Dr. Pergam: Thanks, Dr. Fries. That was great data to compliment what's been previously discussed. I want to get back to the Influenza B, and I'm sorry I'm kind of stuck on this. But I think you had in, at least in the data for those currently in service, about 200 or so Influenza B cases, but you're only able to sequence 6. Maybe this is just a quick question. Were most of those B-positives from the rapid testing or from PCR? That's, so it was probably potentially false positives potentially. Is that what you guys are estimating from that?

Dr. Fries: That's our working thought at the moment. Yeah. We could only get our hands on so many, and to Dr. Wentworth's point earlier, there is a concerted effort by a lot of our labs going forward to lineage type those, but it does require that extra typing.

Dr. Pergam: Okay. Thank you.

Dr. El Sahly: Dr. Portnoy.

Dr. Portnoy: Yes. Thank you. I'm always pretty much overwhelmed by all of this information, but I do have two questions, two brief ones. Do you, in addition to measuring anybody titers to the influenza vaccines or strains, do you also measure cell mediated immunity? And do you have any information about that? Or does anybody measure cell mediated immunity? And my second question is, do you know what the durability of the VE of the response is? How long does this antibody response last and does it wane over time after the vaccine has been given?

Dr. Fries: Unfortunately, yeah, to both of those questions, those would probably be best answered by Dr. Wentworth in the human serum data. You know, we rely on the ferret antisera data that we see, and we sort of glean from the CDC, so I would have to defer to CDC on that question. Sorry.

Dr. Portnoy: Okay. Thank you.

Dr. El Sahly: Hmm. Okay. We will have an opportunity to ask additional questions during the Q&A. One brief question I have is, given sort of the homogeneity of the population, especially in the active members data, do we see,, in the individuals who have influenza and have been vaccinated, which was 94% of the population, do we see that the strains are any different between those 6% and those 94%? And I ask this question just because you have sort of a controlled environment here.

Dr. Fries: So the first point to emphasize that this year, with the early season, we did not see that high rate. Yes. In the last five years, we can estimate that 94+% have been vaccinated at least once. To your point about some sort of impact of heavy, induced vaccination, those heavy rates, it does create sort of like a natural sieve environment of vaccine sort of pressure. And there are a number of studies being done throughout the DoD and partnership with CDC and NIH on those exact questions of looking at sort of a sieve effect of that. But I'd hesitate to sort of speculate any kind of real heavy impact because of the ability to just drift on a whim sometimes for these viruses, specifically influenza.

Dr. El Sahly: All right. Thank you, Dr. Fries. I see no additional raised hands. To discuss the candidate vaccine strains and potent reagents, Dr. Manju Joshi will be joining us now. She's the Lead Biologist, Division of Biological Standards and Quality, Office of Compliance and Biologics Quality at CBER. Dr. Joshi.

Candidate Vaccine Strains & Potency Reagents — Dr. Joshi

Dr. Joshi: Hope you can hear me. Thank you for the kind introduction. As she mentioned, I am the Lead Biologist in the Laboratory of Biochemistry, Virology, and Immunochemistry in the Division of Biological Standards and Quality Control, in Office of Compliance and Biological

Quality at CBER. In today's talk, I'm going to just give you an idea about the candidate vaccine strains and the potency reagents, very important ones, which are needed for vaccine testing. Next slide, please.

So mainly, I'll just cover two aspects. One will be what are the WHO recommendation for 23-24 northern hemisphere influenza vaccines. And I will give you an idea about the availability of the potency testing reagents for each of the recommended strains. Next slide please.

So, WHO recommended viruses for Influenza A, H1N1 type for 23-24 Northern Hemisphere vaccine season is different from the 22-23 Northern Hemisphere season, and is also different from what was recommended for 2023 Southern Hemisphere season. For egg-based vaccine, WHO recommended that A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-derived vaccines. While for cell culture or recombinant based vaccine, WHO recommendation is for A/Wisconsin/67/2022 (H1N1)pdm09-like virus, which is MDCK cell derived. Next slide please.

So as far as the availability of the candidate vaccine viruses are there, this was from the most recent list from the WHO website, and I'm sure more viruses will be added to the list in the due course as the candidate vaccine viruses become available. But for A/Victoria/4897 wild viruses as well as candidate, CVV, which is IVR-238, has been made available by VIDRL in Australia. Next slide please.

For A(H1N1)pdm09 CVVs, for cell culture-based vaccine, two viruses have been recommended, which are available on the WHO website currently. And one is the A/West Virginia/30/2022. And the second one is A/Georgia/12/2022, which are available from CDC in US. Next slide please.

So we have to always think about the potency reagents. In the event this committee approves or goes with the recommendation made by WHO, potentially testing reagent will be required for this new strain. As always, CBER will work with essential regulatory ERLs, essential regulatory laboratories, the ERLs, and with manufacturers to prepare and calibrate the required reference antigen for testing of the vaccines produced in egg platform and cell culture, and for recombinant vaccine, as well. And since the serum production takes some time, we are already planning into the process of making antiserum for this train, provided Committee approval of this train. Coming to the next slide. Next please.

So as for Influenza A of H3N2 type is concerned, WHO recommended virus for 23-24 Northern Hemisphere season vaccine is same as for that recommended for 22-23 Northern hemisphere season. And it's also same as the this which was recommended for 2023 Southern Hemispheres season for egg-based vaccine. WHO recommends that A/Darwin/9/2021(H3N2)-like virus be used in the vaccine. And WHO recommendation for cell culture- or recombinant-based vaccine is an A/Darwin/6/2021(H3N2)-like virus. So since these strains have been used for past two seasons, candidate vaccine virus is, many of them are available and have been successfully used in past vaccine production campaigns, and they are all the state on WHO website. Next slide please.

So if, again, every time I had to reiterate that if Committee approves of this strain to be included in the vaccine for US campaigns, I'd like to give you an idea about the potency testing reagents, which are available for testing of vaccines. As always, we work in collaboration with essential regulatory laboratories all over to ensure that reagents are available for testing. Here in the table, I have listed all the reagents which are required for testing of vaccines made in different platforms. Just want to highlight what we have available in our stocks is for the

A/Darwin/9 cell-based, reagents for A/Darwin/9 SAN-010 CVV. At the same time, we have the reagents, both reference antigen as well as antiserum, available for A/Darwin/11/2021 cell platform, as well as A/Darwin/6/2021 for the recombinant platform. Additional reagents are also available for various different assortments or viruses from our ERL partners as well. Next slide please.

Coming to the Influenza B for the from the Victoria Lineage, WHO recommended virus for 23-24 Northern Hemisphere season for both trivalent and quadrivalent vaccine is same as the one for 22-23 Northern Hemisphere and what was for 2023 Southern Hemisphere season. WHO recommends that for egg-based vaccine, B/Austria/1359417/2021-like virus be used. For cell culture or recombinant vaccine, it's the same virus. Same virus, which is MDCK cell derived. Again, candidate vaccine viruses, many are available. And as for H3N2, these have been used in past vaccine production campaigns. Next slide, please.

Just to give an idea about that, if this strain was included and how are we going to be dealing with and what are the reagents available for these strains? Again, I would like to point out that for past campaigns we have produced reagents for the egg platform. In the interest of time, I'm not going to read all the details of it, but here's B/Michigan/01/2021, which is a B/Austria-like antigen and was used in vaccine. CBER had provided reagents for testing of those vaccines. At the same time, we had prepared reference antigen reagents for B/Singapore/WUH4618/2021, which is a B/Austria-like antigen and was used in cell platforms, and as well as for B Austria reference antigen, that strain, which was used in recombinant platform. So all these three agents are available from CBER currently. There are other reagents as well, available as well, which are listed on the table from our ERL partners as well. Next slide please.

So coming to the second B strain, which is from B/Yamagata Lineage, WHO recommended virus. For 2023-24 Northern Hemisphere season is same as the one which was for Northern Hemisphere campaign last year, and as well as for the ongoing Southern Hemisphere season. And as all of us, we know that this has been a part of vaccine for several, many years. So it's a B/Phuket/3073/2013-like virus for egg vaccine. And same is true for the recommendation for cell and recombinant vaccine. Next, please.

Again, I've listed here, if Committee approves of this inclusion in the vaccine, the reagents that will be needed for the testing of vaccines are available as listed up here. Reagents for egg platform testing, as well as for cell and recombinant platforms, are available from CBER, as well as from other essential regulatory laboratories as well. So next slide, please.

So I would just like to conclude in saying that I've provided you the situation about the vaccine testing reagents if the WHO recommended strengths are approved by today's committee and are included in vaccine. Just, not so much for committee, but for the general audience who are listening to this meeting, I just wanted to say is they can, as far as CBER reference standards and reagent ability and shipping is concerned, they can contact us at this email address I have provided here. And if you have any questions regarding, or you have any feedbacks or comments or any general inquiries regarding reagents or testing of the influenza vaccine, we have our CBER influenza feedback mailbox, and the email address is provided here. So we can be contacted, and we will be happy to help it out. So we are going to direct all our efforts to make sure that all the reagents are available in timely manner and the vaccine testing and release goes on, for the public, the vaccine testing goes on in a smooth manner. Thank you. And I can take any questions.

Dr. El Sahly: Hmm. Thank you, Dr. Joshi. Any of the committee members with questions for Dr. Joshi, please use the raise your hand function. I do not see any raised hands. Thank you, Dr. Joshi.

Dr. Joshi: Thank you.

Dr. El Sahly: To provide comments from manufacturer representatives, we have Dr. Elizabeth Neumeier, Director of the Technical Lifecycle Management, Influenza Global Vaccine Manufacturing, science and Technology at GSK. Dr. Neumeier.

Comments from Manufacturer Representative — Dr. Neumeier

Dr. Neumeier: Yes. Thank you very much. Thank you, Dr. El Sahly. I'm having trouble to start my video. I apologize for that. So I would first like to thank the VRBPAC committee 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. Specifically, these are Sanofi, AstraZeneca, Seqirus, and GSK. Each of these manufacturers has contributed to this presentation. Next slide, please.

So here is my disclosure statement. I am an employee of GlaxoSmithKline, and I own shares in the company. Next slide, please.

So to summarize some of the key messages and to give an overview of my presentation, I will give an overview of our vaccine production, release and distribution timelines, the preparations that we make together with the public health service organizations throughout the year, and some insight into some of the challenges that we face as vaccine manufacturers. Next slide please.

So, a successful influenza vaccination campaign is a team effort. The goal is clearly to provide an influenza vaccine that is well-matched to the circulating influenza viruses in sufficient quantities and well before the start of the influenza season, so that everybody for whom vaccination is recommended can be protected in time. If we start from the top and move around clockwise, the first key success factor is to have a vaccine that is well-matched to circulating strains. And we heard some allusions to that already today, that the H3 virus seem to be a good match. And this is visible in the good protection. This selection of well-matched strains is based on ongoing and robust surveillance of circulating influenza viruses. And this data provides the WHO and this committee with the required information to make that decision.

The next circle shows that the time needed to select the best strain must be balanced with the time that is needed by manufacturers to produce and distribute the vaccine before the start of the influenza season. So here, it is critical that strain selection and supply of candidate vaccine viruses and potency reagents is in time for manufacturers to evaluate the available CVVs, and to select the ones that work best in our respective manufacturing processes so that sufficient quantities can be produced. All these elements play together to produce a well-matched vaccine that is available before the start of the influenza season in sufficient quantities to protect all those who need it. Next slide please.

This slide gives an overview of the influenza detections reported to FluNet in the United States since 2019, meaning before the start of the COVID-19 pandemic. The pattern clearly shows the impact that the COVID-19 pandemic had on flu circulation after the onset in 2019-20. There were very few cases during the 2020-2021 season. However, there were isolated pockets of influenza activit,y and antigenic drift continued so that antigenically distinct variants evolved

even though influenza circulation was very low. Influenza activity resumed, then, late in the 2021-22 influenza season, but went on far into the first half of 2022 in an unusual biphasic curve.

Now in this influenza season, the 22-23 season, we saw an early onset of influenza circulation with a very high peak that for the influenza detections exceeded the pre-Covid level but dropped off early rapidly in January. And we heard all about it from Dr. Grohskopf and Dr. Wentworth. Influenza circulation appears not to have returned to the pattern that we were used to seeing before COVID-19, but although circulation has been low and irregular in some seasons, the evolution has continued and required updates to the vaccine composition. Next slide, please.

So if we look back at the Northern Hemisphere 22-23 season, there were two strain changes recommended by the WHO and confirmed by this committee. Both components had already been a component of the preceding 2022 Southern Hemisphere vaccine. That means that candidate vaccine viruses and potency reagents for the new strains were readily available at the time of the vaccine recommendation. And their availability was not a limiting factor in the production campaign. So the 2021-22 season was not one of the more challenging ones, because virus and reagents were available early. And also an important factor, the new viruses had acceptable yield in the manufacturing processes. Next slide please.

This slide gives a snapshot of the main activities that occur each season that have to be done to achieve the US supply timeline. Many of you may recognize this slide. We have used it in in previous years already. So in order to meet the vaccine demand, manufacturers begin to produce at least one of the three or four vaccine components at risk before the vaccine strain selection meetings. And to mitigate that risk, we use surveillance data that is available at the time. This is shown in the yellow bar. And just a general comment, the slide is broken down into

the upper panel, which shows the activities that go on in public health sector, and the lower part of the graph shows the activities that are part of influenza vaccine manufacturing.

So once the annual strain selection meeting occurs, and it is shown as the blue triangle on top of the graph, once that meeting occurs, production of all vaccine component begins. And of course, if there is a strain change, we have to start with producing new working virus seeds. And in parallel, potency assay reagents are produced by our public health partners. So since we can only produce, or since we start to produce these working seed viruses once the vaccine composition is confirmed, this already emphasizes how important it is to have these viruses available early.

Production continues, then, with all four components. Not all four components may have the same yield, so different amounts of batches may be needed. Towards the end of the campaign, balancing of manufacturing is done to ensure that we have equal amounts of each vaccine component produced. And the antigen yield of the least productive vaccine strain is actually the rate limiting factor and determines the number of vaccine doses that are supplied and also the supply timelines.

In order to formulate the vaccine, which is shown by the blue triangle just between May and June and the arrow that is pointing down from the public to the manufacturing section. So in order to start blending the vaccine components, we need potency reagents, and we start immediately once those are available. But of course, we need to wait until these are available from the health authorities. So again, a very critical time point in the manufacturing campaign. When, after secondary manufacturing has started formulation, filling, packaging, and distribution can start. And this process extends into the fall, when vaccination is recommended.

You can see from the slide that it takes about six months to manufacture, release, and start distribution of the volumes of vaccine doses that are required for the season. The timelines are very compressed. In a period of eight months, we have to supply, so all manufacturers have to supply a total of up to 200 million doses to the US market. And most manufacturers also supply other countries. And the total volume that is produced and distributed globally is more than 500 million doses. Early demand planning is very critical to ensure sufficient supply of vaccine, because once the campaign is planned and ongoing, it is next to impossible to produce more volumes than have been planned well before the season. If any of the components in these timelines start to slip, it will impact vaccine delivery for the annual vaccination campaign and will delay the volumes that are available to the patients.

So, in summary, influenza vaccine manufacturing is determined by the need to distribute and administer vaccine well before the season peak, the availability of the candidate viruses, and critical potency reagents for the vaccine suppliers. Next slide please.

The seasonal influenza vaccine supply requires a well-coordinated timing among a number of key players. And some time ago, we came up with this analogy of a relay race, where members of the team take turns performing their roles. So the race starts with the strain selection process by WHO collaborating centers, the essential regulatory laboratories, and the high yield reassorting laboratories, who then hand off the baton to the manufacturers. At the time of the strain selection, manufacturers, as I said, have already started to produce vaccine at risk, and we are at full speed when the handoff occurs of the new strains and the new formulation.

There are some special challenging for influenza production in this relay race, and this includes multiple candidate vaccine viruses, production of multiple reagents, and also multiple vaccine types. Multiple providers, such as WHO collaborating centers, essential regulatory

laboratories, and high yield reassorting laboratories. For each season, we are also facing hurdles that can be specific for that season. For example, in the 2022-23 season, we had two strain changes for H1N1 and H3N2. However, as I said, CVVs and reagents were readily available, so there were no delays due to the availability of these critical components. The Nagoya protocol, which I will discuss in some more detail in a couple of slides, can also impact timely availability of the best matched vaccine virus or DNA sequence. In the 22-23 season, the CVVs were not impacted by the Nagoya protocol.

For the 2023-24 season, if we take an outlook, the WHO recommended to change the H1N1 component. If this committee follows the WHO recommendation, new CVVs and reagents will be needed for the H1N1 vaccine component. And Dr. Joshi, just before my talk ,already laid out some of the details for this process. For the currently available CVVs for the new H1N1 component, we also do not expect issues coming from the Nagoya protocol.

I think this is a good time point to take the opportunity to really thank our collaborators in the public health sector and to acknowledge the successful collaboration we had over many years, which enables manufacturers to provide the required number of doses at the time when they're needed. So thank you very much on behalf of all the manufacturers that supply the US markets. Next slide please.

So here I'm showing the cumulative number of doses distributed in the United States over the last three influenza seasons. We can see at the first data point that a relatively high volume was available early in the season. And if we move on through the timeline, most of the required doses have been largely distributed by November. To date, in the current season, approximately 175 million doses have been distributed. This is comparable to the 2021-22 season, but it falls

short of the flu season of 2020-21. On the next slide, this is even more visible. If we can move to the next slide, please. Thank you.

So here we see two graphs that show the accumulated number of doses distributed to the US market over time. And if we start with the bottom right graph, it shows the evolution of the vaccine demand over the last 40 years. So there has been a steady increase and an overall rise in the total doses over time. However, it also shows what I just said, the drop after the 2020-21 season, and you will notice that the graph stops with the 21-22 season. So we expect either the same level or potentially even lower for the current season.

Apparently, the influenza vaccination uptake has also been slower and lower than in previous seasons, and I cannot speculate what the reasons are for that. But it is critical to understand that the supply of vaccine doses is driven by demand, and it is very critical to emphasize the importance of vaccination for all groups for which vaccination is recommended. I mentioned it earlier that planning of production volumes occurs well before the influenza season and higher volumes cannot be produced at short notice. For example, if a severe influenza season is expected. Next slide please.

So to summarize our review of the 22-23 season, we had a very high influenza peak early in the season. Influenza vaccine was available early. The vaccine demand was lower compared to previous years. And as we also heard the good news that in this season the VE flu vaccine provided substantial protection, which is what we are all working towards. Next slide please.

So I'm now switching gears and I will present a few slides on the Nagoya protocol and the impact of the Nagoya protocol on seasonal influenza. Just to provide a little bit of background, the Nagoya protocol on access and benefit sharing is an international treaty supplementary to the Convention on Biological Diversity, CBD, which was adopted in 2010,

with the objective of fair and equitable sharing of benefits arising from the utilization of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity. An increasing number of countries have enacted Nagoya protocol and/or national ABS, so access and benefits sharing legislation. And in many cases, genetic sequence data are now included within scope. Next slide, please.

For the influenza surveillance in the Influenza Surveillance Network, most national influenza centers continue to supply influenza viruses under the agreed terms of reference as part of the Global Influenza Surveillance and Response System, GISRS. However, there is often a lack of legal clarity if the viruses can be used for vaccine manufacturing and research. If we look at the two world maps and compare the locations of the National Influenza Centers in the WHO GISRS and the countries that are party to the Nagoya protocol, that's the map on the right hand, it is very clear that there are already significant overlaps. And as more countries become party to the Nagoya protocol, this may have an impact on increasing number of national influenza centers that supply viruses to the WHO network. Next slide, please.

If we take a step back and look at the more global impact of the Nagoya protocol, it is important to realize that the sharing of pathogens and their associated information must be fast, easy, and legally certain. In recent years, national Nagoya and other access and benefits sharing legislation requiring bilateral negotiations has created significant bureaucratic hurdles which make it increasingly difficult to achieve. There are already more than 100 distinct ABS laws around the world, which potentially impose legal requirements for benefit sharing that companies must navigate in return for access to pathogens.

Although the Nagoya protocol recognizes the importance of public health, only 12 countries out of 137 have ABS rules that include a public health emergency provision, which is

critical for rapid and unimpeded sharing of pathogens. This has weakened legal certainty in access to pathogen samples and sequences, with negative consequences seen already in the sharing of a number of viruses, including seasonal influenza. In the case of influenza viruses, since 2018, vaccine manufacturers have seen delays ranging from three weeks to nine months before being able to access around 40 important influenza samples. And if you remember the timelines I have shown previously, a delay of nine months makes a virus unusable for a given influenza season. Next slide please.

So, the timely sharing of pathogen samples and information is critical and essential for responding to potential epidemics and pandemics. The inclusion of pathogens, including influenza under national ABS legislation continues to cause delays and disruptions. Approximately 40 influenza viruses have already been impacted by national Nagoya protocol or ABS legislation, incurring significant delays before legal clarity could be obtained. And the legal certainty regarding the number of the status of pathogens sharing is essential in the context of vaccine manufacturing. Next slide, please.

So, I'm including, or we manufacturers are including, one slide on the circulation of avian influenza viruses in wild birds and poultry. This is a topic that has very high attention at the moment because, since October 2021, an increasing number of outbreaks of avian influenza has been reported in wild birds and poultry worldwide, with expanding geographic regions being impacted. Another important point is that infections of mammalian species have been reported with high frequency. Despite all that, the risk of human health is currently still considered to be low. And of course, this is continuously monitored carefully. If new antigen variants emerge, new CVVs that match these variants are prepared by the WHO network and are made available to industry. The response to a potential pandemic threat requires coordination among all

stakeholders in the public and private sector, and a continuous dialogue to guide the efforts of industry so that we reach the best possible level of preparedness. Next slide please.

So to summarize, two components of the 2022-23 influenza vaccine were updated to match circulating viruses, CVVs, and potency assay reagents were available early. To date, approximately 173 million influenza vaccine doses were supplied to the US market. However, it has to be noted that vaccine demand was lower compared to previous years. Influenza vaccine provided substantial protection this season. The Nagoya protocol and ABS legislation is posing an increasing challenge and impacts the ability to select and manufacture the best vaccine strains. Confidence in influenza vaccination continues to be of great importance as flu circulation returns to pre-COVID-19 levels. Next slide, please. So I would like to thank you for your attention, and I'm happy to answer any questions.

Q & A

Dr. El Sahly: Thank you, Dr. Neumeier. Please use it, the raise your hand function to ask questions to Dr. Neumeier. Okay. So I have a clarifying question. The flu distribution, it's also the uptake, right? Not just what went into the market, it's what went into the arms?

Dr. Neumeier: My understanding is it's the doses distributed to the market, not necessarily what has been used to vaccinate.

Dr. El Sahly: Okay. Okay. So to that, I may have a question then to Dr. Grohskopf. Did we see that trend you know, the distribution going year by year, also the uptick? Has it been going year by year in the last two, three years?

Dr. Grohskopf: You mean, sorry, Dr. El Sahly, has it been increasing, has the, has coverage been increasing or changing the last two, three years?

Dr. El Sahly: Yes. The distribution has been decreasing according to Dr. Neumeier's data. But that is distribution. Has the uptake also been decreasing, or is it more steady in our country?

Dr. Grohskopf: It depends on the group that you're talking about. There have been drops in coverage over the last two seasons, particularly in some groups. And they're more in some racial and ethnicity groups than others. Coverage among pregnant women has been a bit lower the last two years. So there has been some concern about drop in coverage.

Dr. El Sahly: What about individuals older than 50 or 60? Are we still, they used to have the best coverage. Are they still good there?

Dr. Grohskopf: In general, theirs tends to be more stable.

Dr. El Sahly: Thank you. And then I have a question about the Nagoya protocol. I know we hear about it every year, but I wonder if it has more of an impact on avian pandemic influenza than seasonal influenza. I guess in my, I guess simplistic interpretation of what I see, that may be the case. But what are your thoughts on that?

Dr. Neumeier: The impact is primarily on seasonal influenza vaccine manufacturing and strains. At the moment, for pandemic viruses, they are also in scope. However, we do have a framework already for the availability and distribution of zoonotic influenza viruses, the PIP framework. It is still under discussion whether there's also obligations for pandemic viruses under the Nagoya protocol or whether that is covered by the PIP framework.

Dr. El Sahly: Okay. Alright. Thank you. Couple of questions. First, Dr. Perlman.

Dr. Perlman: Yeah, I just had two almost technical questions. So the first, with the problem about getting some of the viruses shared, do the manufacturers have the ability to use recombinant technology to just make the viruses instead of having to get them shared? Or is there something more to sharing than that?

I had previously given a presentation to this committee regarding anti-vaccine lobbying, and today is simply an update to that information. Next. Anti-vaxxers represent a cultural force that goes beyond questions about vaccines. As we shared last time, there are numerous anti-vaccine 501c3s, c4s, LLCs, and PACs that work often in tandem with one another to accomplish an overall anti-public health agenda. Next. However, these groups are also the source and funding behind numerous petty lawsuits, and that's a trend we've seen growing. As the director of research for SAFE, I see firsthand how many active lawsuits are a direct result of anti-vaccine efforts. Next.

These lawsuits, again, the anti-vaxxers themselves, are quite candid about the origin and purpose of these lawsuits. And these lawsuits often target public health employees and agencies and their employees. And regardless of whether a lawsuit is successful, the mental strain and financial burden is real. Those are resources and time that could be spent on other more legitimate efforts. The most alarming example I have found of this involves an attorney general who is working directly with local anti-vaxxers and openly displayed anti-vaccine propaganda while deposing Dr. Fauci. Next.

Now, I know that sounded kind of scary, but the good news is that SAFE is working in partnership with other grassroots groups such as Louisiana Families for Vaccines. Louisiana Families pushed back against the rising tide of anti-vaccine legislation in their state by showing up with friendly faces and important information. And because of their efforts, all of the anti-vaccine legislation in Louisiana was successfully killed in 2022. We're obviously hoping for a repeat of that in 2023. Next.

The bad news is that anti-vaccine extremism is growing, and we've seen with that a rise in the total number of vaccine related legislation introduced all over the United States. Montana

is in particularly bad shape, as they are currently debating a bill that would prohibit Covid vaccinated persons from donating blood, and they are the first state poised to expand non-medical exemptions to routine school immunizations in over 20 years. I can confirm that not only are the anti-vaccine groups working hard to get these bills in Montana passed, but they're also doing so with direct assistance of the legislators in that state. Next.

Without naming names, I think it's important to put into perspective how much the largest anti-vaccine organization is spending on their efforts to roll back public health. Next. After going through publicly available job listings, I estimate that the largest anti-vaccine organization is at an absolute minimum spending 1.3 million a year just on payroll. All of these job listings offered insurance and 401k, but without knowing the quality of those benefits, I simply excluded them from this estimate. If we were to include benefits, travel events, and the copious amounts of money they are spending on lawyers, my best guess for their yearly operating budget is no less than 10 million. Next.

Yes, one anti-vaccine organization, just one, is almost certainly spending at minimum 10 million a year. And that might seem like a scary number. And truth be told, I hope it scares you just a little bit. Some of you are probably wondering how they can afford such a large budget, and I can confidently tell you it's because this same organization, by my estimate, has raked in well over 20 million dollars in the past few years. And some of those pieces of information, it's hard to quantify that because certain financial documents and 990s have not become public knowledge yet. But I imagine that our understanding of exactly what this anti-vaccine ecosystem looks like will change as more this information comes out. Next.

So, SAFE Communities Coalition is a team of three and one volunteer, and that is me. And as I said, I do not get paid. I have no conflicts of interest. I am a volunteer. I do this out of

my own time and passion for this issue and for how much I care about it. And I see how much more resources the anti-vaxxers have versus all vaccine advocates. And I'm not just talking about SAFE Communities Coalition. I do not think, but this is just, the estimates I gave you were from one organization. If we were to take the totality of all of the anti-vaccine organizations that are working together, I mean, that number, I don't, we didn't even know where to start. So I just want to emphasize the importance of promoting vaccine, pro-vaccine legislation, promoting pro-science candidates. And obviously SAFE Communities Coalition is here as a resource for anybody, whether it's the people on this call or anybody listening now in the future. You know, please reach out to SAFE Communities Coalition. We have excellent information. I can attest to that from firsthand knowledge, excellent information on the anti-vaccine movement and where the pro-vaccine movement is going as far as legislation and lobbying. So I really thank you all for your time. And if you have any questions, please email them to us at info@safecommunitiescoalition.org. Thank you very much.

Ms. Vashio: Thank you, Sarah, for your comments today in your presentation. We appreciate it. This concludes the Open Public Hearing session for today, and now I hand over the meeting back to our chair, Dr. El Sahly. Could you please start the next session?

Dr. El Sahly: Thank you, Ms. Vashio. So, during the next portion of our meeting, for which we have dedicated one hour, we will be discussing the four questions that we will be voting on. Dr. Paydar, should we display them or just begin the discussions first?

Dr. Paydar: We need to display the four questions and discuss them.

Dr. El Sahly: Alright, let's display. Okay, so here are the four questions to be discussed today. I'm going to go over them. First question one. For the influenza A (H1N1) component of the 2023-2024 influenza virus vaccines I the U.S., does the committee recommend an

A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-based vaccines and an A/Wisconsin/67/2019 (H1N1)pdm09-like virus for cell- or recombinant-based vaccines? And that is a change.

For the Influenza A H3N2 component of the 2023-2024 influenza virus vaccine in the US, does the committee recommend an A/Darwin/9/2021 (H3N2)-like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)-like virus for cell- or recombinant-based vaccines? And that is a change.

For the influenza B component of the 2023-2024 trivalent and quadrivalent influenza virus vaccines in the U.S., does the committee recommend inclusion of a B/Austria/1359417/2021-like virus of the B/Victoria lineage?

For quadrivalent 2023-2024 influenza vaccines in the U.S., does the committee recommend inclusion of a B/Phuket/3073/2013-like virus of the B/Yamagata lineage as the second Influenza B strain in the vaccine.

So I invite our committee members to use the raise your hand function so I can see who has a question. And I think all of our presenters from this morning and the FDA are present to help answer questions or listen to our comments. I see the first hand by Dr. Gans.

Committee Discussion, Recommendations, and Vote

Dr. Gans: Thank you so much, Hana. I'm going to leave my camera off if that's okay. I really appreciated all of the really in-depth presentations that we had this morning and usually have during this meeting. And really gets us to be able to review the data that actually would obviously contribute to these questions. So I am in support of the recommendations that come forth from the thorough work that the WHO and CDC and our other colleagues put forth. I do

want, just because we seem to always be in the same situation, these are highly effective mechanisms for helping public health, obviously, and vaccination is the way to go. And we have these vaccines that are helpful in really contributing to the particularly severe outcomes, as we've heard.

I just want to put in the record some of the things that have been discussed previously, but apparently, we need to get them into the public record that we really do need to move the conversation forward. And that includes from the epi side more subtype testing, and a lot of that was already raised, that that is being done. But we really need to be able to understand the strains and clades that are moving this forward and how we choose these. We need more nuanced information in terms of what, how to break down some of the epi data, not just taking a hammer to it. And that includes different populations who may be at more risk and more value of these vaccines and some of the more nuanced outcomes in terms of ICU and mortality. We also need information, as been raised, that influenza doesn't circulate alone. And what are some of the coviral infections or other co-infections.

We also, obviously from the immunology standpoint, which we've been talking about for a long time, even though we call the humoral immunity, these correlates of infection, we need more nuanced information about immunology and T-cells. We've been asking for a very long time. And we also need the studies that would allow us to move the components of the vaccine forward, as we've discussed with the H3N2. It seems that our inability to get that information maybe has allowed the H3N2, which now we see as predominating. We really maybe allowed that to happen because we've done such a good job with the other ones. And obviously there's other environmental stressors that are going, or impacts, that are going along with that.

And lastly, I think what I would love to see, and I'm sure other people on the committee, but I won't speak for them, is to really bring forward also the continued and great work that's being done looking at the safety of these vaccines, which we know are incredibly safe. And it would be lovely to have those, that data that we know is collected globally, as well, really come forward and discussed when we're looking at these vaccines so that we could look at all the data together. So I appreciate the work that has been done. I appreciate the conversations that we've been having to move this discussion forward, and I just wanted to put that into record.

Dr. El Sahly: Thank you, Dr. Gans for the summary and the comments. I have a question from the morning to Dr. Wentworth. It's more of a clarification regarding the process. So what we saw that, for the H1N1, the ferret sera, there wasn't much of a distinction between the Victoria of last year. Is it Victoria? Yes, the Victoria of last year and the currently circulating strains. However, when we used human sera, we did detect a divergence in the antigenicity between the vaccine that was used last year and the circulating strains. And I think, as I understand it, it has to do with the recognition of the epitope, kind of in the northeast of the HA, as you displayed it for us.

But what if the reverse is true? Let's say the ferret data would show diversions, significant diversions between the strain used previously in the vaccine and what's beginning to circulate. Yet the human data don't show that divergence by virtue of recognizing other epitopes. Would, what, how would that have changed recommendations? Or would it?

Dr. Wentworth: Yeah, that's an interesting hypothetical question.

Dr. El Sahly: Oh, so it doesn't happen ?

Dr. Wentworth: Yeah. Yeah. Well, I mean, it is, it doesn't really happen. So the ferret is a model, an animal model, and it, like all animal models, is imperfect. And what we've grown to understand is with the H1N1 pdm09 viruses in particular, it tends to be quite immunodominant to

that site SA side of life and not as immunodominant to the SB side. So you were dead on in your question. So now let's imagine that that inverse happen. We're seeing distinction in the ferret, but we're not seeing it in humans. So there'd be the triangulation of multiple types of data. So you have the genetic data of all the viruses that are circulating, and the evolution that you're seeing there, which is kind of a reflection of generally immune escape. I mean, that's the biggest fitness driver in humans for influenza drive, influenza viruses, is immune escape. And so sometimes you might see parallel evolution that's happening that's in agreement with the ferret data or in disagreement with the ferret data. So you would have, you would have that aspect of it.

Then we would take the human era and we would break it down. Right? So if you were to look at the 6 month to 36 month old age group in humans, and you're not seeing something that the ferrets are seeing, that would suggest that the ferret model is actually incorrect in that scenario. And to top it off, if you had VE that was consistent with H1 VE, and you had those viruses cocirculating at the time. So that's a, there's a couple of ifs there. Sometimes you don't have enough of the variant that's cocirculating for VE to be an estimate. But if VE wasn't changing, then you would believe the human side of the equation.

But if the opposite was true, we're seeing it in naive kids. There is evolution happening. That's really, really looking like this is a fitness advantage. And we use a lot of different tools there in the genetic space, local branching index. So how many changes are happening in that site. Known epitopes and crystallography with human monoclonal antibodies, understanding that they're in known epitopes is very important. That's why I show the molecular structures and point out certain amino acids. And so it would really be, it's never just one piece of data. It's the triangulation of multiple pieces of data.

And then, finally, kind of getting to some of our discussions here, which population would be at greatest risk, and does that population suffer severe disease from that particular subtype? And so that might also influence where you'd want to de-risk. You know, you'd want to err on the side of caution for an age group, like over 65, or under 3 or something like that. Did that answer your question?

Dr. El Sahly: I guess we'll wait on some committee meeting in the future for that.

Dr. Wentworth: Yeah. I mean there, I think basically there's going to always be times where the ferrets don't quite pull something apart. Or, more often, humans are just very fuzzy because we have so much prior history in our immune response, And very few antigens are given to humans, right? So we can give ferrets every new emerging virus, whereas we can't do that with humans.

Dr. El Sahly: Okay. All right. Thank you. Dr. Portnoy.

Dr. Portnoy: Alright, thank you. I have a comment and then a question for Dr. Wentworth. My comment is that we've been meeting, I've been meeting with this committee for a number of years now, and at the end of the last vaccine committee meeting for the Southern Hemisphere, we sent very strong recommendations to the pharmaceutical companies that they should consider looking at other strains, maybe trying to get a new licensure or modification of the licensure that they have. And it doesn't seem to me like any progress has been made on that. We're still basically allowed to vote on these same four types of questions that we've been voting on all along.

I guess one concern I have is that if we decide to vote no on one of these, let's say number two, we say no. Well, what's the option then? Is there another option that we could vote for? I thought that we have to kind of be in harmony with the whole planet with the WHO. And so if

we say no, there's not really an alternative, we kind of have to vote yes. So I'm not sure that we even are given an option for that. I would kind of like to hear a comment about that.

My question for Dr. Wentworth is, kind of, I asked it before, do you have any information about cell mediated immunity and human responses to influenza? How durable is an immune response to influenza vaccine? Is that dependent on the strain or the individual or what determines that? How long before the flu season should someone get the vaccine and not worry about it wearing off before they actually get the influenza? Do we have information about that?

Dr. Grohskopf: Dr. Wentworth, this is Lisa. I can take that if you like. Is that okay?

Dr. Wentworth: That would be great. Well actually ,I think the first part is for FDA and the second part is for us, but it'd be great if you start on the second one too.

Dr. Grohskopf: Referring to the waning immunity question.

Dr. Wentworth: Yeah, yeah.

Dr. Grohskopf: There are a lot of studies on that currently, and while there does seem to be some waning of immunity, the results sort of depend on a number of things. One is, it seems to be more common among older adults. There aren't as many studies of people at the extreme, other extreme of age, children. And the results are kind of mixed with kids. It seems like it might be more common with H3N2 than with H1N1. It does raise some complications with regard to policy recommendations for timing of vaccination, because as we've seen, sometimes we have early seasons. We did have an early season this season, but it wasn't the first time that that's happened over the last 40 seasons or so, roughly between 1982 and 2021. There was one that peaked in October and one that peaked in November and others that peaked in December. So it’s not unheard of.

So recommendations for timing the vaccination are somewhat made a little tricky by those things. But there, there is general acceptance. I think that there is waning, but it's not seen in every study consistently, and it's not seen cross populations consistently.

Dr. Portnoy: Do these vaccines create cell mediated immunity? Do you know?

Dr. Wentworth: Yeah, maybe I can, I can chime in there on the cell mediated piece, unless Lisa wants to. Okay. So yes, they do. And the natural infection creates cell mediated immunity. And as you're clearly aware, cell mediated immunity is kind of a much trickier thing to analyze in a high throughput fashion. There's a number of extraordinarily funded investigators from the US government, primarily through NIH, as well as many other investigators globally that study T-cell recognition of influenza viruses. And so cell mediated recognition, but by, primarily through T-cell recognition.

And the way that's working is many small peptides of every protein of the virus are really generated to make T-cell recognition epitopes, and some more prevalent than others. And flu does actually slowly mutate to evade those, you know, some of the primary ones. But really, when you consider cell mediated immunity, most of what flu is doing at that annual level is in response to antibody mediated immunity. And so that the cell mediated piece is, I'm not trying to discount it, because obviously it's an important arm of our immune system and likely pays a big role in protection from severe disease and clearance of infection. So after the acute phase of infection, you know cytotoxic T-lymphocytes and T-helper cells are really important in generating new killing off virus infected cells and general generating new. Antibodies through T-cell help and things.

But anyway. When it comes to the vaccine part selecting antigens, what I showed you is that HA molecule. 566 amino acids. Three or four are different. Six are different, right? This is

not going to kill off a T-cell response, right? You see what I mean? So this is why the updates are primarily driven, because what we're trying to do is protect people from infection and then symptomatic disease and then, of course, severe disease. And so the short of it is, a lot of the T-cells will work regardless of which antigen we select.

Dr. Portnoy: Okay.

Dr. Wentworth: You know, they'll get stimulated and boosted by almost any antigen we pick. There might be one new prime to something like Darwin, where the linear part of that epitope, which you're seeing in three dimensions, is actually quite different and spurs new T-cell recognition, for example.

Dr. Portnoy: Thank you. And what happens if we vote no on one of these?

Dr. Wentworth: Oh yeah. So that I think is really a question for FDA, and my interpretation would be it's a question of what are you saying? Vote no on a strain antigen selection.

Dr. Portnoy: What if we, what if I don't think that the, A/Darwin/9221 should be used this year? What, why are we being asked to, why are we being asked these questions?

Dr. Wentworth: I'll turn it over to Dr. Weir. And then I may follow up Dr. Weir, because I could add to something maybe.

Dr. Weir: Okay. So yes, we have, maybe I didn't say this at the start. I think I usually do. Generally, we put these out as a starting point, and if the committee should vote no, then I think the committee would have to come up with an option, a proposal for something else to vote on. Might not be that easy, but I think that would be how it would have to work. Because again, these are licensed vaccines with four components. And it's our job to select something. So I think

it would be incumbent upon you, the rest of the committee that voted no, to offer an alternative. Like I said, we usually do this, and we just assume we would deal with it if, if that happens.

Can I make one comment about the T-cell recognition though? Just to throw something out. One of the things that was noted many, many years ago is that particularly a CD8 response to influenza was mostly directed, if not all, directed against internal proteins, which of course, are not in any sort of, are not really included in the current vaccines. And in fact, vaccines that are subunit, that are proteins like this don't actually induce a very good CD8 T-cell response anyway. So it's not that it's not important, it's not, but it's probably a fairly minor component of this type of vaccines. Over.

Dr. Portnoy: Thank you.

Dr. El Sahly: Dr. Bernstein.

Dr. Bernstein: Thank you. I had a question for Dr. Wentworth and one for Dr. Fries. I recall, I think last year, I mean you present such detail and so extensively. It's incredibly impressive. And I remember, I believe last year, and then again this year, that the 5a.1 is lower in the pediatric population. Again, the response, particularly children 6 months through 35 months of age. And I was wondering how does that relate, if at all, to the fact that there's a higher than average number of pediatric deaths, for example? And how should that be considered, if at all?

Dr. Wentworth: Okay. Thank you for that question. Really insightful. So the 5a.1s, the vaccine, of course, which we ruminated more on last time around was 5a.1 versus 5a.2, because the 5a.1s had made a kind of a rebounding effect. But the likelihood, from the committee's perspective and the WHO committee's perspective, was that it was going to decline. And it has declined tremendously. The reason you see that in that age group is because, and this is the case where that age group is a little more like a naive animal model, in that the 5a.1s and 5a.2s are

very energetically distinct to a naive host. But they both come from a 5a background. So they both have the same kind of progenitor viruses. And the 5a.1s circulated prior to the 5a.2s.

And so as you get into the older age groups, they've been either vaccinated and/or infected by 5a and 5a.1 viruses. And that's why when we boost with a 5a.2, lot of those conserved epitopes across them are likely being reactivated. And so we do see neutralization. So that the gist of it is, exactly why we see neutralization, maybe I'm reaching a little bit into immunological memory. That's the most likely scenario. But we see that any of those older age groups now neutralize the 5a.1 viruses as well.

And so then with the pediatric deaths. I don't, we don't actually, don't have the numbers for H3-caused pediatric deaths and H1-caused pediatric deaths this year. Maybe Dr. Grohskopf does. But we had pretty even cocirculation of those two. That's being monitored. What Dr. Grohskopf showed was from the United States where we had an overwhelming amount of 5a.2 viruses. So those pediatric deaths are likely actually not vaccinated. Generally, and we don't get that information, I think, until later in the season, but generally about 80% of the pediatric deaths are non-vaccinated individuals. And so I don't think that the 5a, the loss of recognition in the 5a.1 group was the reason we saw those pediatric deaths. I know they were a mixture of H3 and H1, because we had so much H3 circulating early. And there were some pediatric deaths then. And we didn't have that much in the way of 5a.1 viruses in the United States.

Dr. Bernstein: Thank you. And then I had a question for Dr. Fries. It's not directly related to strain selection. But the question that I had is, you mentioned that, in the military, that flu vaccine is compulsory. And I was wondering whether that included their dependents and children from six months of age on up. And also for those that are, the 6% that are not vaccinated, what exemptions are accepted?

Dr. Fries: Thanks for the question. I can, the first point, no. It is only the active-duty component that is required. So the kids and other dependents are not required. As to the distribution of those 6%, I know there are religious exemptions. I know that there are other people on this call, perhaps a Dr. Badzik, may be able to speak more directly to other exemption components of that. But yeah, I don't know exactly that distribution. I do know that religious and/or… Well, yeah, I guess the only one I can say for a certainty is the religious. And 94% is typical. I've seen higher numbers. I've seen 97% in some of the services, so I'll just state that as well, that they're not always that 6% each year. I hope that helps sir.

Dr. Bernstein: Yeah. Thank you. And do you use, we periodically talk about exploring vaccination history over a number of years looking at different issues. Has the military, the group that since they're getting vaccinated annually and being part of the military, have they been explored as far as the impact of vaccination history?

Dr. Fries: Yeah. Now I do know that that is an active research avenue, and I'll confirm that one of my colleagues just texted and said that it is primarily religious and medical exemptions for the avoidance of the, for that 6%. As to the active research towards vaccination history, as I think I alluded to in the end of my talk is that, yeah, this is an extremely heavily vaccinated, we know all of the, you know, a good portion of the vaccination record. That does offer some insight into, especially in congregate settings, like a Naval Academy situation, where an H3N2 outbreak occurred at the beginning of the 21-22 season. Does offer some unique perspective as to what protection is provided by the vaccines. But as the specific efforts, those are in collaboration with folks at NIH and the CDC in terms of how those heavily vaccinated rates might impact vaccine or sort of antibody generation.

I will say that there have been discussions about, and I don't want to over-speak, and this is purely me, just anecdotally saying that there have been discussions about not vaccinating every year in certain populations to see whether it gets a better response. But there would have to be a tremendous amount of data to support that policy. And I'll just say that people are examining that, and our colleagues at CDC and NIH are helping. Over.

Dr. Bernstein: Thank you.

Dr. El Sahly: Dr. Berger.

Dr. Berger: Thanks. This is a question for Dr. Neumeier, actually. So, Dr. Neumeier, you laid out a really tight timeline for being able to deliver the influenza doses that are going to be manufactured. And you also mentioned that there's a total of around 500 million total doses that are being delivered worldwide. I guess what I'm trying to think about is if, what's the capacity for developing discordance vaccines with whatever is going to be eventually the licensed vaccine and used in order to facilitate some of the research that's needed here to understand the, to generate the evidence base to be able to make a change to the existing licensure?

So what is the capacity to be able to generate those additional doses that would be needed for that? Is the 500 million currently the maximum that you're already at? Is there additional capacity that's needed to be able to facilitate this? I'm just curious what kind of capabilities that industry would have to be able to conduct the clinical research that's necessary here.

Dr. Neumeier: Mm-hmm. Thank you for that question. So the development of a quadrivalent vaccine with a different composition than the licensed one is a development project, similar to the move from trivalent to quadrivalent. So I think I can say that the development will not interfere with commercial production and provision of the volumes that are required in the US market and globally. If we speak about, if I understood your question right, it was primarily

about development, but potentially also about different vaccine compositions in the market. That would be a real challenge. Because in that case, we would have to produce not only four, but potentially five or more components. So I can't, I cannot speculate on those scenarios, but that would be a real challenge, if not impossible.

Dr. Berger: Thanks. and that's kind of what I'm trying to figure out is right now the licensure seems to be that it has to be one H1N1, one H3N2, a B/Victoria, and B/Yamagata lineage. And so what we heard earlier when we were speaking with Dr. Wentworth was we don't really know what the proper composition is going to be at the end of the day. And so there might be a need to generate different types of vaccine compositions to be able to have, at least in my mind, a licensure that could allow for greater flexibility in being responsive to whatever virus happens to be circulating. It is likely going to be the most impactful for any given season. So I'm trying to understand like, what's the clinical research side of this look like and how much can you actually, are you able to respond to be able to develop that? So thank you.

Dr. Neumeier: Well, as I said, the development would be comparable to the development of the quadrivalent after the trivalent vaccine. So we would have to generate, first of all, the analytical tools to analyze two closely related, antigenically distinct, but still closely related H3 components, for example. Then, preclinical and clinical data would be needed to find out whether there is any type of interference between the different components to make sure that the immune response to all the components is there. It was mentioned earlier today already that it is conceivable that if two H3 components are included in the vaccine, the immune response would be predominantly directed to the conserved epitopes and not to the epitopes that have changed during antigenic drift. So all these things, we don't know them today, and they would have to be

part of the research program to develop a vaccine with a different composition than the one we have today.

Dr. Berger: Thank you.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yeah, I had a couple of questions for Dr. Wentworth. One of these may be one that was answered many, many years ago. But when one changes the composition of the vaccine and puts in a new antigen that's slightly different, so recognizing the changes, do you have a sense in how much of the immune response actually responds to the new antigens as opposed to the conserved ones, which we've talked about extensively?

Dr. Wentworth: Yeah, that's a good, great question. No, I don't have a direct answer. I mean, I think what I would say is you don't get a huge prime to the new epitope. You get a prime to the new epitope, but you do get a good boost to epitopes that are cross neutralizing between the new antigen and what you've seen previously. And that's evident when you look at those serology panels. You do see, when we change antigens, so like when we changed to Darwin/6 the first time, though there was a good prime against Darwin/6, it was the highest titer response. So you're more of an immunologist than I am, frankly. And so I would say that that's telling you that you are seeing some priming effect.

I think it's different. It's not always the same. Like some years we may not get as much prime as we would like to the new antigen. And it's likely dependent upon kind of your exposure history, so certain age groups and what they've seen in the past and things like that.

Dr. Perlman: The other question I had is when, you have such a huge database now, which is really great. It, do you, with the new mutations that arise in either the H3N2 or the H1N1, can

you go back like 10 years or 20 years, do those same mutations, were they there and then disappeared? Or these all new mutations, all the time?

Dr. Wentworth: Yeah, yeah. This is a great question, and yeah. You can actually do this yourself now as a lot of the data is existing in from the database can be displayed in GIS8 or in NextStrain up to about 12 years. And what you'll see is, if you start really looking at certain positions, you'll see the same position changing and rolling, what I call rolling forward. So it would go from an isoleucine to a phenylalanine to a serene, or something. So you'll see it change forward. You won't, you'll rarely see it ever go backwards unless, it kind of did when we went from seasonal H1N1 to pdm09 H1N1. And that's, I think, really a testament to what population immunity always drives. You know, even though that's a very hotspot, a hot position for mutation that is impactful, it will change to something new rather than flip back. And so that's just a general thing.

Other times, it's the context of the current hemagglutinin, so it's not always the same position. So there's seven positions that Smith et. al, Derek Smith's team, actually published quite a while back now that really, we know are important in the various epitopes, primarily A and B. But there's also the context of the current hemagglutinin sometimes puts a position to have a huge antigenic impact, when in the past it really hasn't ever been used and it hasn't had much of an impact, or it's been there and then just kind of died off, like just in a small number of virus and never gained traction. And so either that mutation, while it is causing antigenic escape, it causes fitness loss in receptor binding or some other feature, Or it's the new context of all the other mutations that are surrounding the area that's allowing that change to make a difference.

Dr. Perlman: Okay. Thanks David.

Dr. El Sahly: Dr. Chatterjee.

Dr. Chatterjee:Thanks, Hana. My question is for Dr. Neumeier as well. I am curious about those 300 million doses that go elsewhere besides the United States. Are you able to share that information with us?

Dr. Neumeier: In a general way, certainly. So most manufacturers that that supply, or all manufacturers that supply the US, also supply other markets in the world. And that may be different from manufacturer to manufacturer. So I think that's all I can say.

Dr. Chatterjee:Okay. Thank you.

Dr. Neumeier: Unless you have a specific question.

Dr. Chatterjee:No, I was just wondering, because it seems like a pretty significant proportion of the total number of doses that are that are made available. And while the US population is definitely pretty significant, there are other large population centers in other countries. And I was curious whether these manufacturers supply, for example, the Russian market or the Chinese market and things like that.

Dr. Neumeier: Yeah. I'm afraid I cannot comment on that.

Dr. Chatterjee:Thank you.

Dr. Neumeier: But in Russia or China, because you mentioned these examples, there are also several local manufacturers that supply these markets.

Dr. Chatterjee:That's what I thought would be the likely answer. Thank you.

Dr. El Sahly: Thank you. So quick question, I guess to the FDA, and to a degree to Dr. Wentworth. So the complications of having two H3s, two H1s, et cetera. I mean, the moment I start thinking about all the permutations and what potentially can go wrong in terms of interference, et cetera, it's a complicated process. But we do have evidence that B/Yamagata is no longer posing health threat to the public. And that we also have a reassurance in the back of

our mind that, to a degree, the B/Victoria does cross-react with the B/Yamagata. So not all would be lost should Yamagata rear its head again. The amount of developmental research that needs to go in removing Yamagata, I presume, is not there. It's not a high list kind of thing. So what, in your opinion would be the downside of removing Yamagata now from the vaccine?

Dr. Weir: Was that to me or to David or both of us?

Dr. El Sahly: Let's begin with you. I'll allow David a breather.

Dr. Weir: Okay. I'll start. But I think some of it's been covered. The downside, of course, is that the lack of certainty that that strain of the Yamagata has really, no longer exists. And you know, you just saw some of the slides that said that only a very small proportion of the B isolates were really typed. So there is some downside to taking it out too early. I think that was your primary question. The other downside of taking it out is that, and I kind of stressed this earlier, I think, if it's going to be… Okay, so from a regulatory point of view, it can be taken out. That part is actually hard because manufacturers are licensed to produce trivalents or quadrivalents.

Dr. El Sahly: Yeah.

Dr. Weir: The real issue is coordination, though. I don't think you're going to see one manufacturer just decide to take it out by themselves because then they will say, well, how does this play in the public? How is this going to be marketed when everybody else keeps four? So that's back to the whole issue of, if it's going to be taken out, it probably needs to be coordinated globally, just for, otherwise it's just not going to happen. Regulatory-wise, yes, we can deal with it. That's not a problem.

I think we've already discussed though, besides the issue of taking it out, there is the issue of coming up with a different composition, and that's the one we've mentioned several times, that there's just got to be some more data generated so that we don't basically do something wrong

with a vaccine and actually have something that doesn't work as well. And I think Elizabeth mentioned the fact, some of the details about, in the development work. There are some issues that can only be solved by developmental research. And that's coming up with potency reagents for two things that are very closely related, coming up with serology reagents for two things that are closely related. It's not that those are insurmountable, that just takes some work. I may have covered most of it, but looks like David can also chime in here.

Dr. El Sahly: So I could not agree more with you on the issue of if we are to choose two H1s or two H, et cetera, or if we advocate for that the amount of research that has to go through before this even begins to become a reality is huge. But the Yamagata question, I feel is separate, that it's been, even pre-pandemic, there was a decline. In the pandemic, there was nothing. In our previous meeting, we indicated, well, let's have another cycle of robust influenza circulation before we can make up our mind. So would it be another season of a similar Yamagata zero, close to zero circulation before we are confident that we probably —?

Dr. Weir: I think you're probably right. And when I talked to Dr. Subbarao who's also I think the chairman of the VCM, this particular time, I talked to her last week, she indicated pretty strongly to me that the WHO intended over the next year to have meetings, both with interested stakeholders, that included manufacturers, to just address these types of issues around the B/Yamagata. When is it going to be, when is everyone going to be comfortable that it no longer exists? Is there more data that we need to be to get to that point? So I did get the strong impression for her that there were going to be follow-ups this year by WHO to address this issue. David, you were at the meeting. You can —

Dr. Wentworth: Yeah, that's exactly right. I mean, so there's a goal to do some follow-ups. There's a goal to do some targeted work in the younger age group in particular. Because they

would be likely the most susceptible, based on population serology type work. But that is also the risk. It's to that age group wouldn't have any prior infection history with Yamagata-like viruses. They wouldn't be… So for example, if we went to a trivalent for that had a B/Victoria, you do get some boosting of the Yamagata responses in older people. But you wouldn't see that in that very young population. It would be just like my answer about the 5a.1s and 5a.2s with the H1, but it would be more striking, because there's many, many amino acid differences between those two lineages. And so that's one of the risks.

What's the benefit, is another question that maybe the committee wants to ask themselves. You know, what's the benefit of removing it if you don't have something else to switch to? And then I think in the trivalent scenario, probably in the US we're okay, but I think there may be some challenges to moving to trivalent in Europe, because I'm not sure their licenses are maintained if they're not continually used. And that would be a question for Dr. Neumeier.

Dr. El Sahly: Okay.

Dr. Weir: And can I add one more thing while I'm thinking about it? You mentioned, and you and David both touched on the cross reactivity. Just remember, back before there were quadrivalents, it was often a real struggle to pick which one of the B lineages to include. And we were essentially wrong about half the time, certainly at least a third of the time. And you could see clinical consequences when that choice was not well matched. So it's, the cross-reactivity doesn't save you. Over.

Dr. El Sahly: Okay.

Dr. Wentworth: Yeah. Thanks for pointing that out, Jerry. I didn't mean it in a way that you would be completely safe by having Victoria in there. I was trying to get at the age

difference. My recollection is some of those times the VE would go down in the twenties when you, when the tri — this was before my time, but when the trivalent was used and say for example, a B/Victoria was selected and we had a B/Yamagata season, or vice versa. So I wasn't trying to say everything would be fine in that respect.

Dr. El Sahly: All right. Well thank you both for sharing this viewpoint. Dr. Pergam.

Dr. Pergam: Yeah. So I had sort of a different question. You know, we've been talking a lot about sort of the vaccines and targeting those specific subtypes, et cetera.

But one advantage of influenzas, we have therapies that actually are effective. And I've been curious that we haven't really seen much transition to oseltamivir resistance strains or baloxavir resistance strain. In these seasons, last two at least, considering for baloxavir, it's very little genetic differences between those that develop resistance. It's maybe a mutation or two that can lead to it. So one of the questions I'm curious maybe Dr. Grohskopf can talk about this from the CDC, or others, is have we seen differences in treatment of those who are influenza positive? And I wonder as we have more Covid testing and more combination testing strategies available for both Covid and flu and RSV for that matter, is that potentially a change that we need to be sort of on the lookout for?

And then as a follow up to that, Dr. Wentworth, can you just clarify sort of how, since there are all of these genetic tests that are done on different strains and there's subtests that are done, can you just clarify how the decisions are made to look for resistance and what percentage, if at all possible, these are done to look for resistance within the strains of particularly Influenza A that we have?

Dr. Grohskopf: For the first part of the question, I'm not aware that we have any particular insight or surveillance on use patterns of the anti-influenza antivirals that are currently in use. We do have guidance for their use, but I'm not aware of any mechanism that we have to monitor changes in practice patterns.

Dr. Perham: Thank you. And then, so towards your second question. So there's a combination of things done. Like we do for antigenic phenotyping, we now use a genotype to phenotype kind of systematic approach, where we're using genetics first and then selecting viruses for phenotyping. And that's true for antigen analysis as well as antiviral susceptibility analysis. And so with the neuraminidase, we can look around the active site for mutations that could impact sensitivity or resistance to like, say for example, oseltamivir-like compounds. Neuraminidase inhibitors, most of them are targeting the active site of the enzyme. And so then we would take those, and we can test them phenotypically. Now often, so for example, in H1s, there's an H275Y substitution. So that's a very specific substitution. And it leads to highly resistant phenotype, or not sensitive phenotype to that particular, to oseltamivir or other drugs that are neuraminidase inhibitors. And so that's a very kind of genetic signature that we almost always know the phenotypic outcome. But in the H3N2, for example, there can be many substitutions in and around the active site. We're not sure if it's really impacting in this particular context. And then we'll test it phenotypically to see if it's considered sensitive or resistant to the compound. And the same is true for baloxavir. We look around where the region where the compound interacts and our… That one we have a lot less experience cause it's a newer drug. But, and we then we go into a phenotypic assay. And for that one, rather than doing an ELLA-based neuraminidase type assay, we use the HINT assay again, which is really looking for the virus replication in the presence or absence of drug.

Dr. El Sahly: Thank you. Dr. Monto.

Dr. Monto: I'm going to take us back to the Yamagata situation. And I just want to remind us all that, in terms of Covid strain selection, because things were not moving quickly at WHO, the US took the decision to make a different recommendation from the one that was made by the WHO advisory group. I don't think we should do that here. I think the flu vaccine is a global, some people would say commodity. And that's part of the problem. I think without moving towards identifying our discomfort with the fact that. We've gone for several years. Granted, we had the pandemic, and everybody has been busy with other things. That we really haven't looked towards some of the solutions to increase VE by including additional strains or even more of the age three and two in a trivalent vaccine. And I feel very uncomfortable at this point in continuing to recommend a B/Yamagata strain. I'm not going to go as far as to vote no, but I will abstain, because I don't feel comfortable in continuing to ignore what looks like a situation where B/Yamagata is no longer circulating. And we're not really trying to figure out what we should do to at least use the same antigenic weight that we have in the current vaccine of 15 micrograms times four to improve to improve vaccine effectiveness. We really need to send a message, and I'm not so sure that's done if it's only private conversations that indicate that something may be brewing, because it needs to include the manufacturers, as well. Over.

Dr. El Sahly: Thank you, Dr. Monto. Okay. I don't see any raised hands. Please use the raise your hand function if you have any final thoughts or comments about flu vaccine strain selection. Okay. Well, question two, Dr. Wentworth. So we didn't have Yamagata for, well, it started going away a little before the pandemic, and then it went away during the pandemic, and during a really heavy flu season, it didn't rear its head yet. I'm going to ask you to use your crystal ball, which we always ask you to use. If it were to come back, would it, like, all of a sudden take

over? Should we expect it to take over? Or maybe allow us time to recalibrate in a subsequent season? I mean, I, it's only one out of four. H3 is always the one that trumps us with morbidity and mortality anyways. I'm not dismissing the others, but I'm trying to put it in context. And in light of what Dr. Monto said, that we should start moving in different directions at one point.

Dr. Wentworth: Well, okay, so I think number one, I would comment to Dr. Monto. I actually agree that we really need to be moving forward and to see what we can do, because it takes a long time to license something new. And so I'm in complete agreement with that. I would say that I think the question here is, which, it's a licensed product for a quadrivalent vaccine that has a B/Yamagata component. So the question is really, do you put Phuket in it, or what else do you put in it? So to me that that's more of an FDA point, but to me that's the way I read these questions.

And then to the crystal ball piece, it entirely depends upon what kind of Yamagata reemerges, if one does. So, there was some very odd-looking B/Yamagata viruses in the Netherlands prior to its not being isolated anymore. Really antigenically distinct. And so if something like that were to reemerge and be fairly fit, it could move through our population in the same, I would guess, the same speed with which the triple deletion B/Victoria viruses moved through our population, which was within about six months, it was a sweep to that whole strain. So that's kind of one vaccine cycle. Now, depending on when that catches us in the vaccine cycle, that could be very bad, or it could be not very bad at all, right? If it looks a lot like the viruses that we saw in 2019 that were kind of the run of the mill, they were very B/Phuket-like antigenically, even though they were quite old. A few years since that virus was isolated. Then, I think they would move relatively slowly, and you would have this kind of petering, you know, with years' time.

And so I think it really depends on what emerges, but I don't think it's out of the realm of possibility that something antigenically quite distinct could emerge. I mean, that's really what you saw with H3 through the Covid bottleneck. You know, something quite distinct eventually kind of really took hold. And so it's not a very much of an answer. It probably doesn't make you feel very better, but you know, I think that's really the case. I mean, you look at B/Victoria, it's swept in about six months.

Dr. El Sahly: Okay. Dr. Monto again.

Dr. Monto: Does that mean, Dave, that whatever we vote for, which is a very old strain, would likely be a mismatch anyway?

Dr. Wentworth: Yeah. Well, if something reemerges, it would be a mismatch given that scenario. It could be, you know, I think the last virus isolated in March of 2020 was kind of antigenically like B/Phuket here. But it could be, if it's something very different, that it is a drifted variant. I think I would still argue that you would be better off with Yamagata if that did happen. You'd be better off with Phuket in there than with nothing. Because as you know, it's still a boost to all your previous Yamagata and some priming to some aspects of it. So that's a great question. Something for the committee to think about.

Dr. El Sahly: One last question from me, David. I don't see any raised hands yet. So we have a, I guess a cohort of our population that's been vaccinated against Yamagata for the last few years with not much exposure and definitely not much virus or drifting or and new antigenic sites to react to. Are we responding well? I mean, are we still seeing some of those cohorts you are following? Are they B/Yamagata?

Dr. Wentworth: Yeah. Yeah. We're seeing pretty good response to Yamagata. We didn't, I didn't show you human serology data, because we did not do a panel of human serology. We did

do a screen of the vaccinees to see that they responded to the Yamagata component. But there's no new emerging variants to test against, so it's kind of pointless to do that.

Dr. El Sahly: But they're responding to the antigen that's in the vaccine despite that?

Dr. Wentworth: Yeah, but they're responding to the antigen that's in the vaccine. Yes. They're responding to the antigen that's in the vaccine. In our quadrivalent vaccines. And that's really the only vaccines we have in our serology testing. So I don't, we don't have a trivalent.

Dr. El Sahly: Okay. Final opportunity for committee members to ask questions, provide comments before the vote. Okay. All right. Thank you all. Dr. Paydar, so do I read, do we display the questions? Do I read the questions again, I'm sorry. Or how should we proceed?

Dr. Paydar: Oh thanks for asking. I'll just go ahead and read the voting script. And then from there I'll have you read the questions one by one. We do it consecutively, and then we will have the final voting explanations all the way at the end. So alright, so let me read the script first. Only our 12 regular members and one temporary voting member, a total of 13, will be voting in today's meeting. With regards to the voting process, Dr. El Sahly will read the voting questions for the record, and afterwards, all voting members and temporary voting member will cast their vote by selecting one of the following options, which include yes, no, or abstain. You'll have one minute to cast your vote after the question is read. Please note that once you've cast your vote you may change your vote within the one-minute timeframe. However, once the poll has closed, all votes will be considered final. Once all the votes have been placed, we will broadcast the results and read the individual vote aloud for the public record. I'm going to ask if anybody has any questions regarding the voting process before I begin. If no, okay. Dr. El Sahly, if you would be kind to, please go ahead read the voting question number one for the record.

Voting Question #1

Dr. El Sahly: Voting question one. For the influenza A (H1N1) component of the 2023-2024 influenza virus vaccines in the US, does the committee recommend: an A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-based vaccines and an A/Wisconsin/67/2019 (H1N1)pdm09-like virus for cell- or recombinant-based vaccines?

Dr. Paydar: Great. Thank you. At this point Joseph will move all non-voting members out of the main room. For those of you who are non-voting, please stay tuned. Please don't log out of the Zoom. We'll be back in a few. Joseph, let me know when all the voting members are present. Thank you. All right. Opening up breakout room now.

Dr. Paydar: I will now read the results for the for the public record. Dr. Hayley Gans, yes. Dr. Hana El Sahly, yes. Dr. Jay Portnoy, yes. Dr. Steven Pergam, yes. Dr. Stanley Perlman, yes. Dr. Arnold Monto, yes. Dr. Paul Offit, yes. Dr. Douglas Badzik, yes. Dr. Archana Chatterjee, yes. Dr. Amanda Cohn, yes. Dr. Holly Janes, yes. Dr. Adam Berge, yes. Dr. Hank Bernstein, yes. Okay. Hana, if you would be so kind to read question number two for so we can go ahead and vote on that one.

Voting Question #2

Dr. El Sahly: For the influenza A (H3N2) component of the 2023-2024 influenza virus vaccine in the US, does the committee recommend: an A/Darwin/9/2021 (H3N2)-like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)-like virus for cell- or recombinant-based vaccines?

Dr. Paydar: So for voting question number two, again, we have a unanimous vote. 13 out of 13 members have voted yes. And I'll read the names for each of the votes for the public record.

Dr. Steven Pergam, yes. Dr. Adam Berger, yes. Dr. Haley Gans, yes. Dr. Archana Chatterjee, yes. Dr. Arnold Monto, yes. Dr. Paul Offit, yes. Dr. Hana El Sahly, yes. Dr. Jay Porto, yes. Dr. Amanda Cohn, yes. Dr. Stanley Perlman, yes. Dr. Hank Bernstein, yes. Dr. Holly Janes, yes. And Dr. Douglas Badzik, yes. Hana, if you would be kind to read the third voting question for the public record.

Voting Question #3

Dr. El Sahly: Voting question three. For the influenza B component of the 2023-2024 trivalent and quadrivalent influenza virus vaccines in the U.S., does the committee recommend inclusion of a B/Austria/1359417/2021-like virus, B/Victoria lineage?

Dr. Paydar: All right, we are ready to share. Okay, great. Thanks, Joseph. Again, we have 13 members who voted yes for voting. Question number three. It was a unanimous vote, and now I'll read the votes for the public record. The official votes. Dr. Archana Chatterjee, yes. Dr. Paul Offit, yes. Dr. Jay Portnoy, yes. Dr. Hayley Gans, yes. Dr. Stanley Perlman, yes. Dr. Amanda Cohn, yes. Dr. Hank Bernstein, yes. Dr. Steven Pergam, yes. Dr. Adam Berger, yes. Dr. Holly Janes, yes. Dr. Douglas Badzik yes. Dr. Hana El Sahly, yes. Dr. Arnold Monto, yes. Okay. With that, we will move to our final voting question, voting question number four. Dr. El Sahly, if you could please read the question for us?

Voting Question #4

Dr. El Sahly: For quadrivalent 2023-2024 influenza vaccines in the U.S., does the committee recommend inclusion of a B/Phuket/3073/2013-like virus of a B/Yamagata lineage as the second influenza B strain in the vaccine?

Dr. El Sahly: We are ready to display. Great. Thank you. Okay. We have 13 Voting members for voting question number four. 7 out of 13 have voted yes. 2 out of 13 have voted no, and 4 out of 13 have abstained from voting. Now, with that, I will read individual votes for the public record. Okay. Dr. Archana Chatterjee, yes. Dr. Hayley Gans, yes. Dr. Adam Berger, no. Dr. Jay Portnoy, yes. Dr. Stanley Perlman, abstain. Dr. Paul Offit, no. Dr. Amanda Cohn, yes. Dr. Arnold Monto, abstain. Dr. Hank Bernstein, yes. Dr. Steven Pergam, yes. Dr. Holly Janes, abstain. Dr. Douglas Badzik, yes. Dr. Hana El Sahly, abstain. Okay. This concludes the voting portion for today's meeting. I'll hand the meeting back to Dr. El Sahly for asking the committee for the vote explanation. Thank you so much.

Voting Explanations

Dr. El Sahly: Thank you. Thank you, Dr. Paydar. So to start us off, I see a raised hand from Dr. Weir. Dr. Weir.

Dr. Weir: Yes. I'm sorry to have to say this. There was a typo in question number one. The second part of it, the Wisconsin, should have been 67/2022, not 2019. So I'm not sure what we need to do about it, but I thought I better point it out now rather than later.

Dr. El Sahly: Should have given it a different name, right? Would've been much easier.

Dr. Weir: We looked at this at least a dozen times.

Dr. Paydar: Don't worry about it, Dr. Weir.

Dr. Weir: Okay.

Dr. Paydar: We'll adjust the writing, and we'll resubmit it when we web-post the final. It's okay. We'll adjust at that point. As long as the committee is comfortable with the voting, based on the current information, we should be okay.

Dr. Weir: Okay. Thank you.

Dr. Paydar: No worries. Yes.

Dr. El Sahly: The committee wants the strain displayed by Dr. Wentworth. Okay. So I'm going now to go over the virtual table and request that the committee members provide the rationale for their votes as briefly or as expansively as you wish. And I'm going to go in the order that the names appear here on my screen, and I think it's Dr. Berger.

Dr. Berger: Two weeks in a row, I get to do it first . So, but at least it's just one explanation. I'm going to skip my, my votes for questions one through three. I think those are self-explanatory as to why those are needed components of the vaccine. So I'll say I voted no one the last question around the inclusion of B/Yamagata for the same reason I voted no in the last meeting. The inclusion of a strain that's not circulating doesn't seem to offer additional protections for the public. And this isn't to vote against continuing the currently licensed quadrivalent, but at this point I think we really need to send a strong signal that, in the interest of public health, we need to be conducting the studies to generate the evidence base for a much more flexible vaccine composition now. So that's the reason why I voted no. That's it. Thank you, Adam. Dr. Cohn.

Dr. Cohn: Great, thank you. I will also skip my first three votes, which were yeses. I voted yes for the fourth vote to include the Yamagata because, even though I completely agree with Dr. Berger's points, I did have concerns about what would happen to the quadrivalent vaccine and the program if we didn't have a usable vaccine for this year. And so in the spirit of ensuring that we had accessible choices of vaccines while we continue to move forward with improving those transfer in there. I voted yes.

Dr. El Sahly: Thank you, Dr. Cohn. Dr. Chatterjee.

Dr. Chatterjee:Thank you, Dr. El Sahly. So I will follow in the footsteps of my co-committee members and not explain my yes vote for the first three questions. I basically looked at the data that were presented and it seemed reasonable to include those three strains. With regard to the B/Yamagata, I've given it a fair bit of thought, and I do not disagree with the comments already made. I do think, though, that the concern that Yamagata may reemerge, the fact that a large proportion of the B strains were actually not subtyped, so we don't know exactly what they were, were concerning to me. One other thing I will say with regard to including a strain that does not appear, at least from the data we have at hand, to be circulating at this time is something that I haven't brought up before but has been in the back of my mind. And that is, including an antigen that doesn't perhaps provide any benefit and yet certainly has some element of risk, although it might be minimal attached to it, but mostly the expense that it involves to grow up those viruses, to get those viruses ready, through recombinant mechanisms, and to have them available for using the quadrivalent vaccine. So I was really torn in trying to decide between those two things.

And I came down on the side of being prudent and cautious and voted yes. Because I do think that probably a little more time is needed to make those decisions. But I would echo my co-committee members' comments about the powers that be working on trying to remove Yamagata from future vaccine compositions.

Dr. El Sahly: Thank you, Dr. Chatterjee. Dr. Monto.

Dr. Monto: I think I explained previously what I was going to be doing. It even if we voted no, we're only advisory, and the staff could be moving ahead with the global recommendation, and it really would have very little effect this year. However, we've waited a long time for some action about a questionable choice to continue with B/Yamagata I disagree with some of the opinions we've heard. The evidence for the need for the quadrivalent is mixed. And there are a

number of studies which were conducted when both vaccines were being used in the United States, which showed very little benefit, at least in an adult population. I think the evidence in children may be different, and perhaps at that time the data were not sufficient to really observe the need. But I think we really need to move ahead on this. We are giving vaccines which have good benefit, not great benefit, and we need to do everything we can to improve the vaccines. And one of the things we know does improve the vaccines is giving more antigen. And we should give the right antigen. Over. Thank you, Dr. Monto.

Dr. El Sahly: Dr. Wentworth. Oh, you're non-voting. I'm sorry, Dr. Badzik.

Dr. Badzik: Yeah. Good afternoon, everybody. So, hang on a second. I have a video to kick on here. So kind of as the rest of the group, as you know, previously stated, I'm not going to go over my reasons for voting yes for the first three, because I think it's self-evident. I did kind of struggle with voting on the fourth one. I ended up casting a yes vote for that, mainly because I didn't really see an alternative. There wasn't an alternative provided. That being said, I think that going into the future, it has been stated previously, I think it's important just not to go and maintain the course unless there's data to support that.

I'm a bit concerned, as you know, we come out of the pandemic, and we see the increasing fervor of the anti-vaccine crowd. And I'm concerned that if we just continue to maintain this this lineage in the quadrivalent without data to back that up, that type of behavior I think could be misconstrued by some in the anti-vax movement just to further the cause. So I, once again, I voted yes, but I would encourage the manufacturers and those that are collecting that surveillance data to do what we can to justify that for next year.

Dr. El Sahly: Thank you, Dr. Badzik. Dr. Gans.

Dr. Gans: Hi. Thank you. I guess we're all sort of leaning towards explaining our vote for the fourth question here, since we were in agreement with the other ones, and there was lots of data to support it. So, I just want to echo that I voted yes. And the reasons I did that are not because I would like to downplay what others had said. There's definitely data to support us moving in a different direction. And I just wanted to echo, I guess, what Amanda Cohn said, that really reflected on me as the sort of global stage and what we need to do to actually keep the global populations healthy. And not necessarily understanding fully what's going to happen as we all recover from the pandemic and not seeing strains. And maybe there has been some immunity that hasn't been boosted over that period of time.

So I voted yes for that to maintain stability, but really, as my remarks in the past have said, really do urge further studies, not only just for this particular strain, but actually to have some ability to be more flexible in general about the strains at which we actually need to vote on, because this issue may come up again. So while this one is current, it will be a different one next time. And so I just would love some flexibility to respond better to the data.

Dr. El Sahly: Thank you, Dr. Gans. Dr. Bernstein.

Dr. Bernstein: Thank you, Dr. El Sahly. I agree with my colleagues around the virtual table about questions one, two, and three. The issue about number four, I voted yes. And in part, that's why I asked Dr. Weir during his introduction right at the beginning, and to me, his response suggested to me that change was not possible for this particular season. And so that being said, it's not clear to me what precise data are needed and during what timeframe this will happen in order to make such a change, which scientifically seems to make a lot of sense. And so I also didn't want that the public to interpret that the quadrivalent flu vaccine is not necessary, because I think that it's important to get as many people vaccinated against influenza as possible. Over.

Dr. El Sahly: Noted. Thank you, Dr. Bernstein. Dr. Janes.

Dr. Janes: Thank you. I'll skip to my vote for the fourth vote, and I abstained from this vote. You know, similar to the reasons have been stated before, basically I felt that there wasn't adequate data given the absence of, apparent absence of, circulation of the B/Yamagata to make a recommendation as to strain selection. And so I hoped that voting abstain would convey the inability in my mind to make a determination. But I fully support the messages that others have put forward around the continued importance of vaccination and that my vote doesn't call into question the importance of vaccination.

I also wanted to second Dr. Gans's comment and request for additional flexibility in terms of how this committee considers the strains that are included in the vaccination in future meetings. Thank you.

Dr. El Sahly: Thank you, Dr. Janes. Dr. Portnoy.

Dr. Portnoy: Great, thank you. Yes, in terms of questions one, two, and three, again, I voted yes, and I'm okay with those even with the error, the typographical error. So it's not a problem. I voted yes for the Yamagata strain. Not because I think that there's a lot of that, but I don't know, does extinct really mean extinct? The 1350, the Black Plague in 1350 was extinct, and 10 years later it came back. So we don't really know for sure that things like that aren't going to return. Besides if we don't, if we vote no for the Yamagata strain, there aren't really a lot of B strains out there. It's not clear that we even need B strains in the influenza vaccines at all.

So I voted for that just because I'm not sure that it's extinct. But I do want to comment on, though, is that I'm hoping that in the future we will start seeing use of more advanced technologies than these legacies like cellular vaccines or egg-based vaccines. We're injecting eggs with influenza virus and extracting it. That's a very old-fashioned technique. I'm looking

forward to the messenger RNA-based influenza vaccines that not only could be modified very quickly as the strains of influenza modify but could also possibly induce more of a cellular immunity, which I think for long-term benefit could be quite helpful. So I'm hoping that's going to be a possibility. We allow the Covid vaccine to have variants in its strain without having a whole new licensing thing. I don't know why we can't take an influenza, license it for just flu, and then make all of the modifications depending on what strains are present that year. I think a newer technology would allow that to happen, and I look forward to that happening in the future. Thank you.

Dr. El Sahly: Thank you, Dr. Portnoy. Dr. Offit.

Dr. Offit: Yes. Thank you. I, like Dr. Berger, voted no. Because I think that if you're going to inject someone with a biological agent, even if it's only one component of a multi-component product, there should be clear evidence for benefit. I don't think we have any evidence for benefit with this strain, and although I agree that this strain may come back in the near or distant future, that is not a compelling enough reason for me to include it now. Plus, I agree with Dr. Monto's comment that, should it come back, you wonder whether or not it would be distant enough from the current strain as to be of value. So I voted no. Thank you.

Dr. El Sahly: Thank you, Dr. Perlman.

Dr. Perlman: Yes, I think it's going close to the end here. I don't have very much new to say. I think that there's not evidence for including Yamagata. I voted, I abstained, because I thought there wasn't great evidence for including it, and because of where we are in the course of vaccine development. I felt that for this year, it would be okay to include it. I didn't vote against it for that reason. And I hope that next year we don't have the same discussion. I hope that there's either

more data saying we should include it, or we have data showing that we should remove it and have removed it.

Dr. El Sahly: Thank you. Dr. Pergam.

Dr. Pergam: Thanks, Dr. El Sahly. I don't have much to add from what my colleagues have already talked about, but I voted yes because it felt like the strain had already left the station related to the quadrivalent. I don't feel like we can do a trivalent international. At least from what was responded, that's a little harder to do. And I think it's important that the process has sort of already begun in some ways within the world stage. But I think I voted yes with sort of a little bit of trepidation because, I think, as others have commented, it doesn't feel like Yamagata is getting us a lot of benefit. What I think we'd all really like to see as additional data and studies planned for what would be a potential replacement for the B strain, if it is removed. So I encourage the FDA to start working with companies to start coming up with those studies to deliver, identify how that might be advantageous for future vaccines.

Dr. El Sahly: Thank you. I think it's my turn. So I abstained from voting on the inclusion of B/Yamagata. I hesitated between the no and then abstain. But it's definitely not a yes. Influenza virus is not known to be shy. If it was going to circulate in the last four years, we would've picked it up. We do note that the trend preceded the pandemic. And we indicated for, I think two or three meetings now, that, well, the non-pharmacological measures of the pandemic are going over. We're seeing a whole lot of flu, but we're not seeing the Yamagata. We said we'd give it one more season. This season was this year, and we had really an abundant circulation of flu all over the world. And Yamagata did not rear its head. When and if it does, we'd be ready.

From a regulatory standpoint, going from four to three shouldn't be a hurdle, because there is a trivalent vaccine. And no additional research or developmental work needs to happen

for us not to include the Yamagata. And when it comes to implementation and vaccine distribution, also not including the Yamagata should not impact our ability to distribute the vaccine to those who need it each year. So that's why I chose not to vote for the Yamagata this year.

I think we are done with the task that that was given to us. Any final comments from the FDA? Or Dr. Weir, Dr. Kaslow?

Adjournment

Dr. Paydar: So for the closing comments, I just wanted to thank the committee and CBER staff for working so hard to make this meeting a successful meeting. We're very grateful for your presentations and for your input. I'll call the meeting officially adjourned at 3:27 PM Eastern Time. Have a wonderful rest of your evening. Bye-bye.