And then Asia and Africa's data show a mix of A(H3N2) and A(H1N1) with a shift to more influenza B in more recent weeks.

Next, I am going to be moving on to the DoD/USAFSAM Phylogenetic Analysis for the 2017-18 season. These data will probably seem very similar to what you have

seen with CDC as all of our sequencing is sent to CDC and incorporated into the figures that Dr. Katz just presented.

In order to select candidate viruses for the 2017-18 season, USAFSAM developed phylogenic analyses. This map shows where in our network sequence was selected from. For these analyses, a total of 429 samples were collected from sentinel sites and partner laboratories in 14 countries and 5 combatant commands.

Overall, out of 429 samples that were sequenced, 59 percent were A(H3N2), 23 percent were B/Yamagata, 14 percent were A(H1N1) and 4 percent were B/Victoria. Overall, the majority of sequences, as I mentioned, were A(H3N2). While that remained the majority, NORTHCOM, CENTCOM, and our Pacific Command, the majority of sequences from EUCOM and AFRICOM were of the B/Yamagata lineage.

To compare this to the GEIS strain surveillance data that I just presented, most distributions are similar, but the GEIS surveillance indicated more H1N1 in Asia during early 2017 and GEIS surveillance indicated H3N2 circulation in Africa and slightly different proportions of influenza A subtypes.

Here, we are looking at the phylogenetic tree for influenza A(H1N1) All 60 of these sequences were characterized as clade 6B.1. And the current WHO and

current vaccine strains are written in red here and also circled in red as well.

Next for the A(H3N2) phylogenetic tree, it contains a representative of 116 sequences from a total 254 samples that were sequenced. The current vaccine strain here is very small at the very bottom in red and then the WHO-recommended strain is circled in red. The majority, 71 percent were characterized as the 3C.2a2 with another 24 percent in subclade 3C.2a1, 3 percent in clade 3C.2a and 2 percent in clade 3C.3a.

The influenza H3N2 subclade 3C.2a1 was predominant during the 2016-17 season, which you can see here in red as the red bars. But the clade 3C.2a increased proportionally prior to the 2017-18 season and has become more dominant throughout the season. An increasing cluster with clade 3C.2a with mutations in the T13K and R142K and R261Q prompted designation of the subclade 3C.2a2 as Dr. Katz had mentioned. And clade 3C.2a was also the dominant clade during the 2014-15 influenza season.

Next, moving onto the influenza B/Victoria. All 18 of these sequences were characterized as clade V1A. Fifteen of these sequences, primarily from California contained a two amino acid deletion at positions 162 and 163. The current vaccine strain is again in red font with the WHO recommended strain circled in red.

All 97 of the B/Yamagata sequences characterized as clade Y3. The current and WHO recommended 2018-2019 vaccine strains are again circled in red and written in red.

Based on our genetic data, we agree with the following WHO recommendations for the 2018-2019 season as displayed here.

Next, I am going to move on to the last portion of my talk, which is on vaccine effectiveness with DoD groups. Our mid-year estimates are provided by three different groups: the USAFSAM and AFHSBA Air Force Satellite, the Naval Health Research Center, and then the AFHSB, Epidemiology and Analysis section.

All three of the studies used the case test-negative design to estimate VE. For the USAFSAM and NHRC, they considered RT-PCR and viral culture for positives and AFHSB also included positive rapid tests, but individuals with negative rapid tests were excluded from the analysis.

First for the USAFSAM and AFHSBA Air Force satellite results, they have sentinel sites throughout the world. They use that for their specimen collection with a requirement for ILI to have fever greater than or equal to 100.5 Fahrenheit and a cough and/or sore throat. Specimens should also be collected within 72 hours of symptom onset.

The surveillance sites are asked to submit up to ten specimens per week with priority given to the sickest or hospitalized patients.

The USAFSAM analysis is focused on DoD health care beneficiaries. The active component population is excluded from this analysis as it is handled in another analysis that I will present at the end of the talk.

Their analysis time period was October 1, 2017 through February 10, 2018. And the analysis was conducted for both influenza overall A(H3N2), A(H1N1) and B and also by various age groups.

Analyses were adjusted for age, month of illness and region, CONUS, Continental US-based sites and OCONUS, which were all the other international sites.

They identified 1160 cases confirmed by RT-PCR or viral culture, 1383 test-negative controls, and they found vaccination rates of 36 percent among cases and 47 percent among controls. Of all the cases, 53 percent were A(H3), 13 percent were influenza A(H1) and 34 percent for influenza B.

This figure is just depicting the age breakdown of the population of cases and controls. As you will see, the USAFSAM population did include children from two years and up and also adults in a smaller amount of 65 plus.

To look at the vaccine effectiveness estimates here, they looked at overall and then subtype specific VE estimates for all dependents combined and then children and adults stratified when the numbers allowed for that stratification.

Looking at all influenza, among all dependents, they found vaccine effectiveness of 51 percent, which was statistically significant with 95 percent confident intervals from 41 to 59 percent. When you stratify that by children, again, similar VE of 52 percent and in adults 51 percent.

When you look specifically at the A(H3N2) cases, overall vaccine effectiveness was 37 percent and it was also statistically significant. Among children, the VE was 38 percent, which was statistically significant. And among adults, also statistically significant, 35 percent VE for A(H3).

Looking at A(H1), all dependents are lumped together as the numbers were too small to do age stratified analyses. But we found 79 percent vaccine effectiveness that was statistically significant. And for influenza B also relatively high VE of 60 percent, which was also statistically significant.

Here is just another depiction of the same results for the plot. You can see how the confidence interval and point estimates range.

In summary, the USAFSAM VE estimates found that the influenza vaccines were protective and it was significant among children and adults. When you look specifically at A(H3), they found moderate protection both for children and adults. A(H1) adjusted VE was also protective. High vaccine effectiveness that was statistically significant and influenza B also moderate protection.

Next, I am going to move over to the Naval Health Research Centers, VE analysis. They look at civilian populations only. These are civilians at out-patient clinics near the US/Mexico border. This is in collaboration with CDC and the State of California.

Their analyses are adjusted by age group and they identify 201 cases and 114 test-negative controls. Their cases of 13 percent were vaccinated and among the controls, 24 percent were vaccinated. And similar to the other analyses, A(H3) predominated with 78 percent of the cases. Influenza B was next with 20 percent of the cases and 1 percent were A(H1).

Again, this is the age distribution for the NHRC population. Two-thirds of their population were children

under 18 years of age and then another third between 18 to 64 years of age for both cases and controls.

I will note that the NHRC analysis was conducted among cases enrolled between November 13, 2017 and January 8, 2018. They provided subtype-specific VE for A(H3N2). Again, with all dependents combined, we have 52 percent vaccine effectiveness, which was statistically significant. And then they stratified that by children and adults. I will remind you that the only thing they adjusted for in the analysis was age, which is why you do not see adjusted VE estimates here. The crude VE estimates are what you should be looking at. For children, they found a 62 percent VE for H3N2. Among adults, only a 5 percent VE, but as you look at the numbers, they were quite small. This is probably a very unreliable estimate of VE among the adult population.

For influenza B, the dependents were all combined and they found a 62 percent VE; however, it was not statistically significant.

In summary for A(H3N2), VE was moderately protective and statistically significant in the civilian border population. It was moderately protective among children and for adults low, but again very wide confidence intervals in small numbers. And VE for influenza B was moderately protective in this population.

Lastly, I am going to discuss the AFHSB epidemiology and analysis VE assessment. This also was a case control test-negative control design. This analysis focused only on active component service members. This included service members from all four services based both CONUS and OCONUS.

The analysis was restricted to peak influenza months from December 1, 2017 through February 10, 2018. We identified 2926 cases and 2557 test-negative controls. The models were adjusted for sex, age category, month of diagnosis, and a five-year vaccination history.

I will comment that the active component and actually all the service member populations are a highly immunized population. It is required that they receive the influenza vaccination. We have extremely high vaccination rates here with our cases being 89.3 percent vaccinated and our control population, 90.2 percent vaccinated.

We did assess whether the vaccines administered to this population were cell based or egg based. Overall for DoD, about 50 percent of the vaccines that were purchased were cell based. And in our active component population, about 30 percent of the vaccines that were used in this study population were cell based.

The activated influenza vaccine was the only vaccine used this season. And 91 percent of our subjects

again had been vaccinated in prior seasons given that requirement for immunization.

We identified 2190 cases that were influenza A that were not subtyped, 301 A(H3) subtyped cases, and 48 A(H1) cases, and 383 influenza B cases.

Here is the age distribution. Since these are active components, it is only an adult population, ranging from 18 to 40 plus.

For our VE estimates, we assessed any and type of influenza so A and B combined. We found a vaccine effectiveness of 19 percent, which was statistically significant with 95 percent confidence intervals of 3 to 33.

When we looked specifically at influenza A since that was the predominant type of cases that we saw, it was also 19 percent statistically significant VE. When we looked solely at the A(H3N2) cases, we found a point estimate that was higher of 27 percent VE. However, that did not reach statistical significance. And the same with influenza B, a VE of 25 percent, but was also not statistically significant.

Overall for all influenza and influenza A types, we saw low vaccine effectiveness among this active component military population. Influenza A(H3) and

influenza B results were not statistically significant, but point estimates were low.

Just to summarize for all of the three groups, DoD dependent VE was statistically significant and ranged from 37 to 79 percent depending on the population and the influenza subtype.

Border civilian VE was also moderate protective at 52 percent. And active duty vaccine effectiveness was low at around 19 percent, but statistically significant.

Here, again, is just the plot to give you a different depiction of the results that I just presented.

I do want to mention some of the limitations to our vaccine effectiveness analyses. First of all, generalizability. Subjects had to be sick enough to seek medical care in order for them to be ascertained within our population and get tested. We are not able to assess VE on less severe cases.

I will also emphasize that within DoD for service members and beneficiaries that they have very good access to care. We may be identifying more less severe cases, maybe more likely to come for treatment as opposed to the general US population.

The active duty military population is highly immunized. This could have a negative impact on our vaccine effectiveness estimates, which were lower than the

beneficiary populations potentially with methodological issues when you have such high vaccination coverage. You are really only comparing a 1 percent difference, which makes it hard to do methodologically. And then biological effects of repeated immunizations annually may also be playing a role in this reduced VE estimate.

Populations are younger and we were not able to assess vaccine effectiveness in older, high-risk populations.

I will mention since we did have about 50 percent of the population receiving cell based, the USAFSAM and the AFHSB silver spring and air force satellite are hoping late spring to summer to investigate vaccine effectiveness of cell versus egg-based vaccines.

With that, I will move on to acknowledgments. Quite a lot of people contributed to these data and results from throughout the world especially with our USAFSAM group that does the heavy lifting with all the laboratory data.

DR. EDWARDS: Thank you very much. Questions for Dr. Cost?

DR. SHANE: Thank you very much for a nice presentation. I just had a question about vaccine status. Was that purely from documentation or was there any self-report?

DR. COST: There will be. It depends on the group. For DoD service members and the majority of the beneficiaries, we do have medical encounter data on vaccination status. It is chart confirmed. However, for the NHRC border population, that is self-reported.

The USAFSAM population has a small section. They administer questionnaires to all the enrollees for their sentinel surveillance. With that, they can report vaccination status. But then they also try to confirm it with the medical encounters if they can.

DR. EDWARDS: Would there be any data regarding hospitalization? Probably the number of people hospitalized with influenza is probably very small.

DR. COST: Unfortunately for this season, there is quite a bit of delay in us receiving hospitalization data on a DoD level. It is typically about a three-month delay. What we are receiving in AFHSB is the billing code data that comes after the hospitalization.

USAFSAM does get some information and the laboratory data can indicate hospitalizations, but it is too early really for us to get a good assessment of hospitalized cases.

DR. MONTO: I just was wondering about the use of the test negative design in a population in which there is a requirement for vaccination. Do you know the reasons for

non-vaccination exclusions or other things which might bias the design?

DR. COST: That is a good question because I would expect it to be 95 percent. The immunization health care branch does put out reports like that. There may be some misclassification of individuals in the unvaccinated group that were actually vaccinated. It just was not documented. I know they have tried to move away from egg allergies and that sort of thing especially some of the cell based. You have more variety for the service members. But there are some individuals who are listed as exempt for receiving influenza vaccine. I think that is what is making probably that 5 to 10 percent population.

DR. FRIEDLAND: I am just trying to wrap my arms around the data and of course it would be its interim. When you have end of season data, you will have more power around analyses. In general, your adult effectiveness was lower than what was reported in the interim analysis from the CDC. In general, there is a feeling that vaccination can attenuate illness and you are reporting that most of these patients were sick enough that they would have gone for health care. Following up on Kathy's comment about hospitalization, I think it would be very important to try to look at severity of illness and see if there is an impact on severity of illness among your population given

that your results are generally lower than had been reported.

DR. COST: Definitely. I agree with that. As soon as the robust data is available for the whole population, we can incorporate that in our full season analysis.

DR. EDWARDS: Any other questions? Thank you very much.

We now have a lunch break. We will return at 1:30. We will continue our discussion.

(Whereupon, a luncheon recess was taken at 12:30 p.m.)

A F T E R N O O N S E S S I O N

Agenda Item: Candidate Vaccine Strains and Potency Reagents

DR. EDWARDS: This afternoon's session will be on candidate vaccine strains and potency reagents by Dr. Joshi, lead biologist at the Division of Biologic Standards and Quality, the Office of Compliance and Biologic Quality at CBER FDA.

DR. JOSHI: Good afternoon, everybody. I hope everybody enjoyed their lunch and ready for the afternoon session as much as we can be. I come from the Division of Biological Standards and Quality Control and Office of Compliance at CBER. Division of Biological Standards and Quality Control, in collaboration with other Essential Regulatory Laboratories, we call the ERLs, participate in generation and calibration of reagents required for testing of influenza vaccine. Our division also manages and provides these reagents to all US license manufacturers.

In my presentation, I will go over the currently used vaccine viruses and WHO-recommendation for 2018-2019 seasonal vaccine, both trivalent and quadrivalent. In addition, I will provide information about the available reagents for each of the strain, and our division's plans for preparing and supplying the influenza vaccine testing reagents for the upcoming season.

And lastly, I will make a few comments. I can tell you up front only these comments are not so much for the Committee as such, but for the benefit of the manufacturers in the audience. I would like to make some comments about how we are planning for all the testing activities for 2018-2019 campaign, how they should be handling and using the SRID reagents, and an important part of the start of the season where it is required that we do the testing for the monovalent bulk vaccines prepared by the manufacturers.

Coming to the H1N1 strain, the current vaccine virus for 2017-2018 season was A/Michigan/45/2015 (H1N1)pdm09-like virus. Going forward, I will just abbreviate this name instead of reading all of it. X-275 reassortant of A/Michigan and IVR-180 and 180A reassortant of A/Singapore/GP1908, which is also a Michigan-like virus that has been used in vaccine manufacturing.

WHO recommended that the virus for the 2018-2019 campaign continues to remain as A/Michigan/45. If you remember, this has been recommended for the 2018 Southern Hemisphere campaign. I didn’t bother to put all the names of the candidate vaccine viruses, which are available for this strain. But the WHO webpage clearly defines what all is available.

If the Committee approves, and this strain continues to be in the upcoming season, I would like to go over the available reagents for H1N1. So reference antigen for testing of egg-grown vaccine for X-275 reassortants are available from CBER, as well as from NIBSC. Reagents for A/Singapore reassortant 180 are available from TGA, and Australia and NIBSC in London, in UK, and NIID in Japan.

Similarly, reagents from A/Singapore IVR-180A reassortants are available from TGA. For the vaccine grown in cell, the reagents are available for A/Singapore/GP1908, as well as for its reassortant IVR-180. They are both available from TGA.

At CBER, we have prepared an antiserum last year, H1-Ab-1701. We are in the process of making the replacement lots. I would like to remind the audience here that CBER approval of these reagents is going to be on a case-by-case basis. We strongly recommend that you consult with us before starting to use reagents from any.

Coming to the H3N2 strain, the current vaccine virus recommended for the 17-18 season was A/Hong Kong/4801 like virus. The reassortant for A/Hong Kong X-263 and 263B were made available. And in addition, A/Singapore/GP2050, a cell culture derived virus was also available for manufacturing.

As far as potency reagents are concerned, for the past season, all reagents are made available by CBER and all the others, as well. The new recommendation from WHO, they recommend that for the upcoming season, the H3N2 strain needs to be changed. It should be A/Singapore/INFIMH-16-0019/2016 like virus. All of you know that this has been recommended for the 2018 southern hemisphere season, as well.

The candidate vaccine viruses for the egg-derived vaccine are available, which include the A/Singapore reassortant NIB-104, IVR-186, X-307 and 307A. Similarly, the candidate vaccine virus for making the vaccine in cells, the A/North Carolina and A/Canberra are also available.

Coming to the reagents availability, CBER has already started and made the reference antigen log for NIB-104, which will be calibrated as soon as we have the availability. We are waiting for it. As soon as it becomes available, we will calibrate the reagent. Since this strain was recommended for a certain hemisphere, the NIB-104 reagents are available from NIBSC, and reagents for IVR-186 are available from TGA. At CBER, when it comes down to for the reagents required for the cell-grown vaccine, CBER will work with manufacturers to prepare and

calibrate the required reference antigen or the need for the production platform.

Coming to Influenza B and talking about the Victoria Lineage, the current vaccine virus was B/Brisbane/60/2008-like virus. This was also recommended for 2018 southern hemisphere season. B/Brisbane/60, as well B/Hong Kong/259/2010 viruses were used in vaccine manufacturing. Again, ERLs had worked hard calibrating, so reagents for B Victoria Lineage were available from CBER and from other ERLs.

The recommendation from WHO that just came out, and we heard it this morning from everybody, is the recommendation is that this strain be changed and introduce a B/Colorado/06/2017 like virus for the upcoming season. The candidate viruses for the egg-derived ones, I am not going to read all of them. They are listed up here, and they are available for vaccine manufacturing and similarly for the candidate vaccine viruses, which are cell-culture derived. The B/Louisiana and B/Iowa also are available.

It is a new strain coming up. We have to think about how we are going to handle this. The plan is that, as far as production of reference antigen is concerned, CBER will work with the ERLs and manufacturers to prepare and calibrate the required reference antigen. Even for the cell-grown vaccine, CBER is all ready to work with the

manufacturers to prepare and calibrate the required reference antigen for the strain they select for their production. We are in the process of planning and starting the sheep antiserum production in the very near future.

Coming to the influenza B virus from Yamagata Lineage, the current vaccine contains the B/Phuket/3073/2013 like viruses. B/Phuket wild type and its reassortant BVR-1B has been used in vaccine manufacturing.

Again, I don't have to reiterate ERLs work together always to make sure these reagents are available. The reagents were made available by CBER, as well as other ERLs. We worked on a collaborative effort to get them ready.

Now, WHO recommended that the B Yamagata Lineage virus for 2018-2019 should be the B/Phuket like virus. I am not going to go over the list. I think in the interest of time, just look at the website. All the CVVs are listed at the site.

As far as available reagents for B strain, we call this the second B strain in the quadivalent vaccine. Reference antigens are available for wild-type B/Phuket from CBER, from NIBSC, TGA and NIID. We had worked with TGA, and the reagent from BVR-1B assortants are available from TGA, as well as NIBSC has prepared, which is a

B/Phuket like virus. The reagents were prepared for that by NIBSC.

For cell-grown vaccine, both CBER and NIBSC were involved. Each one of us had prepared a B/Utah/09/2014 reference antigen for that strain. Currently, CBER has three lots of antiserum available if this strain continues to be in the vaccine.

Again, I should be saying that each slide is provided. If this strain gets included, if it gets recommended by the Committee and gets included in the upcoming vaccine, we would like to remind the manufacturers that the CBER approval of any reagents is on a case-by-case basis. We would like you to consult with us before starting to use reagents from any other ERLs.

Now, I would make a few comments, which is more relevant to the manufacturers in the audience here, is how we are planning for our 2018-2019 influenza season and our testing activity. We at DBSQC would like that manufacturers provide us the following information. Following meaning that we want to know from you which strain you are selecting because there are multiple CVVs available. Please let us know which strain.

Which reassortant or candidate vaccine you choose in your manufacturing platform? What are your plans for using the reagents? Some reagents are available from

others. Do you plan to use any of them? We would like to know that, whether it is antigen, antiserum.

I think this information is extremely important for the DBSQC because we do all the testing for the vaccine, prepare all the reagents. Because based on the information you provide us, we will be able to work around reagent calibration activity. Again, if you choose to use the reagents from other ERLs, it is very important for us to have those reagents in our domain, which means it involves importing the reagents from ERLs.

And as all of us know, this can be time consuming. We would like to know ahead of time, so that everything can be ready when your sample comes into our domain for testing. All these will kind of help us in running a smooth operation of monovalent testing, as well as when the real lots come for testing, lot release testing.

Now, I will make some general comments about the SRID reagents and their uses. I would like to remind the manufacturers that only CBER authorized reagents should be used to test potency of vaccines marketed in the US. Please consult with us before selecting the reagents and start using them.

Please remember that when CBER authorizes the use of reagents from other ERLs, it is your responsibility to

make sure that those reagents you obtain directly from those ERLs. CBER recommends that the use of reference antigen and reference antiserum from the same source is highly desirable and recommended because this will avoid a lot of discrepancies. Mixing up batching of reagents from two ERLs sometimes can be a problem and all more work. Please consult with CBER with all your reagent-related questions.

Another thing, this points usually, I tell in every meeting, I think it is a good point like the start of season to remind people that antiserum lots, when we prepare them, sometimes the lot sizes are not so big. You have a limited supply of antiserum. And if you begin with the first lot of antiserum, we recommend that you have a little amount for any of your future activity, like when you need to bridge the incoming new lots of antiserum. So just make sure you keep a small amount aside, so that bridging can be performed, and you don’t really do any problems.

We recommend that it is desirable to use the same reagents for our monovalent, and your formulated bulk testings, and also subsequent follow-up studies. Begin using the same reagent will avoid a lot of issues with which you run into by changing the reagent in the middle of the study.

There are sponsors developing new products for them. We suggest that you please discuss the use of SRID reagent in an early phase of your product development. Again, that will help in streamlining some of the activities down the line.

And lastly, I would say for any inquiries regarding CBER reference standards and reagents availability and shipping, please contact the CBER Standards, which most of the manufacturers do it. But I think it helps with the email address right there.

Now the last thing I think is the most important point, as the season starts rolling. I would like to make a few points about the monovalent bulk testing, which we do for all the manufacturers in our division. There are certain points we want you to remember. The first and most important is monovalent samples must be submitted to DBSQC directly. You can email me, at my email address up here, regarding your dispatch of samples, your test results and any question regarding your sample activities.

This year, we want you to know that to facilitate a faster turnaround, we want you to submit your preliminary SRID results, which are based on your first two of multiple SRID tests required to generate the results. In the last few years, we have seen that the samples get submitted, and the results are not submitted. Or either the results are

submitted from way back. All of us know that this can be some decline in initial phase. When the testings are performed in two labs, and we get very different results, and then there are a lot of issues.

We recommend that the preliminary SRID results should be generated within one week of submitting the samples to DBSQC. Once we receive your samples and results, we will initiate testing in our laboratory. Please remember that the testing in DBSQC is performed in the order samples and results are received.

We still want that. And initially, you submitted us your very preliminary result. So please submit your final result. Then once they are ready and gone through internal processes, these results can be submitted to us via email. You don’t have to send us hard copies. Once we will have your results, then DBSQC will communicate CBER test results, and everything will be finalized after that.

In closing, I would like to emphasize that we at CBER are committed to make every effort to assure that the reagent preparation is done in a timely manner, and reagents are available in the right timeframe for you to test your products. And the most important thing I always try to say is that we here at CBER, we believe that making the influenza vaccine available in a timely manner is a responsibility shared by all of us in this room.

Here, all of us, each one of us in this room, work as a team to make sure that vaccine is made, tested and released in the timely manner for the public. I think it is a joint effort. We have been doing it year after year. I think this would be looking forward to having a very successful year ahead with this. Thank you.

DR. EDWARDS: Thank you very much. Are there questions? The next presentation will be the comments from the manufacturers. Dr. Penny Post, the head of regulatory affairs at Flublok Protein Sciences Corporation, a Sanofi Company, will present.

Agenda Item: Comments from Manufacturers

DR. POST: Thank you. I would like to start off by thanking VRBPAC and the FDA for the opportunity to share the industry perspective on influenza vaccine manufacturing. I am making this presentation on behalf of all manufacturers who supply influenza vaccine to the US market. Those would be Sanofi Pasteur, GSK, AstraZeneca MedImmune, Seqirus and Protein Sciences. Each manufacturer has contributed to this presentation.

Today, I will provide you with an overview of our vaccine production, release, distribution timelines, and the preparations that we make in partnership with the Public Health Service Organizations throughout the year. I would like to begin by showing you the volume of vaccine

doses that are manufactured and distributed annually. The amount of vaccine that has been distributed over time has steadily increased.

The left graph shows an impressive steady rise in total doses that have been distributed by the vaccine manufacturers over the past nearly 40 years. The right panel shows the pattern of vaccine distribution over the course of a single season. You can see that vaccine distribution is largely completed by the November timeframe.

To date, this season nearly 155 million doses have been distributed, which is about the highest annual amount for a seasonal vaccine in terms of distribution, exceeded only during the 2009 pandemic. So a we have been talking about today in a number of the talks, vaccine supply requires a timely selection of well-matched strains, time to manufacture enough supply to meet this demand, and timely pre-season distribution.

So in order to meet this vaccine demand, manufacturers begin to produce at least one of the three or four components of the vaccine at risk prior to the vaccine strain selection meetings, using surveillance data that is available at the time. Once the annual strain selection meeting occurs, and as we have been talking about this year was February 22nd for the WHO and today for the US, once

that occurs, then production of all vaccine components begins and production of the potency release reagents begins for any new strains. Sometimes if there is a strain change, a new working virus, vaccine seeds also need to be produced.

Balancing is done later in the season during the summer to ensure that we have equal amounts of each of the vaccine components manufactured. We need the potency reagents available, so that we can accurately blend the vaccine components. Therefore, we need to wait to do our formulation until these potency reagents are available.

Vaccine is then packaged and distributed. This process will extend into the fall when vaccination is recommended. So you can see by the timeline here that this whole process takes about six to seven months to complete this manufacturing release and distribution of the volume of vaccine that is required for the season.

So as I mentioned in the previous slide, meeting the vaccine supply timelines depends on a couple of critical factors. The first is timely selection of vaccine strains, which then allows us to stop manufacturing vaccine components at risk and ensures that our manufacturing efforts are focused on manufacturing the correct strains.

And the second is availability of potency reagents, which sets our timeline for vaccine formulation.

So reagents are produced and calibrated by CBER for any new strains. This process takes several months, as we have heard in the previous talks today.

So there is work that is ongoing right now to help improve the vaccine production timelines. HHS' BARDA has held vaccine mismatch meetings in 2015. These included representatives from FDA, NIBSC, CDC and industry. They have worked on developing a seasonable influenza vaccine improvement initiative.

So some of the suggestions for improvements that have come out of these meetings were aimed at having more representative viruses, or candidate vaccine viruses, identified early and to evaluate yields prospectively, so that manufacturers can have access to the highest-yielding candidate vaccine viruses as soon as possible.

Other improvements were around reagents for potency testing for the vaccine formulation and for release, so that reagents can begin to be prepared earlier and at risk, such as producing additional alternative potency reagents. Any of these timeline reductions for manufacturers that can be implemented can help facilitate a delayed vaccine composition selection. But we are not there quite yet with these improvements.

I wanted to spend a couple of slides talking about what do manufacturers do to prepare for the upcoming

manufacturing campaign? We track surveillance data through summaries of internal WHO teleconferences, which are held to review the surveillance data. They include a table listing of all viruses of interest. We attend NIBSC meetings, BIO/FDA meetings, and we have discussion with WHO Collaborating Centers.

We use websites such as WHO Flunet and CDC Fluview to look at surveillance. We also track availability of candidate vaccine virus strains for manufacturing through WHO chaired teleconferences. These have been running basically since WHO southern hemisphere strain selection meeting in September 2017. They moved right into the northern hemisphere discussions.

Lastly, we used a spreadsheet of viruses of interest that was developed by the NIBSC and the Crick Institute in the UK for planning. Industry also engages very closely with WHO and US agencies at multiple forums. The bar in the middle of this slide here shows the time in between the VRBPAC strain selection meetings, which are indicated in red running from March of 2017 last year to March of 2018 this year.

The light blue boxes represent the seasonal flu meetings. The dark blue boxes are the WHO meetings where influenza may be discussed. Industry representatives attend these meetings and work very closely with the global

agencies to help resolve issues and to get updated information to improve vaccine supply. So these really are key opportunities for us to understand the surveillance and what candidate vaccine strains are available.

This slide gives you an idea of the different strains that we have been evaluating for the upcoming northern hemisphere manufacturing campaign. The strains that are shown in red are those that were selected by the WHO last week. The strains listed underneath are all of the others that we have been evaluating for production for this coming season.

So I wanted to spend a moment to talk about the Nagoya protocol, which we have talked about over the last couple of VRBPAC meetings in our industry presentations. I wanted to give an update at today's meeting.

So for some background, the Nagoya protocol was developed from access and sharing discussions at the Convention on Biological Diversity. It has come into force in 2014 when the 50th region ratified the protocol.

The objectives of this are to ensure access to genetic and related translational knowledge for potential use. It ensures that users and providers of genetic resources and related traditional knowledge agree on fair and equitable sharing of benefits arising from their use. These benefits may be monetary or non-monetary. This was

initially developed for agricultural purposes, but it includes viruses, as well.

So the participating regions in the Nagoya protocol are putting legislation into place around this and are including pathogens. Under the Nagoya protocol, companies would need to negotiate bilateral agreements with the supplying country, which we estimate could take about three months in order for us to receive a particular strain or to obtain permission to work with it.

There is currently a specialized international access and benefit-sharing instrument that has been put in place that has exempted pandemic influenza. Industry supports the WHO and CBD efforts to extend this now to seasonal influenza. So while the United States is not signatory to the Nagoya protocol, there could still be some restrictions on vaccine strain availability for the US manufacturer.

So to illustrate this, I have shown you the slide that I just showed you previously of the strains that we have been evaluating for the upcoming campaign. I have crossed out all the strains that come from countries that are Nagoya protocol signatory countries. So availability of these strains could be potentially impacted depending on local legislation around the Nagoya protocol in these

countries. This could greatly reduce our choice of viruses when trying to find a well-matched strain for the vaccine.

I also wanted to just say a couple of words on vaccine confidence. As we have been talking about today, this 2017-2018 influenza season has been difficult with lower than usual vaccine efficacy. The public health messaging is leading some people to think that vaccination is not worth their time now, given the low vaccine efficacy. Until a universal vaccine is developed and/or production is sufficiently ramped up for alternative production platforms, such as cell-based and recombinant, we think it is still very important to maintain public awareness of the importance of vaccination.

So to conclude, timely strain selection and vaccine supply requires close collaboration between multiple stakeholders to ensure sufficient supply of vaccine each season. The 2018-2019 season manufacturer preparedness is ongoing. However, further improvements identified are to be implemented to mitigate later strain selection recommendations.

Adherence to the Nagoya protocol could result in a delay of an influenza vaccine candidate strain, and the influenza vaccine industry is going to collaborate with CBD to facilitate mitigating this risk. And lastly, we believe, as everyone in this room, that it is critical that

we all work to maintain public confidence in vaccination. Thank you.

DR. EDWARDS: Thank you, Dr. Post. Are there questions?

MR. TOUBMAN: Responding to both presentations, I got from Dr. Joshi's presentation, to put this delicately, a little bit of frustration about some of the process. There have been some situations where information hasn't come from the manufacturers as quickly as would have been helpful. My question is if that is true, are there some things that might require some external assistance to help them facilitate matters?

DR. JOSHI: I am sorry if I did not make it very clear. I think my comment about some of this controversy was not to do with anything else. It is between the way we do the testing activities in our division and getting some back and forth information from manufacturers. It is the smooth line of operation of testing activities. That was more meant for the manufacturers.

We can work out some of the things, so that you know the best activities run smoothly. We do understand that if somebody sends you a sample, they expect, oh, now I am going to get my results. Then for us to do anything, like we require certain baseline things for them to even initiate testing in our domain.

So other than that, I just wanted to make sure with them it was a reminder for the manufacturers that please be more communicative. We can work out it together and plan it better, so that you are done with your anxiety, get over it faster. Your testing is done.

We are like, okay, we have done our job. You are happy with the way we performed in a timely manner. It was more like for the people with whom we deal on a routine basis, when the season starts and all our testing activity happens.

DR. EDWARDS: We appreciate that feedback.

DR. BENNINK: I want to take advantage that you are the one presenting today. Some of the other vaccines have a little bit of neuraminidase, even if it is not tested. Have you considered putting neuraminidase in your vaccine? Will you do that?

DR. POST: It is definitely something we have discussed as Protein Sciences Corporation. But we do have, in our package insert, data that shows that FluBlok is non-inferior. Although we are not claiming it, we have some superiority data in the tables in our package insert without neuraminidase in the vaccine.

We know that FluBlok performs at least as well as vaccines that contain neuraminidase without neuraminidase. But of course, there is always room for improvement.

Agenda Item: Open Public Hearing

DR. EDWARDS: Any other questions of these speakers? Okay, we are going now to turn to the open public hearing. I would welcome the open public hearing session. Please state your name and your affiliation. Both the FDA and the public believe in the transparent process for information gathering and decision-making to ensure such transparency at open public hearing session of the advisory committees. The FDA believes it is important to understand the context of the individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, as you begin to state if you have any financial, personal or other professional relationships with any company or group or individual that may be affected by the topic of this meeting. If you do not have any such interest also, FDA encourages you to state that for the record. If you choose not to address this issue of financial, personal or other professional relationships at the beginning of the statement, it will not preclude you from speaking, and you may still give your comments.

So a number of people have signed up for the open public hearing. Some of the penmanship is not quite as legible as others. If I mispronounce your name, please do correct me. The first speaker is D. Kumlaw (phonetic) from Clarviat Analytic. The second is M. McGill from Sanofi

Pasteur. Okay, I am afraid maybe some of these are wrong sheet signers. If that is the case, then we understand.

Doris Bucher from the New York Medical College, and Doris, are you signing the wrong sheet, too? Okay, thank you. Christian Kropp from Sanofi Pasteur, Katherine Fertile. There was someone that did sign up from the Kentucky Bioprocessing. Is that individual here? Okay, if there is anyone who has not been called or would like to speak in the open public hearing, please stand up and do it now.

So it looks like we don't have any individuals that want to speak in the open public hearing. I think that now it is time for us to discuss the issues at hand. Are there any comments that people would like to make before we go around the room and discuss this?

Agenda Item: Committee Discussion, Voting, and Recommendations

DR. OFFIT: It seems to me that based on Jackie Katz's presentation and, to some extent, Lisa Grohskopf's presentation, that H3N2 appears to drift while being manufactured in eggs. So it would be of value, I think. There are a couple of studies out there, but there could certainly be more, looking at the relevant capacity of either the cell-based vaccine or the recombinant vaccine or

both as compared to the egg-based vaccines in terms of their performance against H3N2.

If it comes to be that those vaccines are superior, and I am not saying in any sense they may be, I wouldn't be surprised if they weren't. But if they are superior, then to what extent is the FDA at all involved in moving us away from egg-based vaccines.

I think this only really sort of came up over the last years because it has been H3N2 dominant seasons, where previously we have had H1N1 dominant seasons, so it becomes more obvious. But it is a problem. It may be the only way to solve the problem is with cell-based or recombinant-based vaccines. But what is the FDA's role in at least encouraging the kinds of studies that would let us look at H3N2 for these two groups of vaccines?

DR. WEIR: I guess I think everyone would agree with you that the studies need to be done. That is a serious limitation in the data that is available. We can all speculate that one type of vaccine might work better than another. But remember, all of these were licensed based on efficacy studies.

So we would be very supportive of having firm, solid evidence that showed that one way or the other, and in which circumstances it might be true. For example, even in this past year, while we may speculate that one type of

vaccine might have worked better than another, we don't know that is true. We don't know that it would be true in every year and every situation.

So I think we would like data like that. If companies or any other agencies would be willing to support those type of studies to generate that type of solid data, I think we would be very supportive of it.

DR. GRUBER: I just want to second that there has been a lot of discussions on this issue. If we do cell-based technology sort of prevails over making influenza vaccines and tried and true very much established technology of using egg production technology. I wanted to add in our center, our scientists are looking at some data for the CMS database and Medicare and Medicaid in subjects over 65 years of age.

I guess they have some data to look at cell versus egg-based vaccine effectiveness. I can't really speak to this right now. The data, as I understand it, are very preliminary. I don't think that we have the subject experts in the room today to speak about this more.

But the point we made, people trying to look at it, FDA is trying to look at it itself. Then we will see what data we get. The issue is cell-based technology or cell-based influenza vaccines, they are young. We licensed them, what, 2012, the recombinant vaccine in 2013. So we

don’t really have that robust of the database. But it is an issue that is under discussion and that is going to be continuing.

DR. EDWARDS: Dr. Katz and then Dr. Monto.

DR. KATZ: I would just like to say for CDC’s perspective is that we know that adaptation affects H3N2 viruses more than the other vaccine components. As a standalone, it is probably not the only reason that our H3N2 vaccines are more. I think this is just stating the obvious again that we really need to investigate not only whether a cell-based vaccine or a recombinant vaccine that is based on a cell-grown virus sequence, or the original virus sequence, actually provides better effectiveness. We don’t know. We urgently need those studies.

CDC is talking to as many groups as we can to encourage those studies to occur, whether it is the private sector or out government partners. I think everybody should be looking everywhere they can. Then there is another piece to the puzzle, which is the repeated vaccination, the priming effect, which I believe anecdotally appears to look like again it is more of an effective with H3N2 viruses. So we need studies, systematic.

What we really need is systematic vaccine trials, where we get good serologic information on the vaccine

failures. Maybe this is what Arnold is going to say. But to understand why the vaccine is failing immunologically.

DR. MONTO: I was about to try to generalize away from the issue of only egg adaptation, which I think is a major issue right now . That is a question of which agency should be involved in this. I think all agencies of HHS need to be involved in this.

FDA's mission is to take data from perhaps one year and to look at the efficacy in that year, and to draw conclusions. CDC is now taking the important role of looking at this across years. We are in a different situation with influenza than with other agents, in which vaccine may or may not be constant over a period of time. Nothing is constant, but it is more constant than the situation with influenza.

We really need to be able to respond and then move forward. I think NIH and developing the research agenda, which has become public today, I believe, is also taking a critical role because they are the agency which really can move a lot of this forward in terms of trying to evaluate the need for neuraminidase, the question about egg adaptation, repeat vaccinations.

My own feeling is until we get a vaccine that doesn't have to be given every year, we are going to have issues about repeat vaccination. So I think we need a

broad approach, which is basically taking us back to the question of what role do we have here at the VRBPAC. That is to do what we are doing right now, to point out the needs and to try to monitor how the needs are addressed.

DR. FRIEDLAND: On behalf of industry, we absolutely welcome this type of dialogue. It is absolutely critical to be able to respond to the generation of solid, credible evidence to make informed evidence-based decisions. We absolutely welcome this discussion in moving science forward.

But it is important to mention, as was mentioned by Dr. Post, let’s remember what we have today. We have vaccines, 90 percent of which are made with egg-based technology. We need to produce upwards of 155 to 165 million doses a year, just for the United States. Then of course, just all around the globe, it needs to be done safely and economically with as was said, tried and true technology, which is that technology right now is mostly egg-based.

We want to make sure that there is confidence. The vaccines that are being used this year, as the CDC reported, and Lisa mentioned earlier today, are preventing a tremendous amount of disease, morbidity and mortality in our population. We don’t want to lose sight of what we have today and then, of course, look to the future.

DR. BENNINK: I think the DoD study may not be that good, but at least they may be able to tease out some of that because they have such a high, in the number of how much cell-based things. But if you look at that on a different aspect and just look at the whole thing, I would have though, and I still do think, that the cell-based would be better because it is not adding these issues.

But that did not increase the vaccine efficacy. It was, in fact, a couple of percent low. It is probably not statistical, but in terms of the other generalities. I would have thought that would have shown up just in the overall vaccine efficacy, as well. It doesn't appear to have done that, although it is probably not a good study that way.

DR. EDWARDS: Jacki, first.

DR. KATZ: I just wanted to comment on Dr. Friedman's point. That is egg-based vaccines are what we have now. We know that they do protect from a large disease burden. CDC is trying to increasingly phrase out communications like that. We have to be transparent. We have to provide the vaccine effectiveness data that we have.

But we also seek to demonstrate the disease averted and the death averted through vaccination. I think it would be great if we could all work together on some

messaging, so that we don't undermine the confidence of the vaccines.

DR. MONTO: Just to comment that the numbers in preliminary analyses bounce around. If you look at the numbers for the CDC vaccine effectiveness two weeks before the closure of consideration, they were considerably different from the ones that were actually published. I think we need to take this for what it is.

We see evidence that we need better vaccines. We know that we need to move forward. We need everybody to work together on the same page. We need to recognize that we need improved technology over the vaccines that were developed in 1943.

DR. EDWARDS: Certainly, the amount of information that we have coming to these meetings for the last three decades, when I first came, we certainly didn't have the genetic sequence of all of these. We didn't have real-time vaccine effectiveness. I think that we should applaud our scientists for what we have, but we still have a number of questions to address.

Any other comments? I am going to then start with Lana. We are just going to go around just giving your overall view on this, if you have any issues or questions you want to bring up. If not, you can say it looks good or whatever.

Then we are going to go over each of the components and vote yes or not. This is just a time we are going to go around and make comments on all of the strains if you have any. If you don't have anything that you want to say that is different, than that is fine, too. And then after going around, we are going to vote.

DR. FRIEDMAN: With regards to the strains and what the information that was presented today, and the real Tour de Force from Dr. Katz to help us understand the information, I feel confident in understanding why those four strains were selected by the WHO, and why they are being presented today as the four strains that we should be considered for inclusion in next year's seasonal vaccine.

DR. EDWARDS: Dr. Offit?

DR. OFFIT: This is my first time here. I just am really impressed with the quantity of information we have available in terms of worldwide surveillance to make this decision. Really, it is impressive, the public to the degree that they are sitting in the audience should also be impressed. Thanks.

DR. EDWARDS: Dr. Monto?

DR. MONTO: I wasn't around in 1943 when the influenza vaccine was developed at the University of Michigan, but almost. Again, Jackie, you have impressed us all with your comprehensive knowledge of what is going on

with the H3N2 viruses, which are driving everybody crazy. I think the complexity of the situation now, and the need to come up with a single strain selection, which doesn't quite answer all the needs is really testimony for what we really need to do. That is to understand better or why our vaccines are and are now working, as we would like. Basically, we have the easy job here, just taking one strain and selecting it because it is the best that we can do.

DR. MCINNES: I have very little to add. I echo everything that has been said. I would say after having served on this Committee for many years, this was one of the most difficult meetings we ever go to. As the data packages get stronger and stronger that get before us, somehow the decision doesn't really get any easier.

You are still sitting with a crystal ball, if you really only understood flu. It is a very serious decision that gets made here. I think we have been through years of sleepless nights after it and hoping we have done the right thing. This happens to be a difficult year. We learn from it, and you move on.

DR. EL SAHLY: I want to thank everyone who presented today and helped enlighten us on what is going on with the circulation. The issue of the crystal ball is what seems to be bothering me, especially with the big

component. I mean, there are all the problems with H3N2, and it has been H3N2 year. This is where more of the uncertainty lies.

The fact that 9 percent of the circulating B is the Victoria 2 deletion, 91 percent being the other. I am a little hesitant about the choice of the B. This is where my dilemma lies now.

DR. EDWARDS: I actually have the same concern to be or not to be. I think that certainly Jackie makes a very cogent point that we have seen this strain several times. People have been multiply immunized.

Since I am a pediatrician, I always worry about the babies or the little kids that haven't been immunized before. I guess that is one of the concerns that I have. But then obviously, if we choose wrongly, and this double deletion comes in, obviously we will be in trouble again. It is very difficult. And certainly, I respect the amazing experts at WHO and Jackie, as well.

DR. WHARTON: So, this is always a meeting where you get to be challenged by all the things we don't know, and we are not going to know until after things happen that haven't happened yet. Some of the concerns that we had about the H3N2 strain this year, I mean, actually there is evidence it worked pretty well in children, which is great, or at least better than we thought it might have. It is

reassuring to see that the recommended strain for this year appears to provide good coverage for emergent H3N2 strains. That feels good.

The challenge is the B strain. But the challenge always is the B strain. I don't know that I have been on the Committee quite as long as you have, but there has been a lot of conversations about B strains over the years. That is, I think, why we now use quadrivalent vaccines primarily in the United States because making these decisions about B strains was just so difficult. In fact, we were really terrible at guessing which B strain was likely to predominate.

I think kudos to the teams. I think the team at CDC, who identified the double deletion mutation and really allowed its identification and tracking, so that its emergent has been documented. We now have the option of including a novel B strain in a vaccine that people have not previously been vaccinated against.

We have the additional benefit, at least in the US, that we can continue to provide in a quadrivalent vaccine, the Yamagata strain, which in fact, was so much more common this year. I feel as good as one can feel about making these decisions when we actually have no idea what is going to happen.

DR. BENNINK: I think for me, as long as in terms of the strain selections themselves, as long as all of the youngest children are getting quadrivalent, it gives you a little bit more comfort with the fact that they are not getting the trivalent. I think that was better.

I think another comment that I will make is in terms of last year's vaccine, I will just take one step back just a second, even though we have had a bad flu year, the strains that were selected, the way that I look at this thing and see the data now, were good selections. I mean, they were as good as one could guess and make, I think, at the time. I don't think we could have done any better.

I am encouraged actually by the fact that particularly the half year to eight years old, it is almost 60 percent effective in terms of this thing. Now, that is probably in terms of getting it right, in terms of what we are trying to do today. I think that is really, to me, good.

It speaks as much as anything about is the vaccine even for that group, and I will make a statement that is probably not completely true, but is more naïve completely, is that the best we can do? I would hope no. I would hope we could have something that was even better than that.

But the real striking thing gets to what Arnold had said and what Jackie had said. That is when you go to the next group, and you go from the 9-year-olds to the 17-year-olds, it is appalling. What we don't understand with the same vaccine, what we don't understand in terms of prior immunity, what we don't understand about these other things and what needs to be done in terms of a vaccine to be better is, in a sense, not what we are deciding today, but what we need, and as we are saying, what we all need to be working toward.

DR. BOK: I think a lot of the things that I had concerns on, as Hannah mentioned, I feel reassured by what Melinda educated me that all the vaccines purchased with Vaccines for Children Fund are quadrivalent. Overall, 75 percent of the vaccine use in the US is quadrivalent. That is my only thing to add.

DR. WIESEN: A couple of quick clarifying points. Most people probably know this already, but sometimes, they get a little bit confused about what the military does and doesn't do, and how it is the same and how it is different. Yes, we have very high vaccination rates because we can require active duty to do that. We pretty much get out to about 100 percent by the end of the year.

Some of these people get it early. Some of them get it late. Sometimes the reason people got flu and

weren't yet immunized because the timing was off. It is not that they were necessarily a group of people who had an administrative or medical exemption.

But the other point is while we do have substantial proportion, they have different types of vaccines. And if that wanted to be looked at, we would certainly be willing to assist. We cannot force people to participate in research that has to be voluntary. So that is one thing that people sometimes misunderstand.

And the other thing is that the population, the median age is about 23 for the active duty. And so they are generally less susceptible to flu anyway. And often, they have been multiply immunized because they have to get it every year. And so I don't know how generalizable any data would be from that.

But we are certainly willing to participate from my level at the Department of Defense, we certainly want to participate. But we want you to know that there are limitations to what we can offer, as well. That is all I had. Otherwise, I had no issues with vaccine selection.

MR. TOUBMAN: I don't have the expertise to really question the judgment of all the folks at WHO and CDC and others, including around the table today. I do appreciate all of the contributions.

My only question I guess, or comment, when Dr. Katz explained the areas that really require research and response to other comments, specifically egg versus cell-based, and also the impact of previous immunization, it would be nice if there was a plan for that for doing those kinds of studies. I don't know how this group can help in that.

As always, there is a financial aspect of the cost of running studies. It seems like given the unfortunate, though it is doing great, also the numbers are low in terms of effectiveness. So if there was a way to come up with a plan to do those studies, I would strongly urge it. Thank you.

DR. EDWARDS: What we are going to do now is we are going to go over each of the questions. We are going to vote yes if we agree to that inclusion. We are going to vote no if we don't.

So the first will be the inclusion of 1A, inclusion of A/Michigan/45/2015 (H1N1) pandemic-like virus. Should that be included in the trivalent and quadrivalent vaccine? Can we vote now? Okay. One strand at a time, this is 1A, so inclusion of A/Michigan (H1N1) Okay. We have to read each of these. Sorry. All of the voters voted yes, Edwards, Janes, El Sahly, McInnes, Monto, Offit, Shane, Wharton, Bennink, Bok, Wiesen, and Toubman.

Okay. The next vote will be 1B for the inclusion of A/Singapore (H3N2)-like virus. If you want to include it, yes. If you don't, no. Can we vote now?

Holly?

DR. JANES: I vote yes.

DR. EDWARDS: Okay. So everyone voted yes with no abstains and no noes. Edwards, Janes, Wharton, Bennink, Bok, Wiesen, Toubman, El Sahly, McInnes, Monto, Offit and Shane.

1C, the inclusion of B/Colorado/2017- like virus of B/Victoria lineage, yes or no? We are ready to vote.

Holly?

DR. JANES: Yes.

DR. EDWARDS: Again, we have 11 yeses, one abstained. Edwards, Janes, Wharton, Bennink, Bok, Wiesen, Toubman, McInnes, Monto, Offit, Shane voted yes, and El Sahly voted to abstain.

Okay, the final question 2A, for the quadrivalent vaccine, the inclusion of B/Phuket/2013 as the second influenza strain in the vaccine. Yes or no?

Holly?

DR. JANES: Yes.

DR. EDWARDS: Okay, so we have 12 yeses, Edwards, Janes, Wharton, Bennink, Bok, Wiesen, Toubman, El Sahly, McInnes, Monto, Offit and Shane voted yes.

I think we have addressed all of the questions. I certainly would join in the comments that Hannah made about the excellence of the presentations. All of them were superb and we really learned a great deal.

Thank you all for your excellent participation. We hope that we will see a very good season next year with very little disease. Thank you.

CAPT HUNTER-THOMAS: Thank you, everyone. Travel home safely.

(Whereupon, the meeting was adjourned at 2:40 p.m.)