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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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150TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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November 7, 2017
8:30 a.m.

FDA White Oak Campus
Building 31, Great Room
10903 New Hampshire Avenue
Silver Spring, MD 20993

KATHRYN EDWARDS, M.D.	Chair
JANET ENGLUND, M.D.	Voting Member
HANA EL SAHLY, M.D.	Voting Member
KAREN KOTLOFF, M.D.	Voting Member
OFER LEVY, M.D., Ph.D.	Voting Member
RUTH LYNFIELD, M.D.	Voting Member
SARAH LONG, M.D.	Voting Member
PAMELA McINNES, D.D.S., M.Sc. (Dent)	Voting Member
ARNOLD MONTO, M.D.	Voting Member
MELINDA WHARTON, M.D., M.P.H.	Voting Member
EUGENE BLACKSTONE, M.D.	Temporary Non-Voting Member
DEAN FOLLMANN, Ph.D.	Temporary Non-Voting Member
DAVID STEPHENS, M.D.	Temporary Non-Voting Member
KARIN BOK, M.S., Ph.D.	Temporary Non-Voting Member
JOHN S. KIRKPATRICK, M.D.	Temporary Non-Voting Member
DAVID GREENBERG, M.D.	Industry Representative
SHELDON V. TOUBMAN, J.D.	Consumer Representative

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M E E T I N G

(8:33 a.m.)

DR. EDWARDS: Good morning, my name is Kathryn Edwards. I'm from Vanderbilt, and I'm the Chair of VRBPAC and would like to welcome all of you to the meeting and call this meeting to order.

I would like to go around the table and have everyone introduce themselves. We have two people that are on the phones, but they also have places here at the table. So when I call their name, Pam and Ofer, if you could just tell us a few words about yourself, that would be terrific. So let's begin with the FDA.

DR. MONGEAU: Good morning, my name is Tina Mongeau. I'm a clinical reviewer with the Office of Vaccines at FDA.

DR. ROBERTS: My name is Jeff Roberts. I'm one of the Clinical Branch Chiefs in the Office of Vaccines.

DR. M. GRUBER: My name is Marion Gruber. I'm the Director of the Office of Vaccines.

DR. EDWARDS: Dr. McInnes, would you like to introduce yourself?

DR. McINNES: Good morning. I'm Pamela McInnes, Deputy Director of the National Center for Advancing Translational Sciences, which is one of the NIH institutes. Thank you.

DR. EDWARDS: Sarah.

DR. LONG: I'm Sarah Long, Professor of Pediatrics at

Drexel University College of Medicine and Chief of Infectious Diseases at St. Christopher's Hospital for Children in Philadelphia. I'm interested in vaccine-preventable diseases and last year saw 800 patients with staphylococcal infection.

DR. EDWARDS: Dr. Lynfield.

DR. LYNFIELD: Ruth Lynfield. I'm the state epidemiologist and medical director at the Minnesota Department of Health.

DR. EDWARDS: Dr. Monto, would you like to tell us about yourself?

DR. MONTO: I'm Arnold Monto. I'm Professor of Epidemiology at the University of Michigan School of Public Health and have been involved in various clinical trials from time to time.

DR. EDWARDS: From time to time.

Dr. Levy. Ofer, would you like to tell us -- say a few words?

DR. LEVY: Sure. I'm Ofer Levy. I'm a physician-scientist, a pediatric infectious disease consultant, and I direct something called a precision vaccines program where we model human immunity outside the body to accelerate vaccine development. I'm at Boston Children's Hospital and Harvard Medical School.

DR. EDWARDS: Thank you.

Dr. Kotloff isn't here, but she'll introduce herself when

she gets here.

Hana.

DR. EL SAHLY: Hi. Hana El Sahly, Associate Professor of Infectious Diseases at Baylor College of Medicine and a principal investigator of the vaccine treatment and evaluation unit.

DR. ENGLUND: I'm Janet Englund, Professor of Pediatrics at the University of Washington in Seattle and do transplant infectious diseases and infectious diseases at Seattle Children's Hospital.

CAPT HUNTER-THOMAS: Good morning, my name is Serina Hunter-Thomas, and I'm the Designated Federal Officer for this Committee. Thank you.

DR. EDWARDS: Melinda.

DR. WHARTON: Melinda Wharton. I'm an adult infectious disease specialist. I've worked in the U.S. immunization program through CDC for many years and am currently Acting Director of the National Vaccine Program Office.

DR. BLACKSTONE: I'm Gene Blackstone, Head of Clinical Investigations for Heart and Vascular Institute, Cleveland Clinic. Also, I'm currently chair of the Multi-Site Clinical Trials, NHLBI.

DR. BOK: Good morning, I'm Karin Bok. I'm representing the National Vaccine Program Office, and I'm a senior scientist.

DR. FOLLMANN: Hi, I'm Dean Follmann, Head of Biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. KIRKPATRICK: I'm John Kirkpatrick. I'm an orthopedic and spine surgeon from the VA in Orlando, and I'm a Professor of Orthopedics at the University of Central Florida.

DR. STEPHENS: Good morning. I'm David Stephens from Emory University, and I'm Professor of Medicine and Infectious Diseases.

MR. TOUBMAN: Good morning. I'm Sheldon Toubman, and I'm an attorney at New Haven Legal Assistance Association in New Haven, Connecticut. I'm the Consumer Representative.

DR. GREENBERG: Good morning, I'm David Greenberg, Pediatric Infectious Diseases, Adjunct Associate Professor, Children's Hospital of Pittsburgh, University of Pittsburgh, and head of medical at Sanofi Pasteur for North America, and serving as the Industry Representative.

DR. EDWARDS: Thank you, everyone, for coming.

Captain Hunter-Thomas will now read the administrative announcements and Conflict of Interest Statements.

CAPT HUNTER-THOMAS: Thank you, Dr. Edwards. Good morning again, everyone, and welcome to the 150th VRBPAC meeting. My name is Captain Serina Hunter-Thomas. I would like to also thank the Committee Management Specialist for this meeting, who is Ms. Rosanna Harvey, and the Committee Management Officer,

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

Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the *Federal Register* notice that was published on September 22nd, 2017.

The FDA CBER press media representative today is Mr. Paul Richards. Mr. Richards, if you could please stand so that everyone can identify you? And reach out to him as needed.

The transcriptionist for today's meeting is Mr. Tom Bowman from Free State.

I would like to remind everyone to please check your pagers and your cell phones and also make sure that they are either turned off or in silent mode.

When making your comment, please first state your name and speak up so that your comments are accurately recorded for transcription. Please keep in mind that, especially for this meeting, we have two Committee members that are on the line, and we would like to make sure we capture their comments for the record.

Finally, I would like to express our sincere thanks to Dr. Janet Englund, Dr. Karen Kotloff, Dr. Sarah Long, Dr. Ruth Lynfield, Dr. Patrick Moore, and Dr. Mark Sawyer. This is the last VRBPAC meeting before your term ends early next year. Thank you for your superior commitment and service to VRBPAC.

Your expertise and wise counsel is greatly appreciated. On behalf of FDA and CBER, we thank you.

I will now proceed to the Conflict of Interest Statement for this meeting.

The Food and Drug Administration is convening today, November 7th, 2017, for the 150th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

At this meeting, in the open session, the Committee will discuss and make recommendations on the clinical development plan for Pfizer's investigational *Staphylococcus aureus* vaccine intended for pre-surgical prophylaxis in elective surgical populations. This is a particular matter of specific parties.

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

With the exception of the Industry Representative, all participants of the Committee are special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations.

Related to the discussions at this meeting, all members

and consultants of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouse or minor children and, for the purposes of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; patents, contracts and grants, CRADAs; speaking, teaching, writing; royalties; and primary employment.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial interests when it is determined that the Agency's need for a particular individual's service outweighs his or her potential conflict of interest.

However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. David Greenberg is currently serving as the Industry Representative to this Committee. Dr. Greenberg is employed by Sanofi Pasteur U.S. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in

the closed sessions.

Mr. Sheldon Toubman is serving as the Consumer Representative for this meeting. Consumer representatives are special government employees and therefore are screened for their financial conflicts of interest and cleared prior to their participation.

Dr. Richard Proctor is a Professor Emeritus at the University of Michigan. He is an expert in *Staphylococcus aureus* and internationally known for these achievements. Dr. Proctor is serving as a guest speaker and will make a presentation on postoperative *Staph* infection.

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

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms, its products, and if known, its direct competitors.

We would like to remind members, consultants, and participants that if the discussions involve any other products

or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves due to such involvement and their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest Statement for the public record, and at this time I would like to hand the meeting back over to Dr. Edwards.

Thank you.

DR. EDWARDS: Thank you very much.

As Captain Hunter-Thomas just articulated, the goal and focus of this meeting is the clinical development of Pfizer's investigational *Staph aureus* vaccine for the prevention of postoperative infection in elective orthopedic surgeries. We will first hear from Dr. Jeff Roberts of the Division of Vaccines and Related Products at the Office of Vaccines Research and Review at FDA.

Jeff.

DR. ROBERTS: Good morning. Can you hear me okay? Great. Thank you for joining us this morning. I want to thank, particularly, the Committee members, because we recognize that there's a lot of time and effort involved in preparing for this and traveling, and we appreciate your being willing to come and help us think about this. We have for you this morning an interesting and important topic focused on Pfizer's investigational *Staph aureus* vaccine.

What I'll start with is to condense down into a very brief overview the topic for the day. The investigational vaccine consists of four *Staph aureus* antigens. You'll hear more later in the day about the antigens and about the dose and the regimen, and you'll hear the vaccine, for the most part, referred to as SA4Ag.

Pfizer has already completed early phase studies of this vaccine, and they have already initiated a large clinical endpoint study of the vaccine, and this study, which you sometimes will hear referred to as B3451002 and other times by the acronym Pfizer uses for it, which is STRIVE, this study is a large, randomized, double-blind study. Subjects are randomized either to placebo or vaccine preoperatively before undergoing spinal fusion surgery, and the objective of the trial is to demonstrate prevention of invasive postoperative *Staph aureus* infection.

Pfizer's plan, should this trial be successful, is to use this to support a licensure application for this vaccine, and what they've proposed, and what we're here to discuss today, is that these data should be used to support an indication for a broader indication: all elective orthopedic surgery.

So the factors to consider when assessing the degree to which safety and efficacy data in spinal surgery, spinal fusion surgery population, could be generalized to all elective surgery, orthopedic surgery, is the question for today.

Okay. So to lay the groundwork for this discussion, we will be hearing a lot of details about both the pathogen factors and the host factors involved in infection. And specifically, these are some of the factors that come to mind when you think about the prospects for a vaccine to be efficacious against *Staph*, and they include the fact that roughly 30% of humans are colonized with *Staph aureus* at any given time; that *Staph* has multiple virulence factors and immune evasion strategies; that the phenotype and protein expression profiles vary depending on host factors and site of infection; and that the protective immune response -- the immune mechanisms are incompletely understood, particularly adaptive immune mechanisms.

So we'll also spend some time talking about clinical manifestations, and we all recognize that there's a very broad range here, everything from foodborne illness to systemic infection. And that means that there are multiple populations at risk: end-stage renal disease patients, athletes, residents of long-term facility populations.

So I think when you think about the expertise that we've convened here on the Committee, one thing that may come to your minds is why are we discussing only elective surgery populations? And I think, later in the day, Pfizer will give you more details about their choice of this population, but I think, suffice it to say for now, that we recognize that this

is a serious clinical problem and that it's inadequately addressed by the current preventive interventions, and it remains a major public health issue.

The other issues we'll spend time with are the host factors, and these can be mapped largely onto the risk factors generally for postoperative infection, and they include these patient-related risk factors, such as nasal carriage, comorbidities, the age of the population, and the overall health status.

And we'll spend a lot of time on the details of the procedure-related risk factors, including the duration of surgery, the implantation of prosthetic material, including the nature of that material itself, the anatomical structures and the tissues involved in these surgeries, and the perioperative care and preventive interventions.

So the key issues are going to be the extent of heterogeneity of these risk factors across the different elective surgery, orthopedic surgery populations, and the anticipated impact of specific risk factors on the prospects for efficacy.

Another thing we'll do today is to spend some time discerning whatever lessons can be learned from previous *Staph aureus* vaccine clinical trials. And I've listed here the two major ones, the vaccine from Nabi, in which it was studied in end-stage renal disease patients in two separate efficacy

trials, both of which failed to demonstrate efficacy; and the Merck *Staph* vaccine that underwent a trial in cardiothoracic surgery also failed to demonstrate efficacy. And in this case, the data from this trial illustrated a potential safety signal for more severe infection among the cases of *Staph aureus* in this trial. So we need to dissect and think about those data and whatever lessons can be learned.

So I've listed here again these factors that we think are important to understand to address the question of generalizability. And as you think about these factors of pathophysiology, clinical manifestations, risk factors for postoperative invasive infection, one of the things that may come to mind are these are the very same factors that you would want to understand in depth if your task was to design an efficacy trial or to think about what a new vaccine might include to predict efficacy.

But I want to emphasize that those are going to be topics potentially for another day, and the reason is we're starting with a fundamental assumption here that the current trial is going to demonstrate efficacy of this vaccine for this specific population. That's the fundamental assumption that is the beginning of the discussion here so that what we hope to understand is how these factors inform this central question of whether these data can be applied more broadly to a broad elective orthopedic surgery population.

So the other thing that we thought would be important to do briefly, before we talk about today's agenda, is to talk a little bit about where this vaccine program fits in the overall landscape.

So we're seeing vaccine development programs more and more for specific populations. And typically, to date, when we use this term "vaccine," it calls to mind a whole host of specific assumptions about implementation, about public health, even about regulatory decision making. And what we're seeing more and more are that vaccines are being developed to target specific populations and to address specific issues such as antibiotic resistance, and this program falls squarely in that new paradigm.

And I think we all need to recognize that this raises particular challenges, and we've listed a few here, and they include the evolution of pathogen virulence in different healthcare settings; the profound effect on the available number of subjects, which has an impact on study feasibility; the issues around benefit-risk and how they can be generalized from one population to another.

So we just thought it would be important for everyone to keep in mind all these factors, while at the same time making sure that the discussion is anchored in the science and the data.

So those are just -- that's a brief overview for our

discussion today. What we specifically will do in terms of hearing presentations, we'll start with Dr. Michael Otto, who is the Chief of the Pathogen Molecular Genetics Section in NIAID, and he'll cover some of the scientific considerations. Then, Dr. Rich Proctor, who is an infectious disease physician at the University of Wisconsin, is going to discuss some of the clinical considerations. And then Dr. Tina Mongeau will cover the FDA's review and consideration.

And finally, Pfizer has a series of, I think, three presentations that cover some of the background, particularly the surgical aspects of this, and covers their proposal more specifically.

As we delve into this agenda, I want to go through the discussion topics for the Committee so that you can keep these in mind throughout the day. We will put these back up before we begin the discussion, but for now I'm going to read these so that you can have them fresh in your mind throughout the day.

So the first discussion topic will be: Assuming that the ongoing study of SA4Ag achieves its pre-specified primary efficacy objective in a population undergoing elective, posterior-approach, instrumented, multilevel spinal fusion surgery, please discuss the reasons why efficacy should or should not be generalized to other elective orthopedic surgical populations.

And the other discussion topic we'll have is: Assuming

that the ongoing study of SA4Ag demonstrates safety in a population undergoing elective, posterior-approach, instrumented, multilevel spinal fusion surgery, please discuss the reasons why safety should or should not be generalized to other elective orthopedic surgical populations.

So I'm going to stop there and invite Dr. Otto, I think, to come to the lectern and present.

Thank you.

DR. EDWARDS: Are there any questions before, for Jeff?

(No response.)

DR. EDWARDS: Okay. Michael, go ahead.

DR. OTTO: So good morning. I am Michael Otto. I'm in the Laboratory of Bacteriology at the National Institute of Allergy and Infectious Diseases, so I'm a Senior Investigator at NIH, and I'm here to give you a basic science perspective of what we're talking about. My laboratory specializes on staphylococci, so we do a little bit of everything: microbiology, host-pathogen interaction around MRSA, *Staphylococcus aureus* in general, and also other staphylococci.

We heard already a little bit from Dr. Roberts that *Staphylococcus aureus* can actually cause a multitude of infections, many, many more different types of infections than the specific infection we are talking about here today. It is particularly well known for being what actually matters or what actually causes a significant degree of mortality and morbidity

if you have a lung infection that might be even caused by an underlying flu. So MRSA very often is actually what causes most problems in these infections, and they are very, very common in hospitals.

Staph aureus is also very well known to cause skin infections. This includes skin infections in people who are not hospitalized; these infections can be community-associated, and I'll come back briefly to that.

Usually, they are moderately severe; they're like carbuncles, furuncles, and they don't even undergo antibiotic therapy. Very rarely it has been found, recently, really very rarely, we're talking about a handful of cases, where this can develop into very serious necrotizing fasciitis infections.

Staph aureus also causes bone infections such as osteomyelitis. It is one of the major causes of sepsis, very often fatal in hospitals. And these blood infections very often stem from the infections of in-running medical devices. So whenever a patient who's in the hospital has any kind of catheter inserted or it might even be a patient who undergoes some surgery for hip replacement and so forth, bacteremia and possibly full-blown sepsis can very often have this underlying cause, when you have a constant seeding of bacteria from a biofilm type of infection on those devices.

And also, there are very specific diseases, very specific toxins in *Staph aureus* can cause -- some strains of *Staph*

aureus produce toxic shock syndrome toxin which leads to toxic shock syndrome.

And last but not least, I should also mention that *Staph aureus* can cause foodborne illness.

As I mentioned already, and I want to talk a little bit more about this, *Staph aureus* is a leading cause of death in hospitalized patients. Mostly, this is related to sepsis. And I cite this from a review here. *Staph aureus* bacteremia is an important infection with an incidence rate ranging from 20 to 50 in 100,000 population per year. Between 10 and 30% of these patients will die from sepsis. And this accounts for a greater number of deaths than for AIDS, tuberculosis, and viral hepatitis combined. In the U.S., invasive immune serious MRSA infections occur in about 94,000 people each year, causing 19,000 deaths.

So this is from a study that was performed in 2007. Fortunately, as you might -- maybe, for example, know from what the CDC has posted on their website, we do see a decline in MRSA infections. But in absolute number, the mortality that is attributable to MRSA is still pretty much on top of the list of hospital-associated infections, and I think the only pathogen that tops MRSA now is *C. difficile*, which is a model for a different case because it's related to antibiotic overuse.

Now, of those infections that I've just mentioned, these 94,000 in 2007, 85% are hospital associated, which, as you see,

already leaves 15% that are not hospital associated, and I will talk a little bit about this in a minute.

But something, of course, that we have to consider when we're talking about vaccines is why do we need vaccines for *Staph aureus*? And the primary reason for that is, of course, that we have an enormous amount of antibiotic resistance in *Staphylococcus*, an enormous frequency, but also multi-resistance to different antibiotics.

Historically, it is quite interesting to see how, in general, how fast antibiotic resistance developed. So if you look at the introduction of penicillin into clinical use in 1941, you already had penicillin-resistant *Staph aureus* a couple of years later. And then another couple of years later, this was pandemic and spread all over the world. Then methicillin, as a drug that was resistant to the resistance mechanism against penicillin, was introduced in '59. It was even faster, that like 1 year later you saw methicillin-resistant *Staph aureus* infections. The first MRSA outbreak in the U.S. occurred in the end of the '60s. In about at the beginning of the 1980s, MRSA was clearly a worldwide problem.

Now, all of these infections that I was talking about so far are basically hospital-associated MRSA infections. But as I mentioned already, there is a new development of community-associated MRSA. These are these 15% that I mentioned earlier. And these community-associated MRSA strains, as the name

suggests, occur in the community, not hospital associated.

And what, from a basic science point of view, these *Staph aureus* strains have in common is that they are, on the one hand, resistant to methicillin, but on the other hand have developed such a high virulence that they can attack otherwise healthy people and don't need an immunocompromised individual or an individual that's undergoing surgeries or for any reason weakened.

These MRSA strains, these new community-associated MRSA stains, do have a virulence that is comparable to the virulence that other strains very often have that don't have methicillin resistance. And I mentioned already the figure of about 15%.

Now, it's very important to see that, in the U.S., these infections that are community-associated are virtually entirely due to one specific strain or strain group of *S. aureus*, which is called USA300, and that name comes from pulsed-field type electrophoresis which is used to characterize *Staph aureus*. So this is pulsed-field type USA300.

In general, community-associated infections, MRSA community-associated infections, are increasing on a global scale while, as I said before, the hospital-associated infections, at least in the U.S., seem to be decreasing. So if we take a look outside of the borders, MRSA is probably even a bigger problem there, or will be in the future, than it is here, both community and hospital associated.

One last thing that is, I think, also very, very important in terms of what we're discussing today is that USA300 is now not exclusively anymore a community-associated strain. It is obviously so virulent and so successful that it has also taken over hospitals and is now one of the predominant strains, one of the predominant MRSA strains, both community associated and hospital associated, in the United States. The global importance of USA300 is, so far, a little bit difficult to judge. There are reports that say USA300 is also spreading in other countries of the world, but on the other hand, there are reports that other sequenced types and other *Staph aureus* types are actually predominantly in other countries. So I think, so far, we can say this is still a relatively specific U.S. problem.

There are, of course, several different strategies that people are looking at when addressing the problem of antibiotic resistance in *Staphylococcus aureus*. The first and most obvious is, of course, to come up with novel antibiotics, but I think most of you know, especially the company representatives, how difficult this is. It is, of course, one reason why we're looking at vaccines.

More, I would say, modern approaches that are maybe not yet mature enough to make it to clinical trials in many cases are anti-virulence drugs, so these would be drugs that specifically attack virulence mechanisms of the bacteria and

not try to kill them, such as conventional antibiotics.

The same can be said for probiotics. I'm not aware of the fact that there is any probiotic under investigation for *Staph aureus* infection.

Monoclonal antibodies, on the other hand, is something that many companies are looking at right now. This would be somewhat related to the anti-virulence drugs. So monoclonal antibodies that are directed against specific toxins, important toxins, of *Staph aureus* could be considered an anti-virulence drug. And there are many companies that are looking at monoclonal antibodies, for example, against leukotoxins of *Staph aureus*, so these are toxins that eliminate white blood cells.

And finally, of course, today we're talking about vaccines.

So I took this from a review of Jean Lee, who is a professor at Harvard and has looked very much into vaccines against *Staph aureus*. This was published in 2008, so this is a little bit influenced by the climax of the community-associated MRSA infections that we have today.

So she's trying to outline here the target populations who could benefit from a *Staph aureus* vaccine, and on the left side is what interests us today, so this is active immunization. And you can see that if you look at military personnel, prisoners, and so forth, she lists here several of the risk

groups that are risk groups for community-associated MRSA infections, so that's why I'm saying that's a little bit influenced of what, about 10 years ago was a very, very focused discussion on *Staph aureus*.

I think it's important to point out in this list that on the left side we have patients undergoing elective surgery, so this is what we're talking about today. And the reason for why she does not list active immunization for several conditions or patient groups here on the right side, where she suggests passive immunization, is mostly that these are people who are immunocompromised, where one would not expect that active immunization works or simply patients where active immunization is not possible for time constraints.

So what do we know from a basic science point of view about *Staph aureus* infections and immunity? So ever since people knew what *Staph aureus* is and what it causes, so that's probably more than a century, one thing became very clear, which is that previous *S. aureus* infection does not protect from reinfection. If you have a *Staph aureus* infection once, there is no protective immunity that develops that would, like in many other infectious disease types, that would protect you from reinfection.

What has also been found, there are several lines of evidence for this, is that *Staph aureus* infections are normally controlled by innate host defense, so not by acquired host

defense. And one of the evidence, and one of many for that, is that in patients that have a specific genetic disorder and that don't have -- so this is chronic granulomatous disease patients. I hate this word, sorry. So, basically, they have a deficiency in leukocytes, and they suffer very, very much from *Staph aureus* infections.

So we know a lot about innate immunity, and I'm going to come back to that briefly. But we can say that, in general, the role of protective immunity to *Staph* infection is really not very well understood.

Now, this is something where I could have, like, dozens of slides about, and I tried to keep this short because obviously when we're talking about a vaccine, we're not talking about innate immunity; we're talking about acquired immunity. But I still wanted to point out the many mechanisms that *Staph aureus* has to subvert innate host defenses.

There is a whole armada of proteins that block pathogen recognition receptors. So this is basically what the innate immune system needs to figure out that *Staph aureus* is around. And *Staph aureus* produces -- and there are many of those. And *Staph aureus* produces a whole lot of proteins that block that recognition, so basically that innate immune system does not even realize that it is around.

Something a little bit more direct, even, and I mentioned that briefly already, is that *Staph aureus* produces also quite

a lot of toxins, and they're very potent, that directly attack white blood cells, so those are the cells that are supposed to eliminate *Staph aureus* in the end. And there are leukotoxins AB, ED, SF, that's also been called the Panton-Valentine leukocidin, and PSMalpha.

Going even a step further, these leukotoxins, at least some of them, work after the white blood cell has ingested *Staph aureus*. This is a very sophisticated mechanism. Oh, sorry, this is back here. So this, of course, causes a particular problem for drug and vaccine development because, I mean, in that state the bugs are very, very difficult to reach; they're inside the neutrophils.

And I'll skip this here, and I just wanted to point out that leukocytes are not the only cell types that *Staph aureus* attacks. It has something against erythrocytes, against basically every cell type.

And last but not least, *aureus*, of course, also senses if there is something really harmful around. For example, an important part of innate immunity are antimicrobial peptides. We find them inside leukocytes as one weapon to destroy the bacteria, but we also find them secreted on the skin, for example, and *Staph aureus* has developed a whole lot of mechanisms first to sense them and then to decrease susceptibility to them.

Now, the role of adaptive immunity in *S. aureus*

infections, this is really a problem because we don't really know very much about it. We know that humans do produce antibodies to staphylococcal antigens, but obviously they do not offer significant protection because, as I said, it can be really infected.

And the protective immunity that we very often see in animal models, when vaccines, for example, are tested in mice, is not really understood mechanistically very well. And more recent research points to the fact that the protective immunity that we see in such cases, at least in mice, could be mediated by T-cells predominantly.

And I don't want to go through all of these, these mechanisms, but basically, T-cells are a very important part of adaptive immunity, for example, in assisting these cells, also in facilitating recognition of intracellular pathogens, which might be important for *Staph aureus*, and in assisting macrophages.

Now, of course, people have tried to figure out why there is no protection from reinfection and how *Staph aureus* subverts adaptive immunity, and something that is already a very old finding is the discovery of protein A.

So what's shown here on the left side -- and I actually took this from a slide by Olaf Schneewind, who unfortunately cannot be here today. What's shown here on the left side is what's been known for quite a while, which is that protein A

binds to the Fc part of an antibody and produces something like a camouflage coat around its surface. It means that these are nonspecific antibodies; it's the nonspecific part of an antibody, so every antibody will bind. So when nonspecific antibodies bind around *Staph aureus*, that means there is basically no more room for a specific antibody to attack, and this is why that's been called a camouflage coat. And, ultimately, this inhibits opsonophagocytosis because, of course, there's no specific antibody.

Something that's been found a little bit more recently is there is another form of the inhibition of antibody responses by protein A because it can also bind to the B-cell receptor and this time to the specific part, the Fab part, of the B-cell receptor, which prevents ultimately the production of antibodies by B-cells. So these are some -- two quite basic and efficient mechanisms for this protein that many basic researchers know more from the fact that it's used as a technique in many lab procedures.

Another thing that my colleague, Frank DeLeo, and I have pointed out about 10 years ago, when the science -- let's say when we found that there are these leukotoxins that also can attack neutrophils after the ingestion of the bacteria. So what we pointed out back then is that basically this is what happens when you have an antibody-specific response, there's optimization, and then with the help of a complement, *S. aureus*

would be ingested by a neutrophil. So if you have antibodies around, if you have a vaccine that everything actually works out quite nicely, there is still the problem that once *Staph aureus* is then inside the neutrophil, where it's supposed to be eliminated, it has quite efficient weapons to fight this and then get out of the neutrophil.

So this doesn't happen in all cases. It might be restricted to very virulent *Staph aureus*. But that, of course, would constitute a mechanism by which, theoretically, the efficacy of every vaccine would be diminished.

Then some of the *Staph aureus* that are either ingested by neutrophils or by non-professional phagocytes also have the capacity instead of causing lysis and destruction of that cell, to simply stay there and persist inside a cell, thus also not be recognizable by the immune system very well.

And Dr. Proctor, for example, is one of the most important people who has found and published the role of small colony variance in that regard. So these are specific metabolically limited cell types of *Staph aureus* or variants of *Staph aureus* that can persist in such an environment.

Biofilms, another reason for why *Staphylococcus aureus* infections might be very difficult to deal with. Biofilms is actually a phenotype that many of you might have heard about. It represents the agglomeration of bacteria in huge clusters, often surface attached but not necessarily.

And these biofilms offer a protection from both adaptive and innate host defenses in addition to antibiotics, by the way, too, although the mechanisms are somewhat different. The protection from host defenses of the -- innate host defenses, that's pretty clear already. If you have a neutrophil, it just cannot get in there that well. And also the antimicrobial peptides that are secreted on the skin might, in cases, in many cases not penetrate very well in such a structure.

By the way, this purple stuff here on the bacteria is, to a large extent, exopolysaccharide. And such exopolysaccharide, such an exopolysaccharide coat has the primary effect on host defenses that it actually shelters very immunogenic parts on the cell surface that might be exposed by something that is by far not as immunogenic, although there are some people also trying to find vaccines against specifically that exopolysaccharide. But, in general, this is a mechanism of protecting the bacteria from recognition by antibodies, as shown here.

Something that we've actually shown some years ago, and I put this slide here only because this might be something that's a little bit more directly relevant for the question at hand, what we did at the time is that we got synovial fluid, so this is the fluid that's in every joint, we got synovial fluid from patients undergoing knee surgery, and we took that synovial fluid and incubated it with *Staph aureus,* and that *Staph*

aureus, which is a very normal culture, is in a single cell form.

As soon as you add the synovial fluid to *Staph aureus*, it comes within 10 to 20 minutes you see huge agglomerates, they're microscopically visible, and they have this deposition of what is fibrin and fibrin antigen on the cell surface. I mention this mostly because this is something that we can expect in any type of orthopedic infection to occur because there's always synovial fluid around.

The mechanism a little bit more in detail would be that -- and we found out a little bit later, is that you have the deposition of fibrin, which you always have in a traumatized joint in its synovial fluid on the surface of the bacteria. And then later on we found that the specific conditions and synovial fluid actually promote a certain type of physiology, and I don't want to go into detail here, but usually the mechanisms that are usually there to disperse the cells one from each other are down-regulated very much in that environment, and this is why these huge agglomerates develop.

Now, coming back again a little bit to the immune system, something that people have learned from the use of specific knockout mice is the relative importance of specific immune cell types in protected immunity to *Staph aureus* in mice. And I alluded to that already earlier. I put here some data. I think they are from Lloyd Miller's lab.

So what these people did is, basically, they took a T-cell knockout mouse, a T-cell deficient mouse, and a B-cell deficient mouse, and you see quite clearly that there is still the same protection in the B-cell deficient mouse in this mouse model with an antigen that doesn't really matter in that context, as in the wild type, and in a T-cell knockout there is a very, very clear effect. And this is why these researchers -- it's not un-debated, there are different results, but these researchers have concluded from this that the protective immunity that you see in mice is predominantly T-cell mediated. And there are other results from other deficient mice that point to T-cell, that point to the role of IL-17, TNF-alpha, and I don't want to go into detail now, but these results pretty clearly show it's T-cells and not B-cells.

There is also very recent research that's still maybe a little bit too novel that would suggest some kind of protective memory that's due to the innate immune system. But I want to point out here again, this is all in mice. Whether this works the same way in humans, we don't know.

A little bit more specifically looking now at vaccination attempts, and I deleted from this list everything that's only passive vaccination. So we're looking at active vaccination attempts here that have made it to clinical trials, and you see that quite a lot of them actually are Phase 1, so they were not really pursued further for different reasons. I mean, I would

say the overarching thing here is they were simply given up.

But there are two that stand out, and they were already mentioned, that made it to Phase 3, and they both failed. And then, obviously, there is the one that we are talking about today, and I want to take a look briefly at the first two.

So Nabi developed StaphVAX, and what I want to point out here mostly is the antigen target. The antigen target was capsular polysaccharide. That comes in type 5 and type 8 in most strains. As mentioned already, the clinical trial failed. What was pointed out later, when people thought about it, was that there might have been poor protective efficacy, that's quite obvious, but for one of the reasons -- one of the reasons might have been that the contribution to virulence of these capsular polysaccharides is just very moderate. This is something that's also been done mostly by Jean Lee at Harvard.

But very important is that the strain I spoke a lot about in the beginning of my talk, USA300, which is the most important cause of MRSA infections in the U.S., does not have a capsule. So this strain could definitely not be targeted with such a vaccine component.

The other trial was the V710 Merck trial, which was directed at one specific surface antigen. There was a very nice basic science study by Olaf Schneewind's lab, and they compared basically every surface, anchored surface protein and *Staph aureus*, and IsdB came up as one of those that showed most

protective efficacy in mouse infection models. And they took four different ones together there and showed in basic science mouse models that this combination of four surface components was quite effective.

I only mention that here a little bit more in detail because if you look at the list, Number 5 was actually ClfA, and that is one component that we're going to talk a little bit more about in a minute.

So that IsdB trial also failed. Actually, there was -- I think there were safety concerns; it means that the placebo group actually did worse.

Now, what people, I think, mostly think about when trying to find optimal antigens is that, of course, they have to be immunogenic in humans. They also should be located accessible on the surface. They need to be accessible for antibodies. They need to be essential so that the *Staph aureus* cannot simply mutate them away and then become resistant. And they should be also widespread in epidemiologically important strains, coming again here to the USA300 story.

So I'm only going to present these antigens, and I guess that probably we're going to hear the same thing a couple of times again today, but I thought I'm going to finish my talk with a little bit, maybe, what a basic scientist thinks about them without trying to give really a personal opinion. I'm just going to present them.

So the vaccine targets in the SA4Ag are a recombinant mature form of ClfA, which I mentioned briefly already; the capsular, conjugated capsular polysaccharides that's virtually the same as in the Nabi vaccine; and a recombinant form of the MntC protein.

CP5, CP8, the capsular polysaccharides I talked about already, they didn't have efficacy in that StaphVAX trial.

Talking about how widespread capsular production is, of course, that depends on what kind of strain collection you have, but there are definitely some strains that are not encapsulated, and that includes USA300, which is important because these studies that I cited here are definitely only one-center studies. These are not bigger studies. But what these studies show is that USA300 definitely is also not a predominant strain in the U.S. in orthopedic and surgical site infections.

As research by several labs, but reviewed in this review by Jean Lee, has shown, that the contribution to virulence of those capsular polysaccharides is relatively modest.

And there is also the effect that capsular-negative mutants can be more virulent than capsule -- than the parental strain, the path capsule.

ClfA, I mentioned already briefly, is a surface protein; it's a surface anchor protein that is covalently balanced to the cell wall of *Staph aureus*. It is important for fibrinogen

and fibrin binding, so it's one of the *Staph aureus* proteins that definitely is very important as we found, too, in the phenotype that I showed you earlier, where you get huge agglomerations in synovial fluid.

It has been shown to be a virulence factor in several types of infections.

Anti-ClfA antibodies were efficacious in mouse models for prevention of sepsis. That was in combination with alpha-toxin or thrombin inhibitors.

There have also been passive immunization efforts, but they were, well, overall speaking, not that great in outcome, and I think there is quite some ongoing fight about whether ClfA alone, by active immunization, provides protection. There are earlier studies, such as that by Josefson in a mouse arthritis model, and that by Narita in mouse bacteremia, and these studies would suggest ClfA is a good vaccine target. There is that more recent by Jean Lee's lab where she looked at several different -- several different mouse models and did not find overall very good protection. And I think Annaliesa Anderson has written a very detailed recent review about that -- I guess we might hear about that again today.

So last but not least, there is the MntC transporter, which is a manganese transporter and which is conserved in staphylococci, not only *Staph aureus* but also others.

In the study by Dr. Anderson, published in 2012, active

vaccination with MntC reduced bacterial load by about 1 log. It was tested in different strains, always roughly around that value in *Staph aureus* but also in *Staph epidermidis*, which I think was one of the -- one of the main messages of that paper that, you know, it could be also used against other staphylococci.

And monoclonal antibodies did equally well in that study and reduced CFUs in infection by about 1 log.

One thing, very last thing, I want to say is that from a basic science point of view, there is the question about whether this protein, which is the lipoprotein with its lipid anchor inserted in the membrane, such as throughout the cell wall, to really offer antigenic epitopes that are accessible by antibodies.

With that question, I think I want to stop and answer any questions that you might have.

DR. EDWARDS: Thank you, Dr. Otto.

Are there questions? Yes, Dr. Follmann.

DR. FOLLMANN: Dr. Otto, you talked about passive immunization studies for ClfA. Were those all treatment studies, or were any of them to prevent infection prophylaxis studies?

DR. OTTO: I think these were treatment studies, as far as I know, yes. But I don't guarantee. I mean, I don't know that. There's so much detail, but as far as I remember, yeah.

DR. EDWARDS: Could you comment on the role of T-cells and how you think perhaps that vaccines might be evaluated in terms of their T-cell responses?

DR. OTTO: This, I have to admit, is a little bit of a difficult question for me because I am not a T-cell immunologist. So that might really be a little bit outside of my field of expertise. I'd rather not answer that because I might say something wrong.

DR. EDWARDS: Yes, Dr. Stephens.

DR. STEPHENS: Can you comment a bit further about USA300? You indicate that it doesn't have capsule. Can you talk a bit more about other virulence factors that are unique?

DR. OTTO: So that it doesn't have capsules is pretty clear because there is a mutation in the capsular -- and it's been shown quite clearly, it doesn't have capsule.

Virulence factors that are unique is -- well, not unique, but it's been very often associated with USA300, that it expresses the Panton-Valentine leukocidin, which is one of the predominant leukotoxins. Further, things that are unique are more metabolism related, and their role in virulence is not so clear.

What I would say is the most important thing to say about USA300, that it, in general, expresses toxins at a very high level, toxins that you also find in the maybe less virulent hospital-associated MRSA strains. So the difference there is

not the presence of the gene or the protein; it's more of the expression.

DR. EDWARDS: Dr. Long.

DR. LEVY: Dr. Edwards, it's Ofer Levy. Is it okay to ask a question?

DR. EDWARDS: Yes, go ahead, Ofer. Sorry. Thank you.

DR. LEVY: That's okay. I had a question for Dr. Otto, and I don't know if this is under his purview, but he mentioned the SA4 antigen vaccine, and I was wondering, is it formulated with an adjuvant?

And related to that question, the MntC protein, is that in a lipoprotein form, and if so, does it have Toll 2 agonist activity as part of the formulation?

DR. OTTO: I think these questions will be answered by Pfizer in their talk. I don't want to -- yeah.

DR. EDWARDS: Dr. Long.

DR. LONG: You didn't mention something that I think is a brand new piece of the epidemiology of staphylococcal infections that we see in children, for sure, and that is that MSSA, methicillin-susceptible *Staph aureus*, seems to be taking on some of the moves of community-associated MRSA USA300, and in some cases, that has been proven, and some of those moves would be diaphyseal osteomyelitis in children, which is very unusual; otherwise, pyomyositis and septic embolism from thrombophlebitis at the site of the bone infection.

So I don't know if the majority of these are organisms, USA300, that's lost its *mecA* gene or if it is MSSA, who has taken on some of the other virulence factors. But I think it is a new piece of the epidemiology that we are seeing MSSA resurgence.

DR. OTTO: I think this is -- the resurgence of MSSA is mostly due to the fact that we are now looking at it. One thing that has to be made very clear is that what you call the moves of CA-MRSA are basically the moves of MSSA; only CA-MRSA has found a way to take up the *mecA* gene and remain as virulent as its MSSA predecessors.

So now we're seeing a resurgence, maybe, of these highly virulent MSSA strains, but they were always there. So this is something that is definitely epidemiology. It's not really related to events such as you described of USA300 having lost *mecA*. I mean, these virulent MSSA strains, they were always around.

DR. EDWARDS: Any additional questions? Any questions from Dr. McInnes or Dr. Levy that we haven't addressed?

DR. McINNES: No questions from me.

DR. EDWARDS: Thank you. Thank you very much, Dr. Otto.

So our next presentation will be on the Clinical Considerations: Postoperative Staphylococcal Infection, Disease Manifestations, and Therapeutic Options by Dr. Richard Proctor, Professor Emeritus of Medical Microbiology and Immunology at

the University of Wisconsin in Madison.

Dr. Proctor.

DR. PROCTOR: So thank you very much for the invitation. And let me just put this into a little bit of perspective. It's July 1st, 1976, and I'm a new infectious disease fellow at the VA hospital in Madison, and I'm called to see a patient, and he walked into the hospital and he was sick and went directly to the intensive care unit, and he had *Staph aureus* on his aortic valve.

So we started him on antibiotics, did all the things that were done at that time, and went home and rounds again on July 2nd, the bed was empty. And I was upset because I was concerned, and my concern was well placed; he was dead. He had walked in the hospital and in less than 16 hours later went out in a box. And that focuses your interest. *Staph aureus* was a bad bug, it caused severe disease, and doing the math quite easily, you could see that four decades later, we're still talking about the same things.

Now, Bill Craig was my attending and Calvin Kunin was the chief of ID, and they both assured me that you had done everything right. That lasted for about 30 minutes, and I was thinking, if you do everything right and the patient goes out in a box in less than 16 hours, you're not doing things right. So from then on, I've been studying *Staph aureus*.

So I'm going to talk a bit about the need for the vaccine,

and Mickey already covered a good bit of that. I'll see if I can get this to move.

And I want to start out with a full disclosure. I've been interested in *Staph aureus* for a long time, and so that brings me to a lot of places where I might have had conflicts, and all of it is listed in your notes. I want to emphasize again, I worked for Merck from 2008 to 2010. That was during the -- well, the V710, the *Staph* vaccine, was being studied by Merck. I didn't set up the trial, and I wasn't involved in any of the data monitoring, but I was involved in looking at some of the basic science, which I'll discuss later.

I'm on scientific advisory boards for AmebaGon. That's a company in Madison that makes amoeba that will go after biofilms, including MRSA. I receive no payments for that.

Destiny Pharma, that's a company in the United Kingdom, and they are looking at a drug for nasal decolonization. I am receiving consulting payments from them.

DePuy Synthes, I consulted on an antibiotic-coated hip prosthesis. It was one meeting, it was here in another room in the FDA, and the decision was it needed to have more studies done, and I have not done anything more with them.

Telephus is a company in Rochester, New York. They're looking at a monoclonal antibody to prevent osteomyelitis. I'm actively involved in the discussions, but I haven't -- there's been no meetings and no payment, but one is scheduled.

Integrated Biotherapeutics is developing a multivalent *Staph* antitoxin vaccine, and I received a consulting fee from them.

And I've been asked by the Green Cross Corporation in Korea to assist with their *Staph* vaccine. I agreed, but there's been no meetings, no payments, or no contracts. So that's the full disclosure.

So at this lecture I'm going to talk about needs, which actually Dr. Otto has covered quite well. Challenges as well, we'll look at that. And there are a lot of challenges because we live with *Staph,* or *Staph* lives with us, and so it's learned how to do that, and it's learned how to subvert much of what we can do to get after it.

And the goals of a vaccine are twofold. And my hat is off to Pfizer. They're looking at a preventive vaccine. I think that's the highest bar and the most difficult. And the other approach would be to reduce severity so we decrease the mortality. And that may be easier, but I don't think it's going to be easy at all.

So the epidemiology suggests a need. And this is a slide I put together about 10 years ago, and then I added a couple updates. But it's a bad disease. I'm not surprised to see the number of pediatricians here on the panel. It's the number one cause for children being hospitalized and needing surgery. It's the number one cause of bacteremia if you're over 65. So

now I'm in that group.

The rate of invasive disease is comparable to H. flu, and we developed a vaccine for that to reduce the disease burden.

The number of cases are large, they're listed there, and the number of deaths are large, and these remain. And one of the things I can say is we look at all this information, and we've heard that there is now fewer cases, but the problem is the mortality rate hasn't changed. So we're not getting anywhere despite our new antibiotics. The mortality rate remains unacceptably high.

So this was the updated one, and when I started looking for new things, I didn't really find anything. There were new publications, but not new news. It's still the same bad news that we have a large problem with *Staph aureus* infections, and the mortality is still much too high. So I think we really do need a vaccine because antibiotics are not the answer.

So all successful vaccines, or I should say most successful vaccines, not all, have a biomarker. We know what you have to have in terms of immunity, for protection, in many cases, and that is if you're making a vaccine for the pneumococcus, meningococcus, you know you go after surface components, and if you have antibody, animal models, human epidemiology, it all correlates, and you get a good result when you raise those antibodies in humans.

The antigens are clearly involved in the pathogenesis, and

immunity is basically pretty well understood in diseases where we've developed a large number of our antibacterial vaccines. That's not the case with *Staph aureus*. And what I can say is if there is any defect in our basic science, and Mickey Otto outlined it pretty well, we really do have a defect in understanding *Staph aureus* immunity, and this is something that it would say has been an underfunded disease. That's a blatant pitch for more money to go into that area.

So to develop a successful bacterial vaccine, it is easier when we understand the immunology and the immune protection. So this would be a big advance, I think, in working. That doesn't mean that we shouldn't be trying to handle this, because we have made vaccines, but we didn't understand the immunology.

So I mentioned that *Staph aureus* is part of the normal flora, so it has a different relationship than many of the other pathogens where we've developed bacterial vaccines.

Staph aureus produces multiple diseases, and I think more about a *Staph aureus* vaccine is perhaps an *E. coli* vaccine, which has caused diarrheal disease, urinary tract infections, and bacteremia. And so I think we need to think maybe we don't need one *Staph* vaccine, we don't need "the" *Staph* vaccine; we may need *Staph* vaccines, and they're going to be aimed at different diseases. This is much like they're doing in the *E. coli* field.

Of course, challenges, there's so many virulence factors. Which one, which antigen is going to be the best to target, and that's problematic.

The anti-toxin animal models are consistent with human clinical disease. So I think the vaccines that are aimed at toxins have a lower threshold because they were probably aiming at reducing severity, and that's going to be easier than prevention.

The anti-surface structure antibodies have not replicated human responses, and I will study mice and look at this, but the murine model has consistently failed. If I were a veterinarian and treating mice, I would have a whole host of vaccines, and I would have a murine *Staph* vaccine on the market because they really work. And our clinical trials that had been based on murine models have not worked.

So I think there's a couple points to remember, and that is carriers have immunity, and people that are chronic carriers of *Staph*, which represents 30 to 50% of the population, they have more infections, they have *Staph* around all the time, but they have less severe infections, and there's a lower mortality. And not all the studies say that, but the majority of the studies do.

The other one is, if you wanted to get sort of a headache, you can read Yosan Streip's (ph.) stuff about the multiple, multiple mechanisms that Mickey already talked about, the way

that *Staph* beats the immune system, and by the time you finish reading these articles, you're sitting there waiting for bacteremia to start because it could happen at any second. It's an impressive array.

So what have we learned about trials that were aimed at preventing infection? Now, Mickey has summarized a lot of that. I'm going to go over this very quickly, but with passive immunization -- and the antigens are listed there -- active immunization, and ongoing trials. And Mickey already covered those very nicely, but we're still waiting -- awaiting outcome for the trials.

The one thing I will say, if I can find it here, in the Aurexis trial that looked at ClfA, that was the one trial of passive immunization that looked at bacteremia. There was a ray of hope there. So I know there are questions about ClfA, but that was the one that had a fairly strong trend. It was not statistically significant, but in the babies the anti-ClfA monoclonal did have a trend toward reduced mortality. So I think that there may be some ray of hope. It may be a small one, but at least it was there.

Do we know why the vaccines trial failed? And I think what was measured was opsonophagocytic antibody. Some of them were just uptake, but some of them were bactericidal tests using phagocytes, but not always, and there's been a question: Is that why they failed? The StaphVAX that Nabi had, which is

an anti-type 5/CP8 capsular vaccine, the Aurexis by Inhibitex, and V710 had high levels of opsonic activity and yet they failed.

There were questions in the Nabi trial: Was that because the antibody levels failed? The problem is, the second part is that if you don't make any antibodies at all -- so people that are agammaglobulinemic do not have an increased incidence of *Staph aureus* infections. There have been a couple papers that claimed that that was the case, but the papers were badly flawed. For instance, in some of them, the people had also received Cytoxan, so their neutrophils weren't functioning very well.

The other is that the -- people have innate immunity that is outside of antibodies, and they're protected. And there was one large series that looked at the number of infections that children got, and the thing that was impressive, if you looked at all hospitalized children with bacterial infection and they're agammaglobulinemic, they seemed to be protected from *Staph aureus*, their rates of infection were much below the average.

Now, what's happening there, of course, is selection bias, because these children were in there, and they had pneumococcal infection and H. flu and that sort of thing. But certainly, they did not have an increased number of *Staph aureus* infections. In fact, we looked at absolute rates in this, and

there are real hard-core statisticians here who can look at that, but I think that it's pretty clear that we don't have good evidence for lack of antibody being a cause. So there's other -- *Staph aureus* stimulates a lot of other pathways, as you would expect with an organism we live with, and it's taken care of still by innate immunity, but by different ways.

There was one study that came -- this was Magnus Hook, who took a look at the Inhibitex antibody, and what they found was the dissociation constant or the affinity of the antibody was too low to block binding to ClfA, and it didn't block the fibrinogen-ClfA interaction. In fact, the antibody was about three orders of magnitude too weak to block the interaction. So would better results have occurred if we had a higher affinity antibody?

So I don't believe that antibodies would protect. Then what do we know about the protective immunity in *Staph aureus*? We know that neutrophils are important, and Dr. Otto already emphasized that, and people with defects in getting their neutrophils to a site of infection.

And I'd like to point out Job's syndrome. That's a STAT3 problem, and they don't put out enough IL-17, which comes from Th17. And those people get an inordinate number of *Staph aureus* infections.

Defects in human immunity, I already mentioned that. And there are animal model papers, most of them murine, and human

data that suggests we have -- antibody is not protective.

On the other hand, cell-mediated immunity is important. People get prednisone. People that have mucocutaneous candidiasis have defective T-cells, and they get recurrent disease. People who are HIV get recurrent disease.

Gamma interferon defective mice: One of the things that's most difficult is you're supposed to keep your mice in a pathogen-free environment, but they still get *Staph* infections because things are not perfect and the animal handlers have hands. So this has been known for quite a while.

So it seems like there's an interaction between neutrophils and cell-mediated immunity, and that comes together at -- if I can get this to move -- through Th17. And this is where neutrophils and cell-mediated immunity coincide.

Certainly, when we see some immunity, we say, oh, well, you're getting an antibody response, so that's what's protective. But, of course, you also activated T-cells before you get your antibody response. And so I think that antibody may be a measure that you had an immune response, and I think the immune response is being protective through Th17.

One of the other things that I'll mention, and has been under study, is that one of the ways that we really are protected at both our lung and our skin immunity is that IL-17 has a very potent effect on mucosal cells and keratinocytes. And one of the things we did is took some cultured

keratinocytes, with and without IL-17, and then just lyse them, and you drop the cell lysate onto a lawn of *Staph aureus* and you get a nice zone of inhibition.

So the peptides that are induced by IL-17 in our surface cells are protective, and I think that that is one of the arms of the immune systems that we generally are not looking at unless you're a dermatologist, and dermatologists and ID people don't seem to talk very often.

So this is a time when most of the medical students in the room would fall asleep, so hopefully I'll try to explain this. And this is a working model and a hypothesis for what's going on, and I want to spend a couple minutes going through this so that we can -- that point is really showing up well, isn't it? Okay, I guess you can see it -- is the interactions between the immune system and *Staph aureus* as we know it. And this is almost all based on what we know about human immunity because murine immunity hasn't predicted things. Absolutely fabulous and beautiful scientific work which I love, but it's not predicting our outcome.

And what I want to start out with is let's look at the cell right in the middle, is the Th17 cells, and a number of murine studies certainly show that Th17 is critical, and we were able to show the osseous of first -- first off, it was Th17 immunity that was protecting the mice with the V710 vaccine.

And Tessie McNeely wondered, well, then, why did we -- the antibody, passive antibody, do things and the reason was is that it agglutinated the bacteria, and then in the mouses' livers, the agglutinated *Staph aureus* activated and released interferon gamma. So we still were in the T-cell cell-mediated immunity type of arm of the immune system.

So the Th17 calls in the neutrophils activates the epithelial cells with the peptides, stimulates IL-26, which it turns out there's an interleukin that's actually a cationic antimicrobial peptide; it has anti-staphylococcal activity.

So I put this at the center, and this is just a working model. One of the things I can guarantee you is that it's so complicated, it's certainly wrong, but it's a place to start out looking at things.

Now, one of the things that I was concerned about when I was at Merck was that -- and I wrote a review for *Vaccines,* and unfortunately, a caution that I put just at the end in the summary was well, we have to be careful of Th17 immunity.

And what happened was is that I was so excited when we did the basic work, and I was involved in some of the basic work on how the *Staph aureus* V710 is working, V710, and it stimulated Th17 and it was protecting through that, and I said, oh, good, because I had felt for quite some time that it was Th17 in the cell-mediated immunity on the immune system was going to be protective.

But I wrote a note of caution that, oh, we have to remember that Th17 is involved in a lot of autoimmune diseases, and its activation can be dangerous. And I think one of the things that happens -- whoops, what happens is I've got a heavy finger, sorry -- is that we change Treg, and Tregs are important because this regulates how vigorous the Th17 response will be. And if it's too vigorous, we get an overwhelming response. And I'm going to go forward to look at some data, and then we can go back and look at this diagram.

And basically, one I want to show you is this was a follow-up study that was published in 2014, where Tessie McNeely and colleagues went back to see if they could figure out what happened because patients that received the V710 vaccine had an increased mortality.

And there was serum that was banked, and they started to look at mortality, and surprisingly, they found out that the people that died after vaccination, and they had developed an active *Staph aureus* infection, invasive infection, 12 died and they had undetectable levels of IL-2, and that was before they were ever vaccinated. And they had undetectable levels of IL-2 on the day of admission.

So the vaccine figured out a subset of patients that had some immune dysregulation, and they were IL-2 defective. And when you compare that to the patients of the controls, this -- there was mortality, but it was very low in the people

with detectable levels in the control population. What happened was you ended up with excess mortality, and it was a hyperimmune response; they died of a systemic immune response. And that's why I'll go back to looking at the Tregs and Th17.

So when we look at this, IL-2 should be activating Treg, and if you don't activate Treg, then Th17 response is overly aggressive. So is that what happened?

And I really like the way Tessie McNeely put it in the paper when she published the results on the follow-up to the trial, is this is hypothesis generating and that's what this model is. It's not final; it's this has been modified any number of times. There's a lot of information here, and any model that you set up is a hypothesis. So this is generating a hypothesis.

But my question is, is if we immunize people and they don't have IL-2, are we then setting them up for a hyperimmune response when they get an infection? And the excess mortality was definitely confined to the immunized people with low IL-2 and a *Staph* infection. If they didn't get a *Staph* infection, it didn't happen. So you needed that immune trigger.

So I mean, I think the numbers are pretty clear, and the outcome unfortunately was really awful. In V710, 15 of 19 died; in placebo, 4 of 22 died. So it seemed to be a vaccine-related event.

So I think I've said all of these things, so I'm just

going to move ahead and go to the bottom line.

So all of our clinical trials aimed at prevention have been based on opsonophagocytic antibodies, and incidentally, in murine models, and they've all failed. So that doesn't mean that the murine model is wrong; it just means that it isn't predictive.

So we'd like to have a model that predicts human responses, and I think when we look at some of the antitoxin activities, antibody levels in humans, antibody levels in mice and outcomes, those have correlated. So toxoids may work. I have more optimism for that.

One of the questions that can be asked, if we move away from opsonic antibodies and we start looking at other types of antibodies, are those going to be more protective? And so I'm thinking that's a possibility, and we'll have to wait and see.

I suspect there will be questions. Thank you.

DR. EDWARDS: Thank you very much.

Are there questions for Dr. Proctor? Yes.

DR. LEVY: Yes, it's Ofer.

DR. EDWARDS: Go ahead, Ofer.

DR. LEVY: Well, it's really, first of all, to commend him for a really very cogent and provocative review. I think to the evidence that innate immunity can be important for host defense against *Staph aureus*, one can also add the primary immunodeficiency known as IRAK-4, interleukin receptor-

associated kinase 4, which is downstream of the toll-like receptor pathway, and evidence from Jean-Laurent Casanova and others that humans born with defects in that pathway, who failed to mount an innate cytokine response to *Staph aureus* and other bacteria, end up with recurrent pyogenic infections in early life, including with *Staph aureus*. So, interestingly, in the case of infants, they grow out of that susceptibility as they reach their teenage years.

So, again, I like the concept of taking lessons from human biology; you did that in your review, and you might add the IRAK-4, which also teaches us that immune ontogeny is a factor here, too, and the ways that the immune system deals with *Staph* might vary in the young versus middle age or older individuals as well.

DR. PROCTOR: You can't see me because you're on the phone, but I'm writing down IRAK-4 right now.

DR. LEVY: Yes, okay.

DR. PROCTOR: Thank you.

DR. LEVY: Yeah.

DR. EDWARDS: Hana.

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

My question pertains to the analysis by Tessie McNeely. When were the IL-2 measurements performed that were eventually predictive of mortality?

DR. PROCTOR: Okay, there were two times. One is when the

patient first went in and signed the papers and was immunized. Before they were immunized, blood was drawn and banked. And then when they were hospitalized for the procedure and day of hospitalization, blood was drawn.

DR. EL SAHLY: So the IL-2 pre-vaccine was predictive of mortality post-vaccine?

DR. PROCTOR: Yes. So to me, that is extremely hard evidence --

DR. EL SAHLY: Uh-huh.

DR. PROCTOR: -- that we have in our general population people that have immune dysregulation. And I'll have to say is that I didn't see this coming, and when they came by and asked, I said, oh, you know, I think this is really a great trial, you know, I'm excited, and then when I found out that it produced -- it was acting through Th17, I was even more optimistic, and then I was devastated when the data monitoring committee had to stop the trial because of excess mortality.

DR. EL SAHLY: And then was there an effect on nasal carriage in the Merck vaccine? Because you showed other data that this was predictive of mortality, too.

DR. PROCTOR: Yeah. I don't know. I can't remember. I can answer that question because I have the *JAMA* trial on my -- the *JAMA* paper, I believe, had information on that. Does anybody know here? I have it, and soon as I can get to my accessory brain, I'll give you an answer.

DR. EDWARDS: I think we all have that paper, too, so we can't remember, either.

(Laughter.)

DR. EDWARDS: Yes, Dr. Kirkpatrick.

DR. KIRKPATRICK: Thank you, Dr. Proctor. You've done what many in medicine find challenging, which is, you've educated an orthopedic surgeon.

(Laughter.)

DR. KIRKPATRICK: I'm glad you left this slide up because this is where my question is. I have heard over and over this morning that the response is different depending on the tissue and the host.

Where, in this diagram, can we put musculoskeletal infection? So bone, muscle, that sort of thing, and/or implants, as far as how we understand the response, or do we not have it to put on this diagram?

DR. PROCTOR: Let me talk in a more general way than -- is that a big part of implant or bone infections is biofilm and the -- once you form biofilm, you get past so many other things. Certainly, antibody. Neutrophils are less effective. Macrophages are somewhat more effective. But once you have an established infection in bone, this becomes a very difficult problem to get rid of.

In terms of prevention, there are models that are looking at innate immunity, and activation of innate immunity does

reduce the number of bone infections. So I think this model is a general model applying to all kinds of diseases. Whether it's bacteremia or skin infection or bone infection, I think there will be crossovers. And you know what? I've learned so much from my colleagues in orthopedic surgery, and being realistic, probably the most I learned was when I went to a conference. It was held just before the Irish Derby, and I met with the orthopedic surgeon for Churchill Downs, and I learned that horses aren't humans, either. Yeah, you can learn a lot talking to your colleagues.

DR. EDWARDS: Could you comment a little bit on the reason that the IL-2 and the IL-17 were decreased? Were those patients, did they have any specific underlying phenotype? Were they lupus patients, or was there something that could characterize their --

DR. PROCTOR: No, that's the real problem. This came as a shock. I mean, the people that were immunocompromised were -- known immunocompromised were excluded from the study, as you'd expect in most vaccine trials. So that wasn't the case, and these patients did not seem to have some underlying disease. It was the vaccine that pointed the patients out.

DR. EDWARDS: Yes, Dr. Greenberg.

DR. GREENBERG: Thank you, Dr. Proctor. My question is about the carrier state. It's been said a couple times this morning, I think that the carrier state leads -- seems to be

correlated with a decreased mortality either with bacteremia or with invasive disease or both, and I just want to make sure I'm clear. Is there any known impact of the carrier state on the development of bacteremia and invasive disease? And that's why there's a lower mortality or their risk of those invasive outcomes are no different than the non-carriers, but there still seems to be some impact.

DR. PROCTOR: Yeah, it's clear that carriers get more disease, there are multiple studies. There's one study that suggested no, but there are five studies that said if you're a carrier, you get more disease. But the studies also show that the mortality is lower, which is one of the driving forces for saying, well, maybe we can get a vaccine.

So if we look at any number of diseases, you know, whether it's bacteremia or skin infections, that sort of thing, it's true, the disease is less severe when you get a repeat infection.

Now, I have a question, and this is one that I think would really deserve a good clinical trial, is if we look at all patients with invasive *Staph aureus* disease, it would be fascinating to see what their IL-2 levels were and find out and look at mortality, because we know patients that are immunized by being a carrier, some of those patients die. Though it's a lower rate, are all those patients defective in IL-2, or a significant number? We just don't know. I mean, these are the

kind of trials that need to get done and need to be funded because this is a huge problem; it's not going away.

I can tell, after four decades of working on this -- in fact, of course, as a new infectious disease fellow, I was going to do some research and figure it out, and we did; we started out figuring out how that *Staph* attached to the valve, and we were going to make antibodies to block that attachment, and that was going to cure things. And, well, here we are four decades later, and we're having a meeting, and we're hoping we can find something. And my fervent hope is, is that this vaccine that we're talking about will work. I mean, that really is.

DR. GREENBERG: So along those lines, or in response to your response to me, in the flow diagram we have here, is there -- are there areas of this that are accentuated by the carrier state that seems -- that you think contributes to the lower mortality?

DR. PROCTOR: I'd have to say I just don't know. We just need to, you know -- we're so deficient in clinical studies that I think this is an area that we need to look at, and we need to fund, and we don't need an ID doctor who's looked at pathogenesis in much more of the organism and mutants and that sort of thing. And this is my weak attempt at looking at immunology, which I will say right off the bat, I'm not an immunologist.

But trying to put this together and trying to figure out what happened, particularly in the V710 trial, this really focuses your mind in, you know, on what's going on. And I think this hypothesis is there to encourage people to find out what's right and what's wrong and what will improve our ability to make vaccines and prevent this disease.

DR. EDWARDS: Dr. Follmann and then Dr. Long.

DR. FOLLMANN: Dr. Proctor, you mentioned that you felt it was kind of a high bar to set a trial to try and reduce or to prevent infection and that maybe a lower bar would be reduction in severity of disease. Could you comment a little more on that? And also mention how you might look at severity of disease; how would you measure it in an orthopedic surgical population?

DR. PROCTOR: Okay, so orthopedic surgery in general, you know, less morbidity, no infections and amputation, fewer patients in the intensive care unit, that sort of thing. So you just have the usual measures of less severe disease. Maybe even shorter time of hospitalization. I mean, there's all the secondary measures that you could look at.

I think prevention will be very hard, and Mickey Otto, he said that -- you know, that one infection doesn't prevent another one. And I think if you have a natural infection and it doesn't prevent it, what you can say is the kids that got boils and had PVL, they got another infection, but the boils

weren't nearly as severe, and the kids, instead of having to be hospitalized, were handled as outpatients and fewer of the boils needed to be lanced and that sort of thing. So something was going on and -- but antibody to PVL was a correlate, but we really don't know what reduces severity.

DR. EDWARDS: Dr. Long.

DR. LONG: I wonder how specifically you're using the term "carrier state." So I can see how that would be confounding of maybe doing better, more infections, if you weren't using it as specifically. I think of carrier as you're colonized, you have no symptoms, and there's some time, there's some steep in time. We don't call a child a strep carrier unless we know they've had it for some period of time, and that could explain why you might get antibodies to the organism or probably the toxins that make, for instance, recurrent staphylococcal toxic shock menstrually associated, less severe, etc.

But the other thing is that colonization at the time of surgery, at the time of a burn clearly increases the likelihood that you'll have a staphylococcal infection. And so I don't know how you're using the word "carrier state."

DR. PROCTOR: So when I was growing up, I had learned that there were three states: there were the permanent carriers, there were the transient carriers, and then there were the non-carriers. And after looking at, oh, probably a decade of research out of the Netherlands, I came to believe that they're

right, is that sometimes people are called transient carriers. It's really the numbers are just lower, and they're still a carrier.

So they call people carriers or non-carriers, and there's research into why people carrying, whether they have receptors or not. So that's the way I use it. And so if you're positive, you're a carrier. If you're culture negative, you're not a carrier. And that's the way the Dutch have come to describe it. Now, it is a level and the numbers of organisms, is that enough to make a difference? I don't know, in terms of developing antibodies to toxins. Don't know.

DR. EDWARDS: Dr. Kirkpatrick and then Dr. Lynfield.

DR. KIRKPATRICK: As a response to Dr. Long's question about carriers, practically, in orthopedic surgery, if we're worried about being a carrier, we're treating you as a carrier if you have one instance of it being positive on your nasal swab. So we don't worry about how long you've been there or whether it's transient or not.

DR. EDWARDS: Dr. Lynfield.

DR. LYNFIELD: Could you go back to the slide, the table of V710 recipients, in which you listed 15 out of 29 died; placebo, 4 out of 22, and the -- yeah, that's it. Thank you. So I may have missed it, but you were saying that the people who died did not have IL-2, and when we look at IL-17, though, the hypothesis is that they then did not have the Treg and so

they had more IL-17. But it looks like on the day of admission, the IL-17 was undetectable.

DR. PROCTOR: Yeah. And that's why I think it's worth probably concentrating on the IL-2.

DR. LYNFIELD: Okay.

DR. PROCTOR: But if you didn't -- you know, because the IL-17 is downstream, and so if your IL-2 is not impacting Treg, is that going to change? So I think that what this really speaks to is there is immune dysregulation in these patients, and that's why I think it's really good to think about this paper in human vaccines and immunotherapy that Tessie McNeely and the rest of the basic research group at Merck put together.

They called it hypothesis driving, and I think we need to study the patients, and we need to look at probably a large number of patients that are being immunized. But I think there is immune dysregulation, and I think that's the best way to look at it.

DR. LYNFIELD: Yeah. No, I understand that. I guess I was trying to understand the pathway, and I thought the pathway was if you do not have the Treg, that you had overproduction of IL-17. And so I thought that was your hypothesis.

DR. PROCTOR: Yes, it is. But remember that the patients -- this is day of admission and pre-vaccine, so they're not necessarily getting challenged with any *Staph aureus* at all.

DR. LYNFIELD: So the day of admission wasn't when they were admitted for infection?

DR. PROCTOR: No, no. No, this is --

DR. LYNFIELD: Okay.

DR. PROCTOR: This is when they are admitted for surgery.

DR. LYNFIELD: Admission into the study, that was done --

DR. PROCTOR: Admission into the study and then --

DR. LYNFIELD: Got it.

DR. PROCTOR: -- admission to the hospital.

DR. LYNFIELD: Thank you.

DR. PROCTOR: It was the day before, 1 or 2 days before they had their --

DR. LYNFIELD: So they were not tested when they were admitted for their infection? They didn't have serum obtained at that point?

DR. PROCTOR: You know, I didn't design the protocol, so it's hard for me --

DR. LYNFIELD: No, I'm just asking.

DR. PROCTOR: -- to remember all the details, but I -- they had the surgery, and of course, most of the infections are happening shortly in the perioperative period, and I don't believe any more sera were taken then.

DR. EDWARDS: A thoughtful question.

Dr. Kotloff. And maybe if you just introduce yourself, too.

DR. KOTLOFF: Hi, I'm Karen Kotloff. I'm a pediatric infectious disease specialist at the University of Maryland School of Medicine, Center for Vaccine Development.

I was confused in the same way and wondered was there a documentation of excess IL-17 reduction in any of these patients? It's a hypothesis.

DR. PROCTOR: Yeah, that's what I'm guessing, but the data that -- the data had to be all done in retrospect because you bank sera, and there were sera that were drawn during the trial, and it was pre-vaccination sera that was taken, and sera was taken the day of admission. But then during the infection, I don't know. That's why, you know, this is a hypothesis, and I think we really need to study this, and I think we need to know is that specific for just this surface antigen, or is it a more general problem?

DR. EDWARDS: Any final questions for Dr. Proctor?

(No response.)

DR. EDWARDS: Thank you very much.

DR. PROCTOR: You're welcome. Thank you for the wonderful questions.

DR. EDWARDS: Thank you.

I think we're very much on target for our time, so we will have a coffee break, and we'll come back and begin at 10:45.

(Off the record at 10:30 a.m.)

(On the record at 10:46 a.m.)

DR. EDWARDS: If everyone could find their seats. If everyone could please find their seat. We're 1 minute behind schedule.

So for the next portion of the presentations, I would like to call Dr. Bill Gruber, Senior Vice President for Vaccine Clinical Research and Development for Pfizer, to introduce the next speakers.

Dr. Gruber.

DR. B. GRUBER: Thank you, Dr. Edwards. Good morning, everyone. My name is Bill Gruber, and I head the Vaccine Clinical Research and Development group at Pfizer. I'd like to thank members of the Advisory Committee for the opportunity to share with you Pfizer's proposed plan and rationale to support a four-antigen *Staph aureus* vaccine indication in elective orthopedic surgery.

We are honored to be joined today by presenters and subject matter experts. Dr. Thomas Errico will describe the burden of *Staph aureus* surgical site infection in spinal surgery and share some of his experience as a STRIVE study investigator.

He will then be followed by Dr. Javad Parvizi, who will describe the challenge of orthopedic infections with emphasis on hip and knee arthroplasty.

And then I will follow with the Pfizer-proposed plan and rationale to support a four-antigen *Staph aureus* vaccine

indication in elective orthopedic surgery.

We are also pleased to have joining us today Dr. William Richardson, an additional expert in orthopedic surgery, and Dr. Mark Shirtliff, an expert in *Staphylococcus aureus* biofilms, to provide the Committee the opportunity to ask questions to gain additional perspective in these areas, if this would prove helpful.

So now let me invite Dr. Errico to the podium for his presentation.

DR. ERRICO: Thank you, Bill.

I'm here in a short period of time to try and give you my overview of 35 years of experience as an academic spine surgeon. These are my disclosures.

I am both in the departments of orthopedic surgery and neurosurgery, but I am an orthopedic surgeon by training. Orthopedic surgery, we share a lot of commonality with other subspecialties. Spine surgery, we tend to start with an intact skin, we cut that skin, we violate the barrier to infection, we cut through the fascia, we go down to bone, we do work there, and that is what we do in life.

In spine surgery, in its most simplistic form, there's only three things that a spine surgeon -- you can list hundreds and hundreds of different procedures we do, but it all boils down to three things. We can take a patient who has a compressed nerve or spinal cord, and we can take the pressure

off of that nerve, and we call that some type of a decompression.

We can take a spine that, over the course of time, has become unstable, and we can stabilize that. We generally rely on a fusion to do that. Typically, that is done with some type of metallic fixation.

We can also take a crooked spine that has occurred over time, and then we can straighten that spine, return it to normal alignment, but that is always accompanied by a stabilization procedure.

This is an example, a 72-year-old woman who had a progressive spinal deformity emanating from an attack of shingles. She had over the ensuing year, the musculature on the flank that had been affected by the virus had weakened, and she got this severe imbalance.

And so we used the two techniques on the bottom, we corrected her deformity, and we stabilized it. So we put in a series of rods and screws, and we resurrected her spine, and that is how she stands afterwards. This is kind of orthopedic surgery at 100 miles an hour. We use very large incisions in spine surgery, and this is what it takes to fix some of these complex problems.

Sometimes the problems we treat are iatrogenic, caused by another -- by an intervention meant to help that didn't help. This was a 63-year-old female, status post-five back operations

in Florida by the same surgeon, and he started with a single-level operation; additional levels four more times; finally advised by her surgeon to seek psychiatric counseling; unable to stand up straight; she could walk less than one block. And although the hardware looks like it's a good position, it has left her spine in a severe imbalance, leaving her to stand pitched forward, unable to look ahead and in severe pain.

So we have surgical mechanisms to make osteotomies into the spine and correct the curvatures but stabilize it once again using metallic implants with screws and rods and a fusion of the area. And we get dramatic post-op results. And you can see that -- although you don't see her eyes, you do still see the smile on her face.

Now, unfortunately, as I was told when I was a resident, any time you cut the skin, you interrupt the barrier to infection, and infections can occur, and we take great strides to prevent this in our surgical practice. But we can't get away from it. Surgical site infection in spinal surgery is 1.9%. If we look at the contribution of *Staph aureus*, it is about half of the cases. Instrumented spinal fusion has the highest incidence of surgical site infections.

And healthcare costs, which we examine on a daily basis in our medical center and all around the country, are nearly twice as high for patients who have SSI compared to non-SSI infected patients.

Despite our efforts to do this, *Staph aureus* still complicates spinal surgery, putting our patients at risk for morbidity and mortality.

This is a case of a case that was infected. This is a 70-year-old female who had significant comorbidities. She presented to us with chronic debilitating back pain; she'd had multiple back operations complicated by *Staph aureus* infection. Because of that, her spine did not heal; she had progressively pitched forward posture, she could not stand erect, and she, in fact, had an osteomyelitis due to MRSA, for which she'd already been on antibiotics for 6 months.

We attempted to surgically fix this. We attempted to eradicate the osteomyelitis by doing an anterior procedure; then we turned her over and did a posterior procedure, and we got her to stand up straight and treated her with postoperative antibiotics.

Unfortunately, about 3 weeks later, she noticed persistent drainage at the bottom of the incision, no fevers, no constitutional symptoms, but elevated markers, inflammatory markers, sed rate 105, white count elevated, and the culture from the wound: *Staph*. The hardware was intact. We decided to try to treat her with antibiotics. We did a small minimal re-exploration at the base. She had an infected seroma, which was debrided. Some muscle flaps were put over by our plastic surgery department, treated her with 9 weeks of antibiotics.

Three months later, she's weaned off her antibiotics; small pinhole incisions come back. She gets a proximal junctional kyphosis, she starts to angulate at the top of the hardware, and her inflammatory markers are high, and she still has a *Staph* infection.

We do advanced imaging, and we see this large abscess. We take her back to the OR, we debride the wound, we remove -- we cut one of the connectors, we did a flap, put her on long-term antibiotics, but at 1 year she presents with new drainage, loosening of her hardware, and we realized that we had to bite the bullet and remove all of her hardware and treat her with antibiotics for 3 months. We kept drains in for almost 3 weeks.

Finally, after 3 months of IV antibiotics, we took her back to the operating room, we re-instrumented her spine, we kept her on IV antibiotics for 3 more months. She's now a few years out on a life-long oral suppressive medication. She still has the risk of long-term recurrences. She's had multiple hospitalizations. She's been in a long-term care facility. I actually just this week had them resurrect all the data and all the hospital admissions, and I was shocked to see that the hospital charges she incurred during her five admissions were $2 million. The hospital was reimbursed 400,000 of that.

So I have been enrolling patients for -- since September

of 2015 in the STRIVE study. NYU has a quite robust orthopedic spinal program, which I have the pleasure of directing; we do about 2,400 cases a year, and I would estimate that about 10% of those patients are eligible for STRIVE.

Yet we've only enrolled about 21 patients out of this much larger pool, and as the principal investigator, I really looked into this, and we have a really good team and more experience, we do lots of clinical trials.

But there's been barriers to enrollment. Sometimes patients just don't want to enroll in a study. They just want to reap the benefits of scientific endeavors, but they really don't want to participate. Sometimes, in this particular study, they don't like the added burden of some additional visits and blood draws. People are afraid of needles. Sometimes the patient has been committed to a large spine surgery, and they're just overwhelmed by their condition and a planned surgical procedure, and they can't even contemplate considering it.

And lastly, although I say we're experienced in clinical trials, most of the trials, as surgeons, we run are medical device trials, and this is a very pharma-heavy, burdened trial for us. I can say that it's been difficult, but we're learning.

And I thank you. And if there's any other questions I can help answer for you, I'd be more than happy to.

DR. EDWARDS: Dr. El Sahly.

DR. LEVY: Yes.

DR. EDWARDS: Wait, Hana's going to speak and then you can speak. Hold on.

Go ahead, Hana.

DR. EL SAHLY: Thank you, Dr. Errico. Were the people who declined enrollment in the trial compared to those who agreed to enrollment in the trial? And were they comparable in terms of risk factors, comorbidities, other things that predisposed them to infection?

DR. ERRICO: I don't think I have that data.

Bill, did we collect that data in the study, the people who declined?

(Off microphone response.)

DR. ERRICO: Yes, Dr. Gurtman would be the best one to answer that.

DR. GURTMAN: Good morning, I'm Alejandra Gurtman from Pfizer Vaccines and the global clinical lead for the program and actually leading the STRIVE study.

So we collect data on patients who are actually screen failures and not necessarily on the patients who are these -- you know, they decide not to enroll in the study. But I can tell you, Dr. Gruber will show later that we have a great deal of patients with comorbidities that are accepted in the study.

DR. EDWARDS: Dr. Levy, did you have a question?

DR. LEVY: This may have already been stated and had gone by, but if pediatric enrollment was mentioned, I'm sorry, can you remind me again what the age range of children is?

DR. ERRICO: Over 18. So no pediatric enrollment.

DR. LEVY: Oh, okay. I thought I heard you mention something about that.

DR. EDWARDS: Any other questions?

(No response.)

DR. EDWARDS: Thank you.

DR. ERRICO: Yeah, I mentioned that we do pediatric and adult surgery; that's why you heard that. Thank you.

DR. LEVY: Okay.

DR. ERRICO: Okay, then it's my pleasure to introduce Dr. Parvizi, who is an orthopedic spine surgeon and does total joints at the Rothman Institute in Philadelphia.

DR. PARVIZI: Thank you very much. Thank you, Dr. Edwards. Thanks to the Agency for giving us the podium today. And I'd like to thank Pfizer for inviting me to be here.

As you just heard, I am an active surgeon doing total joint replacements. I do roughly 10 joint replacements a week. Most of it is done on patients who have infection. That relates to the fact that I have interest in infection. I presided on the Musculoskeletal Infection Society in 2013, and

I have published over 300 peer-reviewed articles just related to the topic of infection in orthopedics. So, hopefully, this gives me a little bit of expertise to be standing in front of you to tell you some of the challenges that we face.

Because of my interest in infection, I serve on various committees. I have been the recipient of a grant from NIH, Department of Defense, multiple other organizations, including some from industry, but the most pertinent conflict of interest today is that I am a paid consultant to Pfizer, and I'm here and I'll be reimbursed for my time, taking time from my clinical practice.

Let me give you a little bit of history. Back in 1890, Gluck was the first person to have experimented with joint replacement. He was a surgeon that served for the German orthopedic society, and interestingly, the joint replacement he did then on knee replacement is very similar to what we do today.

But his problems were twofold. One is that he made his knees out of ivory, which you know is not biocompatible, and unfortunately, all five replacements he did got infected very quickly. And unfortunately, he was then stopped from practicing and ostracized from the German orthopedic society, but he did make one prediction, and that was ailments of humans will be treated by artificial materials, and he was right on that prediction because we do roughly 1.2 million total joint

replacements in the United States alone, and that number is likely to increase in the coming years. And out of those, roughly between 25,000 to 35,000 revisions done per year on joint replacement is because of infection.

And if you look at some of the health statistics, you will see that by year 2030, at the rate we are going today, we might be doing three and a half million knee replacements in the United States alone. And, unfortunately, with the infection being one of the major problems, we'll be seeing this burden increase only with time.

Another visionary man, Sir John Charnley, who really introduced the modern hip replacement into society, he also predicted, in his presidential address back in 1979, that joint sepsis will be the major hurdle in our way in the future. And unfortunately, his prediction was correct because today we deal with problems like this in the operating room because of patients being infected after artificial replacements.

I wrote an editorial, I will not bore you with this, but I believe that periprosthetic joint infection is now the last frontier into artificial joint replacement. It poses a huge challenge to us, and we are running out of options. And I will share those with you.

The true incidence of infection after replacement is unknown, but it's probably around 1 to 4%, depending on what source you read, but it is higher after revision arthroplasty.

And similar to Dr. Errico's presentation in spine, the more complex of a case you do, the higher the incidence of infection. And I'm sure, to clinicians on the board, this would not come as a surprise.

The majority of the infections are caused by *Staph aureus,* and I think, again, the true number is not known, but it's roughly over half of the infections in periprosthetic joint infection likely to be caused by *Staph aureus*.

The incidence of infection appears to be on the rise. Registries underestimate the incidence of infection. Registries don't collect sophisticated data to be able to give you information on the incidence of infection, nor do they collect granular data to allow us to assess the risk factors, etc.

But institutional data has helped us so far, including my own institution that does roughly 12,000 joint replacements per year, again, many of them for treatment of infection.

But I do believe that incidence and prevalence, aside from what has been stated, we looked at the incidence of so-called aseptic revisions, revisions being done for failures that were not thought to be infected; unfortunately, 12% of those were infected. And this comes from an institution that pays huge, huge attention to the issue of infection and investigates patients prior to undergoing revision arthroplasty.

Infection is not a single event. It can occur throughout

the lifetime of the prosthesis. Here's a study I did with Steve Kurtz on the Medicare database, and if you look, a majority of the infections are early, that's that massive drop in the beginning; this is for total hip replacement, but infection continues to threaten the success of total hip replacement and total knee replacement throughout its life. So our patients are unfortunately not protected from infection while they have that prosthesis in place. And again, a majority of them occur within the first 90 days after surgery.

The economic burden of infection is unknown. I have had interest in this area; we published some articles in the past. We're not quite sure, but one thing that is clear is that infected cases cost almost four to five times aseptic revisions. Because of that, there's been interest from numerous bodies, including Infectious Disease Society of North America, Musculoskeletal Infections Society, our American Academy of Orthopaedic Surgeons, and I was the lead of a consensus meeting held back in 2013 in Philadelphia, 400 delegates that came together to address the issue of infection, and this consensus meeting will be repeated next year -- this year in July.

World Health Organization published their prevention guidelines recently. This was rushed through because they realized how important this issue is, and their guidelines that was published in November does have some help that will allow

us to try to get our arms around this issue.

I was a representative of the academy and served on the CDC guidelines for 4 years, and I'm sure most of you know these guidelines just came out. Very useful. Very frustrating time for all of us that served on this committee because, unfortunately, there's not much evidence for the things that we do in orthopedics, and I think I could even generalize that to medicine overall. But nonetheless, this serves as a very, very important document, and CDC, in my opinion, accomplished its objective of trying to come up with guidelines that will hopefully prevent some of these disastrous complications that happens to our patients.

But we've come to realize that, unfortunately, all infections are on the rise and so is the interest in publications. This is just some of the publications related to the subject of periprosthetic joint infection over the last few years, and as you can see, there has been a rapid interest in this subject.

I did a projection, a study, with Steve Kurtz. This was published back in 2008. We predicted that the incidence of infection following total knee and total hip replacement was going to be on the rise, almost an exponential curve. This was a projection study. Obviously, we did not have the data at the time. We used the National Inpatient Sampling database, and quite honestly, we were both somewhat surprised at that steep

curve that we observed. And we met with some self-skepticism thinking that this was perhaps not going to be the case. Unfortunately, we had under-predicted the incidence of infection. Now that we have data for those years from the NIS database, the numbers of infection we had predicted are now much -- they were much lower than what we actually do today.

Roughly 34,000 infections were revised back in 2015, at an estimated cost of $1.6 billion to healthcare. So not only is this psychologically, socially really burdensome on our patients, it also poses a huge economic cost on the society. And again, as I told you, I'm not quite sure about the actual economic cost of this problem, but I can tell you that when the infection is caused by *Staph aureus*, for some reason it appears to carry a much higher economic cost than other infections. And again, this is the study that I did with Kevin Bozic from San Francisco.

It carries high morbidity. Despite doing everything we have in our armamentarium, we do lose the battle in some of these patients. They present with very, very challenging problems, and unfortunately, some of them lose their extremity to this terrible condition. And unfortunately, some of them lose their lives to this condition. So periprosthetic joint infection is actually a fatal disease.

We published a study showing that the risk of death after infection, periprosthetic joint infection, when it was age and

comorbidity adjusted, was four times higher than the septic group. And if I were to show you one graph, which will hopefully capture the gravity of this situation, it will show you that the periprosthetic joint infection carries a higher mortality than some of the common cancers that we see today.

We did another study with Steve Kurtz that was just presented in the closed knee and hip society. We looked at the Medicare database. The questions we were asking was, is the incidence of PJI changing over time, and is mortality after PJI changing over time?

This is the 100% inpatient database from Medicare. Obviously, these patients are all over 65 years of age, about two and a half million total knee replacement patients, of whom 34,000 had undergone surgery for periprosthetic joint infection.

And we used the denominator file issued by the dataset, did a multi-regression analysis, and what we found was, unfortunately, the 1-year mortality was 8% and 5-year mortality, 28% in this patient population. Again, these are all age and comorbidity adjusted. I'm sure most of you will agree that's a terrible survivorship, even judging it by some of these fatal cancers. And when we compared it to breast cancer and prostate cancer, the survivorship after developing infection after total knee replacement matched those of prostate and breast cancer.

So what I think, as a clinician who continues to deal with the challenging problems on a daily basis, I truly believe the future needs to be different. We need to have a truly novel approach, and I think both Dr. Otto and Dr. Proctor have very nicely articulated the challenges we face.

Antibiotics are failing us. We are not able to really deal with that issue. Again, I've been sensitized by serving at CDC for a while, to the issue of antimicrobial resistance.

And we've seen pan-resistant organisms arise. This is one of the CDC reports on pan-resistant *E. coli*. AMR issue continues to attract attention from governmental agencies. This is a report from the British government showing that this issue really is very, very dire and could kill up to 50,000 people in Europe and USA per year. And the report tells us that if we do not get the issue of AMR under control, we could lose up to 10 million people by year 2050, much more than fatality from cancer.

And in orthopedics, you just heard again from Dr. Errico, we don't really have much options. Whether it's spine surgery, whether it's knee replacement, whether it's hip replacement, shoulder replacement, our approach is the same. When infections occur, especially with *Staph aureus*, all we have is to throw antibiotics at these patients, maybe take them back to the operating room, but it does continue to fail us. We continue to use higher and higher amounts of antibiotics and

again, as Dr. Proctor said, we have made no difference to the outcome.

So I think the future needs to look at alternative options, perhaps immunity. And again, I'm the last person to be telling you anything about immunity, but I can tell you that there needs to be a different approach than what we have had so far. Perhaps we should parallel what the oncologists have learned in terms of immune-enhancing strategies that they're using today.

Vaccination, in my opinion, is an exciting and appealing approach. I have had interest in this for the past 7 years and follow this literature very, very closely. So that's the reason I accepted to come here today to tell you the challenges we face today.

In my opinion, there are a huge number of parallels between spine patients who develop *Staph aureus* infection and those who have undergone total joint replacement. Again, you can actually even extend that to include foot and ankle patients, shoulder patients. The demographics of these patients are almost identical. The invasiveness of the procedure is almost identical. The outcome is just as dire, whether it's after spine infection or after total joint replacement.

And I can tell you, as a clinician, I really hope that this vaccine will work, and I cannot wait to have this vaccine

to use in my patients who are undergoing total joint replacement.

So I hope today you will see plenty of scientific rationale to draw the parallel between spine and total joint arthroplasty patients, and no one better than Dr. Gruber will come up here and give you that rationale.

Thank you very much.

DR. EDWARDS: Are there any questions?

Yes, Dr. Lynfield.

DR. LYNFIELD: Thank you. I just wanted to go back to your telling us that there's an increase in infections and showing us those data. Was this because there has been an increase in procedures, or taking the number of procedures into account, do we continue to see an increase in infections? And then also, do you have any hypotheses, if that is the case, as to why?

DR. PARVIZI: Yeah, thank you for that question. It's both. We do more cases, and hence, the actual volume of infected cases we deal with are going up. But on the other hand, we've expanded the indications for elective orthopedic surgery.

In the old days, when somebody with cancer or immunosuppressed disease, the rheumatoids, the lupus, the HIV patients, etc., they may not have been deemed appropriate candidates for elective arthroplasty and are now being offered

this very effective operation. So we have expanded it to include a lot of high-risk patients.

And then my hypothesis is that our protocols in dealing and identifying infection has improved over the years. We have introduced a biomarker, for example, for periprosthetic joint infection. And then I also think people are paying more attention to infection. So when I was, you know, a young attending interested in infection, with my first grant back in 2003 that I got from NIH, I would not be asked to go to any of the meetings, and whenever I gave a talk about infection, I believe the room was empty, and those who were there were probably asleep.

But now there is more and more attention being paid to this problem, and I think Dr. Kirkpatrick probably could confirm, the majority of the orthopedic meetings we go to has a whole symposium on the subject of infection.

DR. EDWARDS: Dr. Kotloff and then Dr. Bok and then Dr. Monto.

DR. KOTLOFF: Thank you. I imagine that a lot of the patients who have PJI have comorbidities, and I'm wondering whether you've been able to tease out the survival of the comorbidities and what the PJI has -- how that, the PJI, has affected the natural history of the comorbidity.

DR. PARVIZI: Yeah, a wonderful question. Of course, these patients who developed infection have several of these

risk factors for developing periprosthetic joint infection in the first place. That includes diabetes, particularly on under or uncontrolled metabolic syndrome, immunosuppressed patients, patients with immune issues, etc. This whole list goes on. So these patients are at risk of developing that problem in the first place and then, of course, because of their underlying comorbidities, they're not able to properly mount the proper immunological response to infection, and hence, it leads to their demise as a result of not being able to fight that infection, which would've probably happened better in a patient that had a better immune system.

In terms of the mortality, so that I actually make that point clear, we did match for comorbidities as much as we could, so the Charlson Comorbidity Index, American Society of Anesthesiologists score, etc. But as you know, that is not sophisticated enough to be able to tease out the difference between a patient that has well-controlled diabetes versus poorly controlled diabetes, or a patient that has an unrecognized immune deficiency versus those that don't.

So, overall, I think these patients are at risk of developing it in the first place, but when they do develop it, the outcome is disastrous because they are unable to mount a proper immunological response.

DR. EDWARDS: Dr. Bok.

DR. BOK: I'm trying to understand how to correlate the

surgeries, and I've never seen the foreign materials that you used. But keeping in mind that *Staph aureus* also causes biofilm, do you have any data on if the surface or the size of the foreign material that you use has any effect on the recurrence of infection or the severity of the infection?

And also, I'm interested in knowing if the size of the incision matters, too, when you compare a spinal with a knee or a hip replacement.

DR. PARVIZI: Sure, thank you. The material we use is the same. We use either stainless steel or titanium, and it's the same material that's used either in spine or total joint replacement, foot and ankle. It's really the same material throughout orthopedics.

The longer the surgery, the higher the incidence of infection. There's a direct correlation between operative time and the incidence of infection. There's a direct correlation between the length of incision and the extent of soft tissue dissection and the incidence of infection. So a 9-hour spine surgery will probably have the same sort of an infection rate as a 5-, 6-hour revision total hip replacement, which also requires a very long incision.

The materials we use are all as you have mentioned. Because being foreign material, all are prone to developing biofilm, and once the biofilm forms, that becomes a very difficult issue.

As far as the affinity of organisms, I think the best person to answer this question would be Dr. Shirtliff, who worked with Dr. Bill Costerton and they got a biofilm, who unfortunately passed away a few years ago. I've seen Dr. Shirtliff give incredible presentations on biofilm, and I will pass this question to him to answer.

DR. SHIRTLIFF: Mark Shirtliff, the University of Maryland, *Staphylococcus aureus* researcher and professor.

We haven't really noticed much of a difference because bacteria, whenever we're dealing with *Staphylococcus aureus*, it's never specifically about the surface itself. It's what sticks to the surface. So when you implant a medical device into a human, it just basically coats and holds proteins, and then that's what bacteria basically end up sticking to. It doesn't really matter the surface whatsoever.

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

DR. MONTO: This may be a little hypothetical, but you mentioned that about 50% of the infections are *Staph aureus*. Is there any evidence that if you prevent the *Staph* infections, you're going to have replacement with something else, given the process of the surgery, etc., because this has become a phenomenon with other -- in other situations.

DR. PARVIZI: Yes. So I am interested in the subject of microbiome. We're doing a huge amount of studies right now. I will tell you, though, I personally think the majority of these

infections cause -- joint replacement are not caused by a single organism, but are caused by multiple organisms, one of which happens to be dominant. And because of *Staph aureus* being a professional pathogen, that usually happens to be the one that we isolate with culture.

And, interestingly, when we see these patients fail later, and up to 25 to 26% of these cases fail later, they fail as a result of another organism. But if you do things like molecular analyses, and we're interested in next-generation sequencing, for example, you actually see that signature of *Staph aureus* still being present.

So it looks like either the antibiotic pressure or our efforts to really eradicate a single pathogen and our dogma that infections are caused by one organism only, perhaps all of these need to be investigated. But one thing is clear, is if you enhance the immunity of the patient, perhaps you will afford a better chance of dealing with the later infections, when or if they arise.

DR. EDWARDS: Dr. Long.

DR. LONG: The staphylococcal infections that are occurring in these situations, both nationally and at Jefferson, which is just down the street from me, what percent are MRSA? In recent years?

DR. PARVIZI: Right. About 36% of all the staphs are MRSA. The majority of them, I think, are again the USA300 when

we see them.

And I know I was very interested in your earlier comment about the diaphyseal osteomyelitis in some of these children. We also see very unusual infections in some of our patients that are presenting with the periprosthetic joint infection. It looks like there is diaphyseal involvement, periosteal elevation, and some of these are so extensive that we have to remove what appears to be healthy bone, which unfortunately has been infected.

DR. LONG: So one of the possibilities of the increase in infections is the competency and density that USA300 has on skin, which was very different than previous MSSAs that live in the nose and get to these other places. MRSA USA300 really lives in high density, which brings me to the next question.

Have you already continued to see increases in rates of infection with applications of bundles of preventive practices prior to surgery, including chlorhexidine baths the day before surgery to decrease the density?

DR. PARVIZI: We have implemented a series of protocols, some of which you have just mentioned, and I believe chlorhexidine wipes and soaps are probably one of the most effective strategies. The literature still remains divided, and that's why CDC made no recommendations about MRSA screening and decolonization. There's been conflicting reports even from governmental agencies regarding that issue. But chlorhexidine,

wipe the entire body, probably one of the most effective strategies.

I'm personally not in favor of the use of mupirocin, again, because of the AMR issue, and we see a lot of our *Staph aureus* be resistant to the Bactroban -- because of that, we moved away to universal decolonization by an antimicrobial agent that is not an antibiotic. So we're doing that on everybody routinely at the moment, including our spine population.

And interestingly, the exact protocol spine surgeons implemented, we have done the same, and we have seen a decline in the incidence of overall infection at my institution.

DR. LONG: And then the last question, again about the increase in infections. I don't know if, on these great big wounds, you use non-suture material, like what we call glue, as we have seen increasing numbers of infections, especially with *Staph aureus*, surgical procedures where people have used glue rather than sutures.

DR. PARVIZI: Yes, we have. But on that front, CDC made their recommendation that we should be washing all of these wounds with aqueous Betadine. Spine surgeons have a habit of pouring vancomycin powder into the wound, and CDC strongly recommends against that practice. There is a correlation with the type of suture material used and the adhesives on the skin and subsequent incidence of infection, which is what you bring

up, and I think that's a very important point.

DR. EDWARDS: Dr. Follmann and then Dr. Stephens.

DR. FOLLMANN: I guess a major reason for focusing STRIVE on the spinal fusion surgery group is because they have a higher incidence of infection. I was interested in your comment that a 4- to 5-, 6-hour total joint replacement would have a similar infection rate to the spinal surgery patient.

And so I was wondering, how well can you predict how long it will take to do a total joint replacement operation, like 5 hours plus or minus 1 hour. Or how would you describe your ability to predict that?

DR. PARVIZI: Yeah, the revision cases in the total joint replacement can be a long procedure, some of them going out to 4, 5, 6 hours. Primary joint replacements, much like a single-level instrumentation, the spine could be an hour operation with a fairly small incision. The rate of infection after a spine, as you correctly suggested, is higher than total joint replacement, and I guess that must have been the impetus for going after that patient population in the cohort. But the interesting thing is -- and again, I will repeat myself. The predisposing factors of developing infection after a spine surgery are almost identical to total joint arthroplasty.

DR. FOLLMANN: Actually, I was interested in a more specific question. Let's suppose you have a patient who's going to have total joint replacement. Could you say, oh, this

guy will take 3 hours and then a month later you get another person with a total joint replacement, and you'll be able to say, oh, this guy will take 6 hours, or are you totally unable to predict that?

DR. PARVIZI: You can. I mean, it will be a very slow and maybe not such a skillful surgeon to be taking 3 hours to a primary joint replacement. But revisions are unpredictable. Revisions can be up to 6, 7 hours. You can somewhat predict what it will take to do these revisions, but you're not always correct in terms of your timing. As the anesthesia will tell you, surgeons will underestimate the length of the operation. But there are some revisions -- and I see John nodding, but there are some revisions that will take up to 5, 6, even longer hours.

DR. EDWARDS: Dr. Stephens.

DR. STEPHENS: I was curious, in your graphs of prolonged courses or prolonged infection rates that occur 1 year or more after infection, can you comment on the etiology of those infections? You kind of mentioned that they may be polymicrobial in nature as opposed to *Staph aureus*, but maybe *Staph* is still present.

And also, there was a history of the attempt to use antimicrobial beads or other things in some of these procedures. Is that not an issue that is currently being pursued?

DR. PARVIZI: So I understood your first question, and I'll answer it, but I just want to make sure I understood your second question.

The first part, I will give you my theory as to why that happens. We don't know exactly why infection throughout the life of the prosthesis can occur, but I think part of it is because there can be an inciting event, like extraction of an infected tooth. It could be a source of infection elsewhere.

The second theory would be that some of these are actually acute and chronic, the patients have a level of -- a steady level of microbiome or organisms that had not manifested clinically either as a result of changing and viewing the stats of the patient and/or the state of dysbiosis. It then manifests itself as clinical infection.

And the third could be that these are actually infections that existed throughout the course of the joint but got investigated later. You know, to have pain after total knee replacement is not uncommon, and most of the time we actually ignore these patients if the components are well fixed and we have no reason to be investigating them. So late investigation could be the other source.

And I think your second part was about the use of beads?

DR. STEPHENS: Just to follow up on the first question, do you still think that a majority of those are *Staph aureus* in those late periods?

DR. PARVIZI: Looking at the organism profile, again, we can look at the CDC and European CDC's data. Most of them, and I'm not going to hold a number here, but most of them are *Staph aureus*. Yes.

DR. STEPHENS: And the second question related to antimicrobial beads or other materials that would be put into the joint itself. Is there any data that shows that that has any efficacy?

DR. PARVIZI: Anecdotal data, but no randomized prospective studies. And I think, again, CDC makes a comment about that issue, and they really are urging the orthopedic community to do a proper randomized prospective study.

DR. EDWARDS: Yes, Dr. Kirkpatrick.

DR. KIRKPATRICK: Just to supplement that concept of antibiotic beads, there are some people that are routinely using antibiotic cement to cement their prostheses in. That's kind of a different category because the beads are a treatment of the infection. The cement concept is to try and prevent the infection from occurring, and of course, that's very controversial because of the development of microbial resistance.

DR. EDWARDS: Yes, Dr. Englund.

DR. ENGLUND: So I have one question about the age of these patients, and the reason I'm interested is because we're talking about a vaccine, and as a flu person, sometimes we know

that older people don't respond to vaccines. I mean, really older people, like the elderly elderly over the age of 75 -- or 85 or 95.

(Laughter.)

DR. ENGLUND: Okay.

DR. EDWARDS: I think, Dr. Englund, you need to be careful.

DR. ENGLUND: Okay, okay. So I am not talking about the young elderly. But at any rate, could you give us an indication of the -- for example, the median age that we would expect for some of these spinal surgeries versus hips versus knees? And the reason I'm asking this is because of the comparability, eventually, of what populations one would like.

DR. PARVIZI: Sure. Average age of patients undergoing total knee replacement is around 63 and a half. The average of age of those undergoing total hip replacement, it used to be around 65. That number is changing rapidly. We're actually seeing both ends of the spectrum now being subjected to total joint replacement. And being a person with an interest in young patients with arthritic conditions, we see a lot of young patients undergoing total hip replacement, for sure, and to some extent, total knee replacement.

So the average age for patients undergoing total joint replacement is declining, definitely, in the USA, but I would say globally. I don't know what the average age of patients

undergoing spinal fusion with instrumentation is, but if I were to guess, I'd bet that's not very different than what we do in total joint replacement.

UNIDENTIFIED SPEAKER: But it's very similar.

DR. PARVIZI: A fair statement. Very similar. So if it shows efficacy, I assume, in the elderly or older population in the spine, I think it's fair to assume that it will show efficacy in the total joint replacement patients also.

DR. EDWARDS: Okay, thank you very much.

DR. PARVIZI: Thank you.

DR. EDWARDS: Dr. Stephens, do you want to turn your microphone off?

DR. B. GRUBER: So, hello again. I'm Bill Gruber, and I head the Vaccine Clinical Research and Development group for Pfizer. And again, I'd like to thank members of the Committee for the opportunity to share with you Pfizer's proposed plan and rationale to support a four-antigen *Staph aureus* vaccine indication in elective orthopedic surgery.

So let me first review for you the presentation agenda, which we'll go through the topics for consideration today that will help support that STRIVE should be representative of expectations for an elective orthopedic surgery population.

First, I'll review with you the significant health burden of postoperative *Staph aureus* infections following elective orthopedic surgery. I will then follow with a description of

Pfizer's proposal, and then this will be followed by a description of the pathophysiology of postoperative surgical site infection and the rationale for vaccine design. And I'll then end with a more detailed description of the STRIVE study design and the justification for application of safety and efficacy to all adult elective orthopedic surgery populations.

So let's begin. As you heard from Dr. Parvizi and Dr. Errico, there's a significant unmet medical need for prevention of *Staph aureus* infections in orthopedic surgery patients.

In summary, *Staph aureus* is the most frequently isolated organism in orthopedic surgical site infections. *Staph aureus* orthopedic surgical site infections are associated with increased length of stay and mortality, and the number of elective surgical procedures in the United States continues to grow: 9.7 million spinal procedures and 17.8 million arthroplasty procedures are anticipated to occur in the decade of 2021 to 2030 in the United States, when a vaccine might be licensed. Assuming the current epidemiology and current attempts to prevent infection, these procedures could lead to 182,000 *Staph aureus* infections, 89,000 invasive *Staph aureus* infections, and 3,200 deaths in the absence of a vaccine.

As you've heard from Drs. Parvizi and Errico, there is significant morbidity for those infected, and the potential for those infections to be due to MRSA compounds this morbidity.

Use of therapeutic antibiotics for suspect and proven infections increases risk for expansion of antimicrobial resistance. And so clearly, there's an unmet medical need for a strategy to better prevent *Staph aureus* infection that a vaccine could fulfill.

To understand the nature of Pfizer's proposal to address the medical need, it's first important to have some basic understanding of the ongoing STRIVE study, which I'll describe in greater detail during the course of today's presentation.

STRIVE stands for *STaphylococcus aureus* suRgical Inpatient Vaccine Efficacy. It is a global, placebo-controlled, randomized, double-blind study evaluating the safety, tolerability, and efficacy of the four-antigen *Staph aureus* vaccine in patients undergoing elective, open-posterior, multilevel, instrumented spinal fusion procedures in adults aged 18 to 85 years.

The study is designed to assess efficacy of the vaccine in the prevention of postoperative *Staph aureus* deep incisional or organ/space surgical site infection and/or bloodstream infection within 90 days.

STRIVE is currently a Phase IIb study with plans to convert it to a Phase III study with approximately 90% power to demonstrate vaccine efficacy with the lower bound of the confidence interval greater than 20% for the vaccine, assuming a true vaccine efficacy of greater than or equal to 70%. To do

this, it's anticipated that approximately 6,000 subjects will be enrolled with 3,000 in the vaccine group and 3,000 in the placebo group.

With this basic grounding, let me now share with you Pfizer's proposal for consideration by the Advisory Committee today. Just as Dr. Roberts shared with you at the beginning of today's presentation, we've asked the Committee to assume a future state in which the STRIVE study demonstrates that the four-antigen *Staph aureus* vaccine has acceptable safety and efficacy for preventing *Staph aureus* infection in adults, as defined by the primary endpoint.

Then we maintain that the STRIVE results should be representative of safety and efficacy in elective orthopedic surgical populations 18 years of age and older.

This would then lead to the following proposed indication and dose: Active immunization for the prevention of postoperative invasive disease caused by *Staphylococcus aureus* in adults 18 years of age and older undergoing elective orthopedic surgery. The vaccine would be given as a single 0.5 ml IM administration in the window of 10 to 60 days prior to the elective surgical procedure.

Now I'd like to share with you the pathophysiology of postoperative surgical site infection and the rationale for vaccine design that makes an elective orthopedic surgical indication possible.

To understand the nature of how a vaccine would work, it's important to understand that the pathophysiology of surgical site infection is consistent across elective orthopedic surgical populations and procedures. It's well recognized that the greatest risk of infection occurs at the time of the surgical incision and when the wound is open during the operative procedure. This is the basis for the use and success of prophylactic antibiotics at the time of surgery, with antibiotics being most effective in preventing *Staph aureus* infection when the antibiotic is enbored at the time of the incision. And the nature of this risk is true whether or not we're dealing with different sites of orthopedic surgery or procedures with or without implants.

If the *Staph aureus* organism has an opportunity to gain access, it immediately sets up housekeeping activities that allow it to adhere and then, if unchecked, goes on to produce late local bacteria, bacteremia, distant organ tissue and biofilm infection, as shown on the last panel of this slide.

Just like an antibiotic, the immune response to *Staph aureus* vaccine needs to intercept the *Staph aureus* organism at this very early critical stage when most infections occur. And, in fact, the Pfizer vaccine has been designed to produce an antibody response to antigens expressed early in infection to provide this level of protection that then prevents all the downstream consequences, I'm showing you on the slide, of

adherence and disease.

What key factors account for efficacy of the four-antigen *Staph aureus* vaccine against *Staph aureus* infection? The vaccine targets three virulence mechanisms, expressed early infection rather than a single virulence mechanism, which has been a limiting feature of past vaccines. And I will describe these in more detail in a moment.

The vaccine antigens have demonstrated efficacy in preclinical models, including invasive disease animal models. And the four-antigen vaccine induces functional antibodies to each of three virulence mechanisms which facilitate killing of *Staph aureus* by opsonophagocytosis and neutralize virulence pathways directly associated with targeted antigens.

The STRIVE population has been chosen as the most stringent population in which to demonstrate vaccine efficacy and safety.

The four-antigen *Staph aureus* vaccine has been designed to target three key virulence mechanisms expressed early in invasive *Staph aureus* infections. These are shown on this slide. The first antigen is Clumping factor A, which targets the mechanism that the organism primarily uses to adhere to host factors. The second is the manganese transporter protein, which is important for nutrient acquisition. And the third are the capsular polysaccharides CP5 and CP8, conjugated to CRM, which allow an invasion by their anti-phagocytic properties in

the absence of specific antibody.

Now, as described in great detail in the briefing document, Pfizer has demonstrated immune responses to each of these early antigens by functional assays. Antibody to Clumping factor A prevents adhesion. Antibody to the manganese transporter protein prevents acquisition of critical nutrients. And for the capsular polysaccharides, the vaccine induces opsonophagocytic antibody that demonstrates not only uptake of the organism, but also killing of the *Staph aureus* organism, which is critical in predicting efficacy.

All of this provided great confidence that the vaccine would likely provide protection. And, in fact, if one looks at the antibody responses, the four-antigen vaccine demonstrates -- and I want to stress this point -- functional immune response that is robust across the entire spectrum of adults 18 to 85 years of age, as described in detail in your briefing document.

In addition, the vaccine also demonstrates a satisfactory safety profile, also as highlighted in the briefing document.

Now, let me orient you to the details of the nature of what's shown on this slide. Each of the panels demonstrates antibody to a specific antigen contained in the vaccine, CP5, CP8, Clumping factor A, and the manganese transporter protein.

On the x-axis for each panel are shown the number of days subsequent to vaccination as a single dose at Time 0. The gray

solid line represents placebo response. The orange line represents the response in vaccinated subjects. And the y-axis provides geometric mean titers on a log scale.

The dotted line represents the lower limits of quantitation of the assay. I think you can quickly see that the placebo recipients have antibody levels that are either slightly above or below the lower limits of quantitation, indicating very little or no preexisting functional antibody that could provide protection against *Staph aureus* infection in individuals that are not vaccinated.

Contrast that with the orange line, which shows a very rapid antibody response after a single dose of vaccine that occurs within the first several days of vaccination that has been well maintained through the immediate highest risk period approximate to the time of surgery, as well as after 360 days. Notably, this antibody response is maintained through the first 90 days when the majority of elective orthopedic surgery infections occur and extends through 180 days, encompassing nearly 100% of the risk period for such infections.

To define this just a little bit more for you, the *Staph aureus* vaccine demonstrates a very rapid response between 8 and 11 days, such if there are log-fold increases, essentially, two log-fold increases shown here against CP5 compared to the time prior to immunization or to placebo recipients.

And remember, as shown here, this is the opsonophagocytic

assay, which is a killing assay, and provides confidence that functional antibody will be on board at the critical time of the incision and when the wound is opened, when infection is most likely to occur.

So encouraged by these results and a satisfactory safety profile in earlier studies, as described in your briefing document, Pfizer has moved forward with the STRIVE study to demonstrate efficacy and safety of the vaccine in an elective orthopedic population that we consider representative of all elective orthopedic populations.

I'm now going to describe for you the rationale for the selection of elective spinal surgery, the study design, and safety assessments. And then I'll follow that by speaking to you why the STRIVE study is then representative of other elective orthopedic surgeries. First, let's go over some considerations for selecting an elective orthopedic efficacy study population.

The population should have a competent immune system. Now, what do I mean by this? The population should include those individuals with common underlying conditions that exist in the elective orthopedic population at large, such as diabetes, obesity, and cardiopulmonary disease. Individuals with stable conditions of these types would be included in such a study because they are representative of conditions commonly seen in the population for which the vaccine would be

indicated.

The population will purposefully exclude those individuals with significant immunocompromising conditions such as cancer, HIV, and individuals on high doses of immunosuppressive therapy. It is anticipated that in such immunocompromised individuals, a single dose of vaccine may not prove sufficient to provide protection.

Another consideration is the ability to be vaccinated prior to a known period of risk, and in the circumstance of elective surgery, as I've shown you, it's possible to identify a period of time before an individual is scheduled for surgery during which they could receive a single dose of vaccine to provide protection.

And there needs to be a predictable incidence of invasive *Staph aureus* disease. And again, a great deal of work has been done to define the nature of the incidence of disease in elective surgical populations that allowed us to move forward with the STRIVE population.

And there needs to be an ability to observe the invasive *Staph aureus* disease clinical endpoint within the defined period of risk, and it's well recognized that in the elective orthopedic surgery population, most infections occur within the 90 days after the time of surgery.

Elective orthopedic surgical populations satisfy these criteria, and in particular, the STRIVE population, those

individuals undergoing that particular subset of elective spinal surgery satisfies all these criteria and permits an expedient determination of efficacy and safety in a representative orthopedic population.

Now, there were challenges to trying to identify what population would work best that led us to conclude that the STRIVE population is the most efficient way to get an answer that is representative of safety and efficacy in the elective orthopedic surgery population at large. I want to share with you some of the challenges that we encountered in thinking about this in reference to alternative populations.

It's well recognized that hip arthroplasty and knee arthroplasty are common elective procedures associated with infection risk, and you heard about this in great detail from Dr. Parvizi. But you can see that the attack rates are at 4% for hip arthroplasty to 0.25% for knee arthroplasty. Now, given the large numbers of such studies that are performed, this accounts for a large disease burden, as described by Dr. Parvizi.

However, for conducting a trial to determine efficacy, these attack rates would translate into a requirement to enroll between 25,000 and 40,000 subjects and would take over 10 to 15 years to effectively conduct such a study to recruit and obtain the necessary number of cases to reach an endpoint. And this estimate already figures in an ability to recruit subjects

perhaps as much as two times faster than in STRIVE.

So if you contrast this, then, with the STRIVE population, a subset of spinal-instrumented multilevel spinal surgery, which was specifically selected for its higher attack rate of approximately 1.4% as determined by published information and available databases, this study would require approximately 6,000 subjects and could be conducted in approximately 6 years, assuming true vaccine efficacy of greater than 70% with 90% power to demonstrate a 95% lower bound of the confidence of greater than or equal to 20%.

Now, it's worthwhile to understand a little bit about the complexity of this study and why, even with the higher attack rate, it takes us 6 years to get to an answer.

After 28 months of enrollment, we've enrolled 1,900 subjects randomized from approximately 100 sites in the United States, Canada, Japan, and six countries in Europe. To reach 6,000 subjects, it's anticipated we will require additional sites in additional countries to be successful.

Even to this -- get to this point, as a required contact with over 1,700 investigators to identify the current 100 study sites, key challenges related to identifying sites include adequate volume of elective multilevel, instrumented spinal surgery, experience in clinical trials, and appropriate clinical research infrastructure, much of what was described by Dr. Errico.

In the face of these challenges, Pfizer is committed to moving forward to a study of 6,000 subjects in STRIVE to secure an indication for all elective orthopedic surgery within 6 years.

And there's a reason why time is important. There's a large potential U.S. public health impact of a 70% efficacious *Staph aureus* vaccine that could be realized in the decade between 2021 and 2030 at the time such a vaccine could be licensed.

Shown on this slide are the number of surgical procedures in that decade. If we just take spinal surgery and arthroplasty alone, you can see that there are a total of 27,500,000 procedures anticipated to be performed over the decade of 2021 to 2030. A 70% efficacious vaccine would stand to prevent over 70,000 infections in arthroplasty alone and close to 100,000 hospitalizations and over 2,000 deaths if broadly applied to an elective orthopedic surgical population, including arthroplasty and spinal surgery.

Moreover, such a vaccine could have a dramatic impact in reducing the morbidity of *Staph aureus* infection and could reduce rates of antimicrobial resistance due to reduced use of therapeutic antibiotics.

An efficacious vaccine will also reduce the significant morbidity of *Staph aureus* infection described to you by Dr. Errico and Dr. Parvizi. So there's clearly an important

need to move forward in an efficient fashion to demonstrate efficacy and safety of vaccine for elective orthopedic surgery, and STRIVE accomplishes that goal.

So let's, then, talk about the nature of the STRIVE study to understand how it helps to accomplish that goal and then how it can be considered as representative of results expected in other elective orthopedic surgery populations.

The STRIVE study is a double-blind, placebo-controlled trial in which subjects are randomized to receive either the *Staph aureus* vaccine or placebo in a 1:1 fashion. The vaccine is administered as a single IM administration in this important window, 10 to 60 days prior to surgery, when antibody levels are at their highest at the time of surgery.

This was begun as a Phase IIb study, but it is our intent to convert this to Phase III, and we are under discussions with the FDA about how to do just that.

Again, the study is being conducted in an elective, open, posterior spinal fusion population that includes multilevel instrumentation to give us that high attack rate of 1.4%, which is at the high end of the spectrum of *Staph aureus* infection.

It's anticipated that we'll enroll a total of 6,000 subjects 18 to 85 years of age, and we are currently enrolling, as mentioned, at sites in the United States, Canada, Europe, and Japan.

The primary outcome of the STRIVE study is the number of

subjects in each treatment group with postoperative *Staph aureus* deep incisional organ/space surgical site infection and/or bloodstream infection occurring within 90 days of elective, posterior, instrumented spinal fusion, which again reflects that key risk period where most of the disease occurs and represents an important measure of the likely efficacy of the vaccine.

But we recognize that there's a broader spectrum of disease associated with *Staph aureus* infection in elective orthopedic surgery, and so STRIVE is also designed to evaluate other *Staph aureus* infection influence.

Postoperative infections occurring after surgery caused by *Staph aureus* will be prospectively evaluated and independently adjudicated through 180 days post-surgery.

Protocol-defined infection clinical criteria utilized the NHSN, or National Healthcare Safety Network, surveillance criteria to define all endpoints. And these include deep incisional organ/space surgical site infections and bloodstream infections; they also include all other invasive *Staph aureus* infections as well as superficial surgical site infections.

So you can see that the Pfizer STRIVE study is designed to provide a comprehensive assessment of efficacy of the vaccine against *Staph aureus* infections in elective orthopedic surgery.

STRIVE also includes rigorous assessments to support the safety of the vaccine. Comprehensive safety assessments are

done from the day of vaccination through 6 months after the indexed surgery. These assessments include assessment of local reactions and systemic events for 10 days via electronic diaries, as well as adverse events from the time of informed consent to the Day 42 postoperative evaluation.

Importantly, all serious adverse events from informed consent to Day 180 postoperatively are obtained. And the safety data has been monitored and will continue to be monitored by an external DMC, which has currently recommended that the trial continue as recently as this month.

Now, having a fundamental understanding of the STRIVE study itself, it's important to consider how these results can be applied to other elective orthopedic surgeries, and I will cover three main topics to make this point. And these are also described in detail in your briefing document.

First, that the pathogenesis of *Staph aureus* infection is similar across elective orthopedic surgeries; second, that patient demographics and risk factors for developing *Staph aureus* surgical site infection are similar to STRIVE; and third, that there are commonalities and procedural risk factors of orthopedic surgical site infections, all of which support the idea that STRIVE results can be representative of efficacy and safety expected across the elective orthopedic surgery spectrum.

So, first, let's talk about the pathogenesis. There's a

common pathogenesis across elective orthopedic surgery types. As I've already described, *Staph aureus* is the most common cause of surgical site infection across elective orthopedic surgery.

Patient colonization is the primary source of *Staph aureus* inoculation for surgical site infections across orthopedic surgery types. Infecting *Staph aureus* strains are not specific to surgery type.

And the primary risk period for establishing surgical site infection is during the procedure. This is the basis for the success of perioperative antimicrobial prophylaxis, which is well recognized to have its greatest utility when an antimicrobial prophylaxis is used at the time of the incision.

And finally, most surgical site infections occur within 90 days after surgery, and this is a feature shared in common across elective orthopedic surgeries.

And the nature of the antibody response is again illustrated on this graph for the CP5 opsonophagocytic antibody assay, shows that antibody will be present in large amounts at the time of greatest risk and will be sustained through the period of risk to provide protection.

So with a common pathogenesis, the antibody response is likely to provide protection across elective orthopedic surgeries and be similar to that demonstrated in STRIVE.

In addition, the patient demographics and risk factors for

developing *Staph aureus* surgical site infection are similar to STRIVE. Shown on this slide are demographics and risk factors for some common orthopedic procedures such as primary total knee arthroplasty, hip arthroplasty, and spinal surgery, with or without implants, compared to the STRIVE population.

And I think you can see that whether we're talking about age, gender, or race, there are commonalities in relationship to these specific demographic factors across the elective orthopedic surgery populations and the STRIVE population.

Likewise, when we look at risk conditions, including diabetes, smoking, chronic obstructive pulmonary disease, congestive heart failure, or peripheral vascular disease, there's a great deal of overlap in the risk factors associated with orthopedic populations, such as arthroplasty or the overall spinal surgery and the STRIVE population.

And, finally, if we look at body mass index and the American Society of Anesthesiologists scoring of individuals, you can see that these populations share features in common with STRIVE. So the demographic features in STRIVE should be representative of those seen in other elective orthopedic surgery populations.

There are also commonalities in the procedural risk factors of elective orthopedic surgical site infections. Looking here at knee arthroplasty, hip arthroplasty, and spinal surgery compared to STRIVE, you can see that in every case the

dermis is first breached, and there's dissection between the muscles, tendons, and nerves to reach joints and bones.

These surgeries can involve implanted materials, including metal alloys, plastic, ceramic, bone cement, and bone grafting material. Implanted materials are associated with a higher risk in infection and absence of implanted material with a lower risk. Importantly, the incision length can vary from 2 to 12 inches with spinal surgery representing the top end of the spectrum. And it's well recognized, again, that the length of the incision and the size of the operative field is directly related to the risk of infection.

So the risk is likely greatest, as reflected by the attack rates in the spinal surgery population within the spectrum of infection in orthopedic surgery. So it's reasonable to presume that if the vaccine can work in this most stringent circumstance, it's likely to work when the incision is shorter.

The same thing applies to mean operative time. Spinal surgery tends to take a longer period of time on the table than the other types of surgery within the spectrum of all orthopedic surgery, again representing the most stringent test of efficacy. So the expectation would be that if the vaccine can protect those individuals that have spinal surgery with a long operative time, it should protect individuals undergoing other types of orthopedic surgery with shorter operative times.

The commonalities and procedural risk factors of

orthopedic surgical site infection predicts that efficacy and safety seen in STRIVE should be representative of that seen in other elective orthopedic populations.

So let me summarize our thinking for you. The STRIVE population is representative of elective orthopedic surgery patients because the pathogenesis of the *Staph aureus* infection is similar across elective orthopedic surgery types, the patient demographics and risk factors for developing *Staph aureus* surgical site infection are similar to STRIVE, and there are commonalities and procedural risk factors of orthopedic surgical site infections.

Therefore, the balance of scientific evidence supports that it is reasonable to assume that efficacy and safety demonstrated in STRIVE should be representative of the efficacy and safety that would be expected in all elective orthopedic surgery patients.

Now, let me finish my presentation by describing how the STRIVE study fits into the overall clinical development program. Shown here in blue are the studies that have been completed in the nonsurgical population to demonstrate safety and immunogenicity of the vaccine, that then encouraged us to move forward into the STRIVE population to demonstrate efficacy in a targeted orthopedic surgery population. Note the numbers of nonsurgical subjects receiving the vaccine in these early phase trials represent a subset of all individuals who have

been exposed to antigens contained in the vaccine.

Shown in green are the anticipated 3,000 subjects who have undergone surgery and have received the vaccine as part of a Phase III STRIVE trial.

In addition, we plan to conduct another Phase III clinical lot consistency study to demonstrate manufacturing consistency of the vaccine, which is a requirement for licensure. This will enroll over 2,000 nonsurgical subjects to receive the vaccine, resulting in a safety database of over 5,000 subjects, of whom 3,000 will have received the vaccine in the STRIVE study. We maintain that this information, combined with the safety and efficacy demonstrated in the STRIVE population, will be sufficient for licensure.

So let me return to the Pfizer proposal once again. There remains a significant need for a vaccine to prevent *Staph aureus* infections in patients undergoing elective orthopedic surgery. In this context, we again ask the Advisory Committee to assume that the STRIVE study has demonstrated that the four-antigen *Staph aureus* vaccine has acceptable safety and efficacy in adults.

Then, based on all the information that I've shared with you today, as well as the information included in your briefing document, we maintain that the STRIVE results should be representative of safety and efficacy in elective orthopedic surgical populations 18 years of age and older and should

support the following indication: Active immunization for the prevention of postoperative invasive disease caused by *Staphylococcus aureus* in adults 18 years of age and older undergoing elective orthopedic surgery.

We look forward to the Committee's consideration and response to this proposal, and I thank you very much. That concludes my presentation, and I, along with my Pfizer colleagues and invited consultants, would be happy to entertain any questions from the Panel.

DR. EDWARDS: Thank you, Dr. Gruber.

I think we should go ahead with the questions, and we can cut our lunch short if we need to, but I think we need to go ahead with the questions.

Dr. Lynfield, please.

DR. LYNFIELD: Thank you.

I have a couple of questions for you about the trial, and I'm wondering, are you -- are the patients that are entering the trial having swabs done for colonization, and are you recording the decolonization regimens that they're on? I have a number of questions. I'll start with that.

DR. B. GRUBER: So yes and yes, that's the quick answer. So yes, we are capturing colonization before, during the trial, and after the individuals are immunized and after their surgery. We're also capturing not only decolonization efforts in terms of use of mupirocin and chlorhexidine, but

antimicrobial prophylaxis, the use of intra-wound vancomycin. So a whole of the full spectrum, again, randomized by site so that we would have a pretty good perspective in terms of recognizing, as you've heard, that the infection control practices differ from site to site.

DR. LYNFIELD: And then we heard earlier, from the Klevens study, that increased age and black race are associated with an increased risk for invasive MRSA infection. I am wondering, I saw the data, that it captures the data of people who are undergoing these procedures, but will you have enough data in those subgroups?

DR. B. GRUBER: Yeah. So, again, of course, the study won't be powered to demonstrate efficacy within the individual subgroups, particularly within minority groups that represent a smaller percentage. But we also are obtaining immune responses in all the individuals in the study, so we will, in fact, have antibody responses across the full spectrum, and obviously, it enriches our ability to discriminate any potential differences that could be associated with a lack or -- of efficacy or with efficacy.

DR. LYNFIELD: And Dr. Otto had told us that there are different strains globally, as well as USA300 doesn't produce capsule. I'm wondering if there are plans to characterize the *Staph aureus* isolates from infections that might occur.

DR. B. GRUBER: So I anticipated that you would ask that

question in particular, since we know you published in that area. So yes, so let me --

(Laughter.)

DR. B. GRUBER: Let me first of all say that yes, by our estimates, and I know estimates vary, we anticipate about 10% of isolates by USA300. Whatever that percentage is, they will be captured as part of the study. I think it is worthwhile, again, in that context, to remember that what we're asking the Committee to do is to assume that we have efficacy, and whatever efficacy we see incorporates whatever data that we have with USA300, and we would have to be satisfied, we and the FDA would have to be satisfied that that's been demonstrated such that it could be translated to suggest that we would see efficacy in other elective orthopedic surgery populations.

DR. LYNFIELD: Thank you.

DR. EDWARDS: Dr. Gruber, I worry a little bit about having so many different sites with so many different orthopedic surgeons with probably so many different preferences in terms of what they do. And so how rigid are your criteria for enrollment in the study? I mean, is that one of the reasons why it's difficult to enroll people, because it is so strict and will this -- will you be able to sort all these factors out?

DR. B. GRUBER: Yeah. So I think, first of all, let me come back to the slide, maybe we can bring up the slide that

speaks to the demographic factors because I think it comes, really, to what you heard from Dr. Errico, I think, is the more compelling reasons around why it's been difficult to bring individuals into the study.

It doesn't really relate to underlying conditions. It relates to their willingness to say, gee, in addition to having to contemplate having major surgery, and you saw some of that major surgery where it involves the whole spine, I have to sort of think about now do I want to have my nose swabbed, do I want to have, you know, blood taken, and do I want to have this long-term follow-up in a context of a vaccine, which we obviously, at this point, don't know whether it's going to be effective or not.

I think if we can show Slide 3. Again, this just represents that I think we're pretty confident, if you look at the STRIVE population, that we're getting a representation of underlying conditions, and so we will have -- I mean, clear within the total number of cases, we may not have the ability to discriminate, based on underlying conditions, the nature of efficacy for those cases, but we may have sufficient numbers, particularly for some of the more common conditions like obesity and diabetes to help discriminate the potential for any differences, and we wouldn't expect any based on our understanding of immune response.

But we will also, obviously, have immune response as part

of the trial to look at. So going in that context, we can look at potential measures that would predict the likelihood of efficacy and whether we see differences, and we've done studies within populations and include risk conditions, and we don't see major differences in terms of the antibody responses that we're seeing.

So I think, all told, recognizing that there will be differences in terms of approaches to how individuals are handled in individual sites, I think, across the course of the study, we will have enough information about demographic features to be able to look and see how that influenced potential efficacy, and we will obviously look for site-specific effects.

DR. EDWARDS: But I guess the question about how rigid your criteria are, does everyone have the same prophylaxis, does everyone, you know, have the restriction of these beads or the cement or --

DR. B. GRUBER: Yeah.

DR. EDWARDS: -- all of these other factors? Will those be so diverse in terms --

DR. B. GRUBER: Yeah.

DR. EDWARDS: -- of the numbers that you'll be able to make --

DR. B. GRUBER: Yeah.

DR. EDWARDS: -- some sense out of it?

DR. B. GRUBER: I think, you know, obviously, we won't know for certain until we get to the end, but the way we planned this study is recognizing that, you know, the purpose of this vaccine is to add to the current standard of care. And obviously, when we're talking about potentially going to, you know, try to identify 100 sites, going to 1,700 investigators, it's very difficult to say we want you to change your standard of care for the individuals involved in that trial; I don't think that's appropriate.

So we are capturing all of that information. Again, there is randomization by site, so we would expect to have equal numbers of subjects, you know, undergoing particular types of procedures by site and across the study, and in the end, we'll just analyze that. And I would say that, for the purposes of the discussion today, all of that analysis would figure in to confidence in terms of the safety and the efficacy of the vaccine, and in that setting, is it appropriate to extrapolate.

DR. EDWARDS: Dr. Long and then Dr. Kotloff.

DR. LONG: First, a pseudo-question about safety. Is there anything about this vaccine, I would imagine it might be the manganese transporter, that has any similarity to the iron surface determinant that would make us think that the V710 findings might be reproduced?

DR. B. GRUBER: Yeah. So I think, obviously, we paid great attention to the Merck experience. The four-antigen

Staph aureus vaccine shares no antigens in common with the iron-binding surface determinant of the Merck vaccine. And the other thing, too, is that it's worthwhile to remember that you've heard a lot of discussion here about the nature of opsonophagocytosis, and I think it's important to be able to discriminate what we mean when people are talking about that. There are two particular key aspects; one is the uptake of the organism, and the other is whether the organism is actually killed. There is no evidence to suggest that the IsdB protein in the Merck vaccine actually led to killing. It did appear to lead to potential uptake, and some have postulated that in the setting of uptake without killing, that may have been, in at least one hypothesis, that may have been part of what led to multi-organ failure that was seen in that circumstance.

In our circumstance, the capsular polysaccharides basically produce functional antibody that not only leads to uptake by phagocytic cells but actual killing. So that provides some confidence. And then we have functional assays that demonstrate functional activity that blocks the manganese transporter protein as well as that blocks adherence from Clumping factor A.

So there's some, I think, discrimination between failures in the past, and I think that's why it's important not to, you know, prejudge the nature of descriptions of antibody responses in the past to what we're talking about because we have

incredibly robust responses with functional activity.

DR. EDWARDS: Dr. Kotloff. Oh.

DR. LONG: I have a follow -- another --

DR. EDWARDS: Go ahead, Dr. Long.

DR. LONG: Is yours in follow-up or is yours --

DR. KOTLOFF: No, go ahead.

DR. LONG: The second one was transportability of the results to other orthopedic surgical procedures. I assume instrumented surgery means there are plates and screws rather than you didn't use retractors and knives and things; is that right?

DR. B. GRUBER: Yeah, so --

DR. LONG: Instrumented surgery, exactly.

DR. B. GRUBER: Yeah, I mean, these are individuals, and there are precise definitions, and we can actually, you know, speak to the nature of what's included and what's not. But yes, you know, as you heard from here, it's basically metals, it's screws, it's much of what you saw in the pictures that were, you know, shown by Dr. Errico. So these are things that are, you know, basically implanted and left in.

DR. LONG: Now, on children, we frequently use bone chips and grafts.

DR. B. GRUBER: Yeah, bone grafts --

DR. LONG: So this --

DR. B. GRUBER: Yeah, bone --

DR. LONG: Are there bone grafts and --

DR. B. GRUBER: Yes.

DR. LONG: -- things also --

DR. B. GRUBER: Yes.

DR. LONG: -- in that spinal?

DR. B. GRUBER: Yes, there can be. Yes.

DR. LONG: Okay. And then the other transportability question is the hip and this knee, they're clearly predominantly joint surgeries, and I imagine the antibody in the joint fluid has something to do with something, and I know that's not close to serum antibody concentration. So what --

DR. B. GRUBER: Well, actually --

DR. LONG: -- can you share about that?

DR. B. GRUBER: Yeah, yeah. So let me share with you, sort of, several lines of evidence that suggest, whether you're dealing with diarthrodial joint or whether you're dealing with the spine, that the nature of what we see in terms of efficacy for the STRIVE population should be predictive.

The first is, is that remember that, you know, we're talking about the nature of the *Staph aureus* actually gaining access all the way down to the joint, so it's really got to go through the gauntlet of all the well-vascularized tissues that have serum with antibody presumably from the vaccine at that point interdicting.

The second thing is that we've actually done studies

looking at antibody in the joint of individuals undergoing a surgical procedure and compared that to serum levels, and what's interesting is there appears to be a linear relationship, so the higher the amount of antibody that's there, the higher the amount that's in the joint. And it amounts to, actually, a nontrivial amount. It's at least 30% or so of the total amount of antibody. And when we're talking about log increases, there are two log increases that still indicate that you have a large amount of antibody.

Now, if you add to that the nature of the fact that these are not normal joints to begin with, that's why the surgery is being done, so there's often an inflammatory response already there, so you've already got, sort of, the makeup of the necessary sort of phagocytic cells that could essentially help antibody work successfully.

And I'll just add one other thing, and maybe I could ask Dr. Parvizi to speak to this, is that, you know, this is not a bloodless surgery, right? You know, blood and serum is getting into the joint at the time of surgery and presumably with antibody on board. I mean, we can just -- I guess, Dr. Parvizi, you can either say yes or no to that, and I think that's true.

DR. PARVIZI: Yes.

DR. B. GRUBER: He says yes.

DR. EDWARDS: Perhaps not his surgery, but I don't need

the surgery.

(Laughter.)

DR. LONG: Sure, thanks.

DR. KOTLOFF: So you proposed that the different surgeries have a similar pathogenic mechanism, and that's basically direct inoculation. I'd like to hypothesize that there may be two mechanisms of infection. One is direct inoculation, but there also may be a proportion of patients who have bacteremic inoculation. That's the pathogenesis of pediatric osteomyelitis, some -- you can have direct inoculation and you can have bacteremic spread in inoculation, often in an injured area of the bone.

And I think that there may be two risk periods for bacteremic spread. One may be in surgeries that are more traumatic to patients and so they end up in an ICU, maybe afterwards, or a recovery room with lots of tubes and catheters.

And then perhaps the other risk period is a little bit later on because I think when you have *Staph* in your body, it's such a virulent organism that it tends not to be indolent, lying, you know, hidden in a surgical site, but that maybe at a later time you'll have one of these bacteremias and you end up with a surgical site infection.

DR. B. GRUBER: Right.

DR. KOTLOFF: And I'm wondering, with the question of

equivalence, are the different surgeries equal in terms of the pathogenesis, if these two mechanisms exist, and is the vaccine expected to be equally efficacious for these two mechanisms of spread?

DR. B. GRUBER: Yeah. So actually, let me take that question in two parts, if I can. First of all, as I sort of already described, the epidemiology supports that the infections are heavily weighted on the front end associated with the incision, and again, 75% occurring within the first 90 days.

And if you actually look at that, the bulk of those infections actually occur within the first 30 days. So one can presume that, again, that really relates to that incident event. It is true that one can have catheters, other things, you know, vascular access put in at the time of surgery, but typically, that's in transient. And again, those things are being put in much of the same time we're talking about the nature of the incision being made when antibody would be on board, presumably helping guard against not only the infection of the joint, let's say, but also an intravascular access device.

And I think, you know, happily -- and I'll let, perhaps, Dr. Richardson speak to the nature of spinal surgery and how often implanted devices, you know, in terms of vascular access, other types of access, is used and then maybe ask Dr. Parvizi

to comment on that as well.

DR. RICHARDSON: Bill Richardson, orthopedic surgeon at Duke University.

So it really varies, but you know, as indicated, for spine surgery generally, if you're going to have a central line or other vascular access or a catheter, it's placed at the time of surgery, so before the skin incision. So similar to pre-op antibiotics, all those would be placed before the skin incision. And if the patient goes to the unit, it's usually with a catheter that was placed at the time of surgery as opposed to later.

DR. B. GRUBER: And just to make a comment about the timing once the intravascular access is put in, how long it typically remains and that sort of thing.

DR. RICHARDSON: Yeah, so I mean, routine for us is to get the catheter, pull the catheter out within 48 hours, and that's pretty standard for most surgeries. And then central access is gotten out as soon as we can and try to stick with peripheral access, if possible.

DR. KOTLOFF: Is there any association between duration of vascular access and surgical wound infections?

DR. RICHARDSON: I'm not aware of any, I mean, so you know, generally bigger cases take longer, so we've talked about the fact that longer cases, more blood loss, longer incisions tend to have a higher incidence. Those tend to be the cases

that would have central access also.

DR. PARVIZI: I agree with your hypothesis or theory. There is the bacteremic infections that occur late, and there are those that occur at the time of surgery, as you know, the so-called acute hematogenous infections that we see later on. But a majority of the infections that occur first in the 90 days are as a result of direct inoculation during surgery, but it doesn't mean that later bacteremic events can't occur.

DR. B. GRUBER: Dr. Errico, you're raising your hand; you wanted to just make a brief comment?

DR. ERRICO: I think I just wanted to make a comment that might be more direct to what you were asking. So in terms of, first of all, late hematogenous spread is very rare in spine surgery. I wrote a paper on this back in the 1980s; we were only able to find four cases spread over four medical centers.

But I want you to think of what spine surgery is like compared to the total joint, which we're trying to make that extrapolation. We're like a car that's going to be driven at 80 to 100 miles an hour. Our hospitalizations are longer, those catheters are going to be in longer. Late re-instrumentation of -- I should say re-catheterization will occur more often in a spine patient than in a total hip patient on the order of about two to one. So I think if it works in spine surgery, the car will go at 40 miles an hour easily.

DR. B. GRUBER: Let me just say actually, just to round

out the discussion on this point, we are capturing, as you saw, as part of the criteria of bloodstream infections, but that includes circumstances where the source of the infection could be an intravascular catheter. So that has the capability, of course, to be analyzed in the context of the overall efficacy. And I come back to the idea that all of this would be analyzed with respect to the overall efficacy of the vaccine as well as, obviously, the safety information that would then inform the STRIVE population being representative for all elective orthopedic surgery.

DR. KOTLOFF: Do you think the efficacy of the vaccine will be equivalent with those two mechanisms of infection?

DR. B. GRUBER: Yeah, I think so. I think the nature, given what you're hearing about the timing of when the intravascular access is placed and the desire of, like, I think, both the individuals working with diarthrodial joints, as well as the spine, to get that access out. I think, you know -- and again, it's comparable, right? So the nature of the risk is comparable. I think that that already helps reduce the likelihood. As you've heard, it seems to be a very uncommon event, anyway, but further reduces that as a potential risk and, you know, I think the vaccine could help.

DR. EDWARDS: I think we have a question from Dr. Levy, which I'll address, and then several other people. I think our questions need to be succinct and the answers as well.

So Dr. Levy said, is the vaccine formulated with an adjuvant? Does the MntC lipoprotein have adjuvant activity, perhaps as a TLR2 agonist? And do the immunogenicity data for the vaccine -- or what are the immunogenicity data for the vaccine with regard to T-cell responses? So I guess that's not very succinct, but I --

DR. B. GRUBER: Yeah, yeah. All right. So let me -- you know, I'll try to capture some of that. The first one is that the vaccine is not adjuvanted. You know, the notion here is that all of us have a lifetime of exposure to *Staph aureus*, which constitutes a great paradox, right, because I showed you the fact that we, despite that lifetime exposure, don't have functional antibody on board to any of these antigens, you know, if we look at that placebo population represented from 18 to 85 years of age. But nonetheless, when we stimulate with the antigens and the vaccine as a single dose, we see that. I'll actually ask Dr. Liesa Anderson, who is our chief science officer for bacterial vaccines, to speak to whether there are adjuvant properties associated with the transporter protein.

DR. EDWARDS: And then also the T-cell quickly.

DR. B. GRUBER: Yeah.

DR. ANDERSON: Very quickly, thank you. Annaliesa Anderson, Pfizer Vaccines research.

So regarding whether or not an MntC is lipidated, it's naturally a lipoprotein, and I'm sure Dr. Levy may have seen

some of our work on other lipidated vaccines that do have agonist activity. However, MntC is expressed without a lipidated tail, so it's not expected to have that activity.

And then the other question regarding have we seen T-cell responses, we did a study with Dr. Buddy Creech at Vanderbilt University to look at whether or not subjects vaccinated with assay 480 vaccine elicited T-cell responses, and we found that they did not.

DR. EDWARDS: Okay, Dr. Kirkpatrick.

DR. KIRKPATRICK: How do you get from spine and joint to all of orthopedic surgery? That's as concise as I can make that question.

DR. B. GRUBER: Well, actually, I may ask you to be a little bit less concise, so what -- tell me the root of your --

DR. KIRKPATRICK: Your premise is --

DR. B. GRUBER: Yeah.

DR. KIRKPATRICK: -- that you want to go from spine and joint to all elective orthopedic surgery.

DR. B. GRUBER: Right.

DR. KIRKPATRICK: I'm asking how can you make that jump?

DR. B. GRUBER: So I think that it basically rests on the arguments that we've already laid out for you today, that the nature of the pathogenesis is the same, the nature of the demographics are the same, so the efficacy that we would expect to see in the STRIVE population would be expected in the other

populations because the nature of the demographics being the same, the immune response that conferred that efficacy is likely to be the same, and the nature of the procedures in terms of the things that constitute risk with the STRIVE population being at the highest end of the spectrum would predict that if we're successful in that population, we should be successful in the others.

DR. KIRKPATRICK: I would ask my Chair, should I reserve my comment to that to the discussion later?

DR. EDWARDS: I think probably yes, that you should, thank you.

So questions of content. Dr. Stephens and then --

DR. STEPHENS: So my question is a follow-up to your T-cell response. Is there any memory induced by this vaccine?

DR. B. GRUBER: Yes. I think you can sort of get some information based on that based on the nature of the length of the immune response that we've seen. We have been able to give a booster dose over a relatively short interval. It turns out that that interval was probably too short to specifically constitute demonstrating a boost response. There is the potential, obviously, as we look longer to demonstrate establishing memory.

But we know, for instance, that conjugated polysaccharides, based on other experience, are very good at stimulating memory, and we would expect the same, certainly,

for those compounds.

DR. STEPHENS: So you would expect to see an anamnestic response with a re-vaccination or --

DR. B. GRUBER: Yeah. Right, because we're actually seeing what we think is an anamnestic response even with the primary immunization.

DR. STEPHENS: And a natural infection?

DR. B. GRUBER: I think the key question is the interval.

DR. STEPHENS: And a natural infection?

DR. B. GRUBER: I'm sorry, say that again? Oh, with a natural infection. Yeah, I think that's a reasonable presumption as well, but the goal here is really not to get to that point; the goal is really to intercept it with existing antibody right at the time of surgery to prevent any downstream consequences.

I want to just come back to the -- again, because there have been some questions about cell -- you know, cell-mediated immune response, Th17 response and the like. Again, just to re-center around the idea that, as Dr. Anderson pointed out to you, we don't stimulate Th17 responses or IL-1 responses or Th1 type of responses.

But it's important to understand that in the end, we will have efficacy or not in the STRIVE population. If we have efficacy regardless of what the immune response was, that accounted for that efficacy and the expectation is, given the

nature of the other populations because of the demographic characteristics and the pathogenesis, that should be predictive in those populations. So I didn't want to leave that hanging.

DR. EDWARDS: Dr. Blackstone and then Mr. Toubman and then Dr. Greenburg.

DR. BLACKSTONE: Yes. Let me turn to operational challenges that you presented on Slide 17 and then extrapolated to 16. You say that you're enrolling less than one patient per month per site, and I'm wondering if the rate-limiting step is the rarity of the instrumented spinal operation, or is it recruiting of patients?

DR. B. GRUBER: It's really the recruitment of the patients. As you sort of heard from Dr. Errico, he's been only able, within the group of patients that would otherwise be eligible, only been able to recruit about 1 in 10 of those individuals. That may vary from site to site, but it's not due to the rarity of the denominator of the substrate; it wouldn't go to -- it's the ability to get these individuals into a study and, you know, again, the reasons that Dr. Errico mentioned.

DR. BLACKSTONE: Okay, so 1 in 10 is actually not terrible for a surgical recruitment. That's about what we get or, you know, unless people are really interested in it. But if you even went to 1 in 10 and then had done instead joints, which are far more prevalent and gotten the same, you might have recruited a whole lot faster. That's why I don't understand

your extrapolation on Slide 16, where you said it would take more than 10, and I think your material pointed to this.

DR. B. GRUBER: Yeah. So let's just take a look at that, if we can, just take a look and I'll be brief. Again, there are two things that figure into this slide in terms of the length of time, is one is just the nature, we're talking about populations, you know, that are four to six times greater that we need to recruit. So automatically that begins to work against us, right?

And then, recognizing what you suggested, it is conceivable we might be able to recruit faster. By our best estimates, based on the experience that we have with the study we have in hand, even at twice the rate that we're currently recruiting, it would take us, you know, more than 10 to 15 years. And again, you've heard -- this is actually a pretty extraordinary undertaking to actually go into a population that's anticipating surgery and be successful in recruitment.

DR. EDWARDS: Okay. Mr. Toubman, please.

MR. TOUBMAN: Yes, thank you.

I have a question about that slide as well, in conjunction with Table 6 of the briefing document, but before that, I have a big picture question, which is, really, why are we here now? What I mean by that is, why wouldn't you just wait until you see if the thing is safe and effective in this group you're testing? And if that's the case, I think that's the normal way

with the FDA, you bring it forward, and you ask for a broad labeling based on the arguments you're making.

Why is it that it makes it -- what difference does it make to Pfizer if you get this go-ahead now or you get it later, and if you were to get a statement now that it's not a good idea to broaden it, will you behave any differently?

And then related to that, I know it's kind of a tough question, but I'm saying --

DR. B. GRUBER: No.

MR. TOUBMAN: -- how is Pfizer's financial interest benefited by getting the answer to that question now? So I'd like you to answer those questions; then I'll ask my quick question --

DR. B. GRUBER: Right. So, first of all, let me say, I mean, it's an obvious question, I mean, why -- you know, a typical sort of setting for a VRBPAC meeting is at the time to review data on safety and efficacy. But for us to be able to move forward successfully, we really need to understand what's going to be required and what indication might exist at the end.

I think, to couple that with your latter question, based on what we presented today and discussed, in the context of a successful STRIVE study in terms of efficacy and safety, Pfizer's position is that application of the four-antigen vaccine indication in elective orthopedic surgery is

scientifically sound, and additionally, this broader indication would benefit public health to a tremendous degree.

If, in the end, the Committee advises against expansion beyond the current population under study in STRIVE, our next step would be to discuss the outcome of today's meeting with the FDA while we continue the STRIVE study to its interim analysis point. Pfizer would then need to assess the resources required to continue the current program if it only offered such limited applicability.

So as I said in my core presentation, we're committed to a study of 6,000 subjects in the STRIVE population that would give an indication for broad elective orthopedic surgery. And we need feedback from this Committee as to whether the Committee considers it reasonable to be able to have that extrapolation so we can engage in the right sort of discussions with the FDA.

MR. TOUBMAN: Well, as I understand your answer, though, you're suggesting that if this Committee were to say no, we don't think it should be expanded, the approval should be limited to these kinds of surgeries, you're suggesting that you would consider terminating the STRIVE study. That's what you basically just said, right?

DR. B. GRUBER: That's one possible outcome, but we would need to obviously engage in discussions, obviously, with the FDA taking into account full opinions around the table to

determine what the best path forward would be. But yes, that is one potential outcome.

MR. TOUBMAN: Okay. And my question on Slide 16 read in conjunction with Table 6 of your briefing document. Slide 16 has these figures that show substantial difference in infection rate of 1.4 for this group, for STRIVE, versus much lower for the other surgeries. But if you look at Table 6, actually, that's a little misleading because that's only the data on -- Slide 16 was only about invasive infection. Just look at regular infection from *S. aureus*. It's very similar. If you look at primary spinal fusion, you got 84,000 cases and 0.85% occurrence of *S. aureus*. If you look at hip arthroplasty, you have 83,000, very similar, and 0.77%. So I'm a little confused why this slide talks about the infection rate being so different, when if you just look -- I guess the question is --

DR. B. GRUBER: Yeah.

MR. TOUBMAN: -- why can't you do a study of these other things which would require far fewer subjects if you're only looking at total infections as opposed to invasive infections? And certainly, wouldn't that be relevant for safety purposes? You don't need invasive results, invasive infections, in order to do a study of safety, and what I'm suggesting is, if you actually look at just total infections, you could do a far smaller set of subjects, which would be far less than 10 years that you've been talking about; is that right?

DR. B. GRUBER: Yeah. So I think a key consideration is where the greatest medical benefit is likely to occur, right? That's part of the decision making in terms of the nature of how we decide on endpoints, and it's quite clear that the greatest benefit is likely to be in association with being able to prevent the invasive types of disease and deep wound infections, the types of things that led to these sorts of complications. So we consider that as the most valuable endpoint.

It's important to recognize that inclusion of any sorts of other populations where the attack rate is lower, even if it's marginally lower, to be able to get to an answer in a reasonable period of time either runs the risk of expanding the subject numbers so much that we, you know, basically delay the ability to get to an endpoint or worse, you delete your -- you dilute your ability to demonstrate efficacy within a specific number, say 6,000 subjects, because now you're taking individuals with lower incidence of disease that increases your probability of a Type 2 error; in other words, essentially failing to demonstrate efficacy when it really exists. So I think, again -- and again, we've obviously engaged in discussions with the FDA about the nature of the endpoints for what was originally a Phase IIb study versus a Phase III study, and it's been agreed that the proper endpoint -- endpoints are the ones that we've identified in terms of primary infection.

DR. EDWARDS: Okay. Dr. Greenburg.

DR. GREENBERG: I'll make it quick, thank you. I have a question about Slide 18 of yours. I was curious why it appears, for the hospitalizations prevented, that the number or the rate of hospitalizations versus the number of surgical procedures seems to be higher for arthroplasty than spinal, because I think you've already said several times that the infection rate is higher in the spinal, overall, compared to joint replacement.

So why is it that there appears to be a greater proportion of hospitalizations? Do they get hospitalized more easily or more readily than the spinal infections?

DR. B. GRUBER: Yeah, this is probably a question maybe for -- best reserved for Dr. Parvizi. I mean, part of it relates, obviously, to the total volume, so you can see that obviously, in terms of absolute numbers, there are more arthroplasties than there are spinal surgery. But you're saying that the ratio, you think, is -- if you look at this quickly, is somewhat different.

And I don't know, Dr. Parvizi, if you'd just comment, is it more likely to have individuals that are undergoing arthroplasty hospitalized if they get into trouble?

DR. PARVIZI: Yes. It has to do with the length of hospitalization both after the elective arthroplasty, not just spinal procedures, and when they develop the complications

afterwards.

DR. GREENBERG: Thanks.

And with regard to transferability to the other orthopedic areas, so I have two questions related to that. One is, in your clinical development program, have there been any or are you planning any studies of the product in the orthopedic populations? Even if it isn't, you know, outcomes based, like these, are you planning any work at all?

DR. B. GRUBER: I think, again, we felt and maintain that the nature of the STRIVE population being representative of the other elective orthopedic populations, if we demonstrate efficacy in STRIVE as well as safety, is sufficient for that purpose. It's quite clear that we'd be engaged in discussions with the FDA and HMOs in terms of taking available databases, either public or in HMOs, post-licensure for a broad indication and use that, as we've done for other vaccines, to look at effectiveness and use. And so that would be, I think, the best opportunity to demonstrate effectiveness across the entire elective orthopedic surgery population.

DR. GREENBERG: Thanks.

And we didn't really talk much about safety, but -- so a related question to that is could you remind us, so for the CRM197, what is the dosage with this product versus your pneumococcal conjugant vaccine?

DR. B. GRUBER: Yeah. So we can actually bring up the

slide that has the -- Slide Number 2, please. So this speaks to the nature of the amount of -- and I think you were focusing on the capsular polysaccharide conjugated to CRM, these are the doses of those antigens versus the doses of Clumping factor A and the manganese transporter.

DR. GREENBERG: What is the µg amount in Prevnar 13?

DR. B. GRUBER: Oh.

DR. GREENBERG: Oh, it's CRM197.

DR. B. GRUBER: Actually, I'd have to add it all up, but it's -- yeah. Dr. Anderson has the answer in terms of Prevnar 13. I have to add it up.

DR. ANDERSON: It's a 1:1 ratio, so the *Staphylococcus aureus* vaccine has a higher level at 60 µg whereas the covalent is approximately 35.

DR. GREENBERG: Thank you. Great. Thank you very much.

DR. EDWARDS: Okay, so the final question will be from Dr. Follmann.

DR. FOLLMANN: Thanks.

So I was also interested in Slide 16, and the idea there seems to be that you're obliged to look at one population, which would just be the hip surgery or spinal surgery. Did you ever consider sort of a blended inclusion criteria possibly with risk stratification of hip and knee surgery so you could have a higher infection rate?

It seems odd to me that you would do a study in one

population when you could have a blended and, you know, more broad inclusion criteria and study the people you want to generalize to.

DR. B. GRUBER: Yeah. So I think the nature of these populations, it's been hard to identify a population that is accessible and doesn't have other confounding features in terms of looking at hip arthroplasty or knee arthroplasty, that would have a higher attack rate than the ones that we've represented here.

And what I mean by that, for instance, you know, there was some discussion about revision arthroplasty in that circumstance. They're harder to come by. As you heard from Dr. Parvizi, even in circumstances where people are doing a revision, they don't think that they were necessarily infected; in fact, they were, and that was really the basis for a problem. So our vaccine is not a therapeutic vaccine. So these, we feel, are the best estimates of a population we could gain access to in terms of the attack rates that we would encounter.

And that said, I'll just come back to the arguments, and I'll try to be brief about this, that I said before, there are really only two options in terms of, in our view, of how you would incorporate these individuals. You would either say, okay, within 6,000 subjects we take some of these folks in, but then you basically dilute your overall attack rate and your

ability to have a Type 2 error essentially goes up. Alternatively, you're faced with the prospect of adding sufficient numbers to independently be able to demonstrate efficacy in the subset, which if you don't enroll 25,000 to 40,000 subjects and enrolling, you know, a smaller proportion of that, you again risk a Type 2 error or even worse with small numbers, having a small number of cases that by chance alone are split in the wrong direction. So either way, it really doesn't help you in terms of enrolling those additional subjects as far as an efficacy trial. And remember, even as part of a safety trial, you're going to be obligated to look for *Staph aureus* infection as an outcome measure.

DR. FOLLMANN: Just a follow-up comment. I mean, really, this is an event-driven study, so you're going to go to 48 cases, and so, you know, saying you're going to cap it at 6,000 is -- could be inconsistent with the idea that you're going to go 48 cases. If it's really 48 cases, you might have to enroll 6,500 or 7,000 to get it, which is what I presume you would do given it's a case-driven study.

DR. B. GRUBER: Yeah. Yeah, I think our estimates are actually -- and we obviously have a pretty good idea now in terms of cases that are being acquired, that our estimate of 6,000 subjects is sound for a STRIVE population where we would anticipate we could be successful in recruiting 48 cases within that population.

DR. EDWARDS: Okay, thank you. There are no more questions, and we will pause for lunch, but we will need to come back at 1:30 so that we can get all of our discussion in. So thank you so much.

(Whereupon, at 12:47 p.m., a lunch recess was taken.)

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

(1:28 p.m.)

DR. EDWARDS: Okay, I'm going to go ahead and read the Open Public Hearing document. We're a little bit ahead, but I think it's important to go forward.

So the Open Public Hearing announcement for particular matters involving specific parties: Welcome to the Open Public Hearing session. Please note that both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee, the FDA believes it's important to understand the context of the individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statements, to advise the Committee of any financial relationship that may you have with the sponsor, its product, and if known, its direct competitors. For example, this financial information includes a sponsor's payment of your travel, lodging, or other expenses in connection with attendance at this meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such relationships. If you choose not to address this issue of financial relationship at the beginning

of the statement, it will not preclude you from speaking.

Do we have any individuals that want to comment in the Open Public Hearing?

(No response.)

DR. EDWARDS: Since there do not appear to be any individuals who want to speak, then we will close the Open Public Hearing, and then we will ask our next speaker, Dr. Tina Mongeau, to present the FDA presentations.

DR. MONGEAU: Good afternoon. My name is Tina Mongeau, and I'm a clinical reviewer in the Office of Vaccines. Oh, sorry. Okay.

So the goals of my presentation today are to provide an overview of *Staphylococcus aureus* surgical site infections, to review the clinical development of *Staph aureus* vaccines to date, to provide an overview of Pfizer's investigational *Staph aureus* vaccine and their proposed clinical development plan, and to discuss considerations for the clinical development plan proposed by Pfizer for their tetravalent *Staph aureus* vaccine.

I'll start off by providing an overview of *Staph aureus* surgical site infections.

While advances have been made in infection control practices, surgical site infections remain a substantial cause of morbidity and mortality. According to data reported to CDC's National Healthcare Safety Network, surgical site infections accounted for 36.4% of healthcare-associated

infections occurring between 2011 and 2014 in the United States.

Overall, *Staph aureus* was the most frequently isolated pathogen from surgical site infections at 20.7%. Of the *Staph aureus* isolates causing surgical site infections, 43 to 45% were resistant to methicillin.

Staph aureus can form a biofilm which predisposes it to cause infections associated with surgical implants. Infections associated with surgical implants are generally difficult to manage because they require a long period of antibiotic therapy and repeat surgical procedures.

The CDC categorizes surgical site infections as superficial incisional, deep incisional, and organ/space surgical site infections.

Superficial incisional surgical site infections manifest within 30 days after the operative procedure and involve only the skin and subcutaneous tissue of the incision.

Deep incisional surgical site infections manifest within 30 to 90 days after the operative procedure and involve deep soft tissue of the incision; for example, the fascial and muscle layers.

And organ/space surgical site infections manifest within 30 to 90 days after the operative procedure and involve any part of the body deeper than the fascial or muscle layer that's opened or manipulated during the procedure.

Current approaches to the prevention of surgical site infections rely on infection control and perioperative prevention. Infection control strategies broadly include hand hygiene, contact precautions, and environmental infection control.

With regards to perioperative prevention of surgical site infections, the CDC has guidelines which include the following:

- Patient should shower or bathe on at least the night prior to the procedure.

- Skin preparation in the operating room should be performed using an alcohol-based agent unless contraindicated.

- During surgery, glycemic control should be implemented using blood glucose target levels of less than 200 mg/dl and normothermia should be maintained.

- Increased fraction of inspired oxygen should be administered during surgery and in the immediate postoperative period with only a few exceptions.

- Antimicrobial prophylaxis is recommended for surgical procedures, and when given, it should be given at times such that a bacterial concentration of the agents is established in the serum and tissues when the incision is made.

- And screening and nasal mupirocin decolonization is recommended for *Staph aureus* colonized patients prior to total joint replacement and cardiac procedures.

Currently, there is no licensed *Staph aureus* vaccine

available.

Depending on the type and severity of the infection, treatment options may include:

- Incision and drainage, antibiotics, and/or surgical debridement.
- Implant-associated surgical site infections may require one or more debridement procedure and prolonged antibiotics to eradicate or control the surgical site infection. The implant is typically removed or exchanged.

Few antibiotics are available to treat MRSA infections. Vancomycin has been the mainstay of parenteral therapy. However, vancomycin-resistant and vancomycin-intermediate *Staph aureus* isolates have been identified.

At this point, I'll now move on and provide an overview of the clinical development of *Staph aureus* vaccines to date with a focus on the two most -- the two candidate vaccines that have been most extensively evaluated in clinical trials: StaphVAX was an investigational bivalent conjugate vaccine developed by Nabi Biopharmaceuticals. It was formulated to contain 100 mg of capsular polysaccharide Types 5 and 8 individually conjugated to a recombinant nontoxic variant of *Pseudomonas aeruginosa* exoprotein A, a carrier protein.

Study 1356 was a randomized, double-blind, placebo-controlled Phase III trial which evaluated a single dose of

StaphVAX against *Staph aureus* bacteremia in 1,804 adults 18 years of age or older with end-stage renal disease and on hemodialysis. The study did not meet its pre-specified primary study objective. It demonstrated no statistically significant reduction in bacteremia in the year following vaccination compared to placebo. The vaccine efficacy estimate was 26% with a lower bound on the 95% confidence interval of -24%.

Nabi conducted a second randomized, placebo-controlled, double-blind Phase III study which evaluated two doses of StaphVAX administered at Weeks 0 and 35 in 3,359 subjects with end-stage renal disease and on hemodialysis. The primary endpoint was moved to 8 months after the first dose of the vaccine. This study did not demonstrate vaccine efficacy in reducing the incidence of *Staph aureus* bacteremia for up to 8 months following the first dose of the vaccine. The safety analyses were consistent with the prior Phase III trial and revealed no significant differences in rates of serious adverse events or deaths between vaccine and placebo groups.

Possible factors contributing to the failure of StaphVAX that have been discussed in the scientific literature include the following:

- First, further investigation suggested possible suboptimal quality or manufacturing of the vaccine lot for capsular polysaccharide 8 antibodies to CP8 elicited by StaphVAX in study 1371 had lower affinity compared to

corresponding antibodies in the earlier study, 1356.

- Second, there's a general immune suppression associated with uremia and/or dialysis that has been noted in patients with end-stage renal disease. This includes complement depletion, reduced phagocytic and killing ability of neutrophils, and deficiencies in antigen presenting cells and t-lymphocytes.

- And finally, it has been noted that anticapsular antibodies alone may not be sufficient to protect against invasive *Staph aureus* infections.

So the second and more recently studied candidate *Staph aureus* vaccine that I'll discuss is Merck's V710 investigational vaccine. V710 contains a *Staph aureus* iron surface regulated determinant B, which is a conserved cell wall anchored protein that is expressed during iron limitation.

In a randomized, double-blind, placebo-controlled Phase III trial, the safety and efficacy of a single dose of V710 was evaluated in adults 18 years of age and older scheduled for cardiothoracic surgery involving a full median sternotomy. The primary objective was to demonstrate that a single dose of V710, when administered 14 to 60 days prior to the full median sternotomy, results in a reduction in the proportion of adults with postoperative *Staph aureus* bacteremia and/or deep sternal wound infections through post-op Day 90 by at least 20% relative to placebo.

Sorry, okay. There we go, okay.

The trial was event driven. Following a review of the second interim analysis and supplemental results, the data monitoring committee recommended permanently closing the study to enrollment because of concerns about a higher rate of mortality and multi-organ failure in V710 recipients than in placebo recipients, in addition to a low probability of success. The sponsor followed the recommendations of the DMC. After locking the database, 7,983 subjects had been vaccinated. There were 22 adjudicated cases among V710 subjects versus 27 adjudicated cases among placebo subjects, and in the primary modified ITT analysis, V710 vaccine -- the V710 vaccine was not significantly more efficacious than placebo. Vaccine efficacy was calculated as 18.5% with a 95% confidence interval, ranging from -48.6% to 55.8%.

In the safety analysis among subjects experiencing any postoperative *Staph aureus* infection, V710 subjects had a higher mortality rate compared to placebo subjects, and V710 subjects had a higher rate of death with multi-organ failure compared to placebo subjects.

A causal relationship between V710 and higher rates of mortality has not been established.

Possible factors contributing to vaccine failure that have been discussed in the scientific literature include:

- A modest and transient functional antibody response in

V710 recipients.

- That anti-IsdB antibodies alone may not be sufficient for protection.

- And that undetectable pre-existing IL-2 and IL-17 levels play a role.

    - In the post hoc analyses, the data suggested that undetectable baseline or pre-vaccination and pre-operative IL-2 levels and undetectable preoperative IL-17a levels were each associated with mortality in V710 recipients experiencing any post-op *S. aureus* infection.

At this point I'll focus on Pfizer's tetravalent *Staph aureus* vaccine.

Pfizer has developed an investigational *Staph aureus* vaccine which contains four surface-expressed *Staph aureus* antigens. It contains capsular polysaccharide serotypes 5 and 8 each conjugated to CRM197, the capsular 8 *Staph* in the invasion of opsonophagocytosis. It contains a recombinant form of *Staph aureus* Clumping factor A. ClfA is responsible for bacterial adhesion to fibrinogen. And it contains a recombinant form of *Staph aureus* manganese transporter C protein. *Staph* requires trace elements such as manganese for growth. Pfizer states that they selected these antigens because they are well conserved and expressed during early infection, and Pfizer intends for this vaccine to be broadly

protective across the range of clinical isolates of *Staph aureus* regardless of antibiotic resistance profile.

The product is to be administered as a single dose intramuscularly between 10 and 60 days prior to elective orthopedic surgery.

The proposed indication is for active immunization for the prevention of postoperative invasive disease caused by *Staph aureus* in adults 18 years of age or older undergoing elective orthopedic surgery.

In July of 2015 Pfizer initiated Study B3451002, a large randomized, double-blind, event-driven global study evaluating the safety and efficacy of a single intramuscular dose of their tetravalent vaccine versus placebo in adults 18 through 85 years of age when administered 10 to 60 days prior to undergoing an elective, open, posterior spinal fusion procedure with multilevel instrumentation.

And I'll go over a few important definitions.

- Spinal fusion is defined as a surgical arthrodesis procedure or fusion of the vertebrae which may involve the cervical, thoracic, lumbar, or sacral vertebrae or the pelvis.

- Instrumentation involves implantation of prosthetic material such as rods, screws, plates, hooks, wires, and/or bone cages and which may be composed of titanium or cobalt alloys, plastics, or stainless steel.

- Multilevel procedures are defined as procedures with

instrumentation involving at least three vertebrae. A single fusion that includes two vertebrae is permitted if instrumentation spans three or more vertebrae.

And this slide reviews some select study eligibility criteria. Subjects with comorbidities are eligible to participate. And the next few bullets review select exclusion criteria, so subjects that are excluded include those with:

- End-stage renal disease or nephrotic syndrome, immunocompromising conditions or other illnesses requiring treatment with known immunosuppressant therapies.
- Any known or suspected malignancy to the spine.
- A history of major surgery within the prior 3 months.
- A history of spinal surgery performed within the prior 6 months.
- A history of any previous spinal surgery resulting in postoperative bloodstream or surgical site infection.
- And antibiotic therapy for microbiologically confirmed invasive *Staph aureus* disease within the prior 12 months.

The primary study objective is to assess the efficacy of tetravalent *Staph aureus* vaccine in the prevention of postoperative *S. aureus* bloodstream infections and/or deep incisional or organ/space surgical site infections occurring within 90 days of the index surgery and confirmed by the event adjudication committee.

Assuming true vaccine efficacy of 70% or greater, efficacy

will be declared if the lower bound on the 95% confidence interval of the vaccine efficacy estimate is 20% or greater.

Infections contributing to a primary endpoint are defined in the protocol and are consistent with CDC definitions.

The study includes prospective criteria to identify multiple organ failure after vaccination and surgery.

Safety and efficacy via secondary efficacy endpoints will be evaluated through Day 180 after the index surgery.

Pfizer's clinical development plan includes a proposal to use safety and efficacy data from Study B3451002 conducted in elective, open, posterior approach, multilevel, instrumented spinal fusion surgery as the primary data supporting the proposed indication in adults undergoing any elective orthopedic surgery.

Pfizer proposes that vaccine safety and efficacy demonstrated in Study B3451002 can be generalized to other elective orthopedic surgical populations because the study constitutes a "stringent" assessment of vaccine efficacy; on average, the study population undergoes a longer and more complex procedure compared to other elective orthopedic populations resulting in a higher incidence of postoperative invasive *Staph aureus* disease at 1.4% versus 0.2 to 0.5%. In addition, the study population is representative of other elective orthopedic surgical populations with regards to risk factors associated with postoperative surgical site infections

and the immunopathogenicity of postoperative *Staph aureus* surgical site infections.

So Pfizer is making the case that patient- and procedure-related risk factors associated with surgical site infections are similar across all elective orthopedic surgical populations and procedures.

Patient-related risk factors include *Staph aureus* nasal carriage, comorbidities, age, and health status.

And procedure-related risk factors include perioperative care, some of which we reviewed on an earlier slide; median procedure duration; implantation of prosthetic material; the length of incision; wound characteristics; site of the surgery; anatomical structures and tissues; and allogeneic blood transfusions.

Pfizer is also making the case that their investigational vaccine is designed to provide protection against invasive disease established at the surgical incision site and that the immunopathogenicity of postoperative *Staph aureus* infections are similar across elective orthopedic surgical populations. When considering this, one should take into account the source of the inoculation, the early pathophysiology of *Staph aureus* surgical site infections, the *Staph aureus* isolates associated with surgical site infections, and the presence of cellular and humoral immune components at surgical sites.

So I'll conclude my presentation with a discussion of

considerations in trying to determine whether Pfizer's proposal is scientifically valid. The question at hand is whether assuming Study B3451002, if we assume that this study meets its primary objective, then can vaccine safety and efficacy data from this study be generalized to adults undergoing any elective orthopedic surgery?

First for consideration is the extent to which dissimilarities across different elective orthopedic surgical populations and procedures are relevant with regards to patient-related risk factors, procedure-related risk factors, and the immunopathogenicity of postoperative surgical site infections.

A second consideration is whether the B3451002 study population and indexed surgical procedures are representative of other elective orthopedic surgical populations and procedures.

And finally, whether Study B3451002 represents a stringent evaluation of vaccine efficacy.

Thank you.

DR. EDWARDS: Are there any questions? Would it be possible for you to put back the questions that Jeff put up before on the screen so that we can look at those? Yeah.

Yes, please. Dr. Kirkpatrick.

DR. KIRKPATRICK: I'm sorry I'm revealing my ignorance again as a bone guy. When you say -- or when the Sponsor says,

and you say, efficacy of 70%, what specifically does that mean? Does that mean out of 100 patients, 70 will not develop an infection, or does it mean the severity of the infection is different? What is the actual efficacy measure?

DR. MONGEAU: I think I'll let Pfizer address that question.

DR. B. GRUBER: So Bill Gruber, head of Vaccine Clinical Surgical and Development at Pfizer.

This is really a placebo-controlled trial, so it basically takes the placebo attack rate, and there's basically a 70% reduction in that attack rate. So it doesn't mean that, you know, if you put 100 people in to get orthopedic surgery, that you're going to prevent 70 of them from getting an infection. If they otherwise would've gotten infection as part of that placebo attack rate, then you presented -- prevented 70% of the infection. Was I clear? Okay.

DR. EDWARDS: Yes, Dr. El Sahly.

DR. EL SAHLY: So we heard that these four antigens are conserved and that's part of the reason why they were chosen, but the two capsular polysaccharides are not prevalent in the U.S. or not even present in the USA300, so -- and which is the main circulating community and hospital-acquired *Staph aureus* strain in the U.S. So that's half of the vaccine is almost out for most of the people in the U.S.

And in the debriefing documents we received prior to the

meeting, I want to say either the ClfA or the mtcA has only 70% antigenic similarity across multiple strains tested. So how do we project that this vaccine -- I mean, why do we say that this vaccine is relatively conserved or addresses conserved strains?

DR. MONGEAU: With regard to that, yeah, I have to defer to the Sponsor.

DR. ANDERSON: Annaliesa Anderson, Pfizer.

So a couple of questions there. I'm going to start with the protein antigens first. And so regarding the Clumping factor A, we find it's present in all disease isolates, and the maximum sequence identity is 92%, which means that that's very highly conserved, so I'm not sure where the 70% was from.

We have a functional antibody assay that measures whether or not antibodies can inhibit the action of the antigen and the fibrinogen to prevent the binding as described in the briefing document. And so there, we've looked at prevalence-based collection of strains that represent the diversity of the Clumping factor A that's expressed by *Staphylococcus aureus*, specifically the most common isolates, and shown that the sequence doesn't stop the antibodies that the vaccine makes from preventing the bacteria to bind to the fibrinogen.

Regarding the MMTC, it's actually extremely conserved. We find that there's really 98.5% sequence ID, and there's a different one and so there again. And then the mechanism of action for that antigen is to prevent manganese uptake, and we

show that antibodies can, you know, recognize that site.

Capsular polysaccharide in USA300 is a much more complex story and is actually quite a contentious one, too. So as Dr. Gruber mentioned, approximately 9% of strains we see in orthopedic surgeries are USA300 versus all the other MRSA and MSSA that we see.

Again, we've done prevalence-based studies in collaboration with the Wellcome Trust in the United Kingdom and found that, you know, when one looks at USA300, it's absolutely true that they do not express capsular polysaccharide when they're grown in vitro, in a test tube.

However, it's a slightly different story when you look at what's being expressed in vivo. We've been able to generate data where we can challenge animals with USA300 strains, and they do develop an antibody response to the capsular polysaccharide indicating that there is a level of expression.

Also, if you extract the bacteria directly from the animal without growing it in culture, in about 70% of cases you find that they are actually expressing the capsular polysaccharide. So the question comes, you know, why is that, because there are mutations in the -- infected pathway.

There's one major mutation that actually causes one of the enzymes to stop and not be expressed, but what's interesting is there's a duplication within the capsular polysaccharide pathway.

And a group in Japan -- and I must apologize because I'm never very good at expressing the name, but there is a slide that shows the publication -- have actually shown that this duplication is true and the dehydratase that shouldn't be expressing the capsular polysaccharide, the one right next door -- thank you. If you can show Slide 3. And this isn't to read; this is so I can remember the name. It's the Merefasa (ph.) group.

So the capsular polysaccharide USA300 has a mutation in the capD gene, but the capE gene is the one which can actually have the same functional activity. And so there is evidence that whereas the mutation may have an effect on preventing capture in vitro, in vivo, I've explained two lines of evidence, the in vivo expression and also the ability of animals to generate an immune response to the capsular polysaccharide.

So as I said, it's not a straightforward story, and I think, you know, to very briefly summarize, we have a four-antigen vaccine, and so the proteins are very conserved, and they have specific mechanism of action to prevent early infection. The capsular polysaccharides induce antibodies that can kill the bacteria. There is evidence that USA300 may have some deficiencies in capsular expression, but there's certainly also evidence that it may still express capsule when in an infectious disease situation.

DR. EL SAHLY: A question. Given an incidence of 1.4% of serious *Staph aureus* infections post-multilevel spinal fusions with instrumentation and 70% efficacy of the vaccine, how many events are we talking about, difference? Because, you know, we are trying to generalize to a large swath of the population based on preventing X number of events, if we have the biostats.

MR. RADLEY: Hello, my name is David Radley. I'm a statistician at Pfizer.

The design of the study requires a total of 48 cases of infection, the primary endpoint, and for the study to be successful, to meet its criteria, there needs to be no more than 14 of those 48 cases in the vaccine group.

DR. EDWARDS: Dr. Kotloff, did you have a question?

DR. KOTLOFF: Yeah, two simple questions. One, we've heard that possibly antibody affinity has been responsible for weaker performance of monoclonal antibody and for vaccine, and I was wondering if you measured antibody affinity in response to your vaccine.

DR. JANSEN: Hi, my name is Kathrin Jansen. I'm heading Vaccine Research and Development at Pfizer.

We have not, per se, measured the affinity of the antibodies, especially from the conjugates, elicited after immunization with the conjugates. However, we have very stringent criteria when we put our conjugates together, so we

have developed processes that are highly consistent. So from time to time to time that we're actually producing them, they are made exactly the same way, and there are very stringent control procedures in place to assure that.

And then we have done immunogenicity studies, not in people, but in animals that show that the immunogenicity elicited, through multiple lots, is essentially very similar and comparable. So we don't think that we have to worry about the issue that was unfortunately observed with the Nabi vaccine.

DR. KOTLOFF: Thank you. And the other quick question just follows the USA300 story. So in your animal models, did you look to see whether the efficacy was the same with the USA300 and non -- you know, and other strains?

DR. MONGEAU: Sorry, who is your question directed at? Is it directed at --

DR. KOTLOFF: Not you; it's directed --

DR. MONGEAU: Oh, okay. Okay.

DR. KOTLOFF: -- to Pfizer.

DR. ANDERSON: Annaliesa Anderson, Pfizer.

So we have tested USA300 strains in our animal models, and we do see efficacy.

DR. KOTLOFF: And it's similar to the efficacy of --

DR. ANDERSON: That's right. Yes.

DR. EDWARDS: Dr. Long. And if you're not using your

microphone, please turn it off.

DR. LONG: You talked about the exclusion criteria for entry into the Pfizer study, and they did also. And part of it, it doesn't seem very exclusionary, actually, from what is written except how you interpret immunocompromising conditions. So I'm wondering about obesity, severe cardiovascular disease, or any kind of cardiovascular disease or diabetes and whether that would be exclusionary or not.

DR. MONGEAU: No, those underlying medical conditions are not considered exclusionary.

DR. LONG: So then I'd like to know the relative frequency of those, especially obesity, that might be different in people getting hips replaced, knees replaced, compared with back, to understanding extrapolation.

DR. MONGEAU: Yeah, I think Pfizer can address that. I think they had a slide that showed --

DR. LONG: You might have, and I think I missed it. Maybe we could see it again, Bill?

DR. B. GRUBER: Yeah, so we could -- yeah. If we could bring up Slide 3, please. So this slide was meant to represent -- of course, this is an intersection in time at the time that this particular number of subjects are in the trial. We now have over -- around 1,900 subjects. But it basically compares, as you can see, the STRIVE population with typical representation in terms of age, gender, race, and then a number

of underlying risk conditions. And as you sort of look across, you can see a fair degree of commonality. These numbers may be slightly different in spots, but take diabetes, for instance, in the STRIVE population, 17.9%. If you look at all spinal surgery plus and minus implants, it's typically around 15. Primary hip, 11.6. Obviously, much bigger denominators. And individuals with knee arthroplasty, 8.2.

So our goal here was really to demonstrate that the STRIVE population, in terms of its demographics, not only compares favorably to the overall spinal surgery population, but actually compares favorably to the populations that -- represented here in terms of elective orthopedics, in terms of hip and knee arthroplasty.

DR. LONG: Before you take that away, have you done something in the STRIVE study for those patients to seemingly be a little older than the usual spinal surgery patient? I mean, what if you ended up with a 10-year difference when you finish the study, between that and trying to extrapolate that to knee arthroplasty?

DR. B. GRUBER: Yeah, I think, you know, we have data that, again, looks at that full range, if you recall back to the immunogenicity data, of 18 to 85 years. There's not much discrimination when you even get to the top end. You still have very high, robust antibody responses. I think, actually, if you look in your briefing package at the back, we have that

broken down in terms of the younger age group and the older age group.

DR. EDWARDS: Dr. El Sahly.

DR. EL SAHLY: This question is more to the orthopedic surgeons in the audience. What fractions of orthopedic general procedures involve titanium or chromium cobalt? Because these are the ones in the -- with instrumentation, I guess, in the spinal cases.

DR. RICHARDSON: So William Richardson, Duke University.

Certainly for, I think, hips, knees, and spine, there are still some stainless steel implants around, but the vast majority are either some sort of alloy of titanium or chrome cobalt. There are some newer techniques with total joints with ceramics, but the vast majority are titanium and chrome cobalt.

DR. EL SAHLY: I asked this question because the indication requested is a little bit more general than knee/hip implants. It says general orthopedic procedures, which -- I mean, I don't know. What else is there? I'm guessing there must be a lot, but --

DR. RICHARDSON: Yeah. Do you want me to answer it, or do you want --

(Off microphone response.)

DR. RICHARDSON: So, certainly, general orthopedic procedures could include arthroscopy, they could include soft tissue procedures. Certainly other types of orthopedic

procedures involving bone would again involve plates, which are either stainless steel or titanium, so all implants are going to be titanium, but there are additional orthopedic procedures that may not require implants.

DR. B. GRUBER: So because I think this gets back to a question, Dr. Kirkpatrick, you were asking perhaps, if I understand this morning. Maybe we can just show Slide Number 2.

You know, our thinking about what we would include as far as an indication is concerned, and I try to think of this sort of simplistically, circumstances where the musculoskeletal system is not incidental to the surgery, so whether it's really the target of the surgery as opposed, for example, to say a neurosurgeon having to go through the skull to essentially work on the brain where really the target is the brain. So if you use that sort of as the calculus for deciding, then these types of surgeries are the surgeries that would be included in an indication.

And I think, harkening back to some of the discussion we had earlier, it isn't so much the nature of the device that's important; it's the fact that there's the potential for a conditioning film of host proteins to essentially coat that device at the same time that that same area will have access to antibody and serum. So the goal is for the antibody to essentially block the organism from binding to that

conditioning material.

The purpose of the broad indication, then, is just as that, you know, that we'd have safety and efficacy that should be applicable across the spectrum. It's then up for recommending bodies to decide and argue the risk-benefit profile for which circumstances you would use the vaccine in.

So if we take, as an example, hand surgery, which right now doesn't even get antimicrobial prophylaxis, the decision might be that in that circumstance, the risk-benefit profile would be such that it's -- even though it's licensed because it's part of all elective surgery, it wouldn't be recommended. So our goal really is to have a broad indication, give -- empower recommending bodies, then, to make judgments about the risk-benefit profile, about how it would be used.

DR. EDWARDS: Dr. Kirkpatrick and then Dr. Blackstone.

DR. KIRKPATRICK: So I would echo the fact that you're getting on the right track. Orthopedics is a very broad field, the pathophysiology and the populations are very different. And I'll leave it up to Dr. Edwards to tell me if she would like me to further discuss that now or reserve that to the discussion period.

DR. EDWARDS: I think you should discuss that now

DR. KIRKPATRICK: So if we could get that list back up. I don't know what slide that was that had the variety of -- yes. So the first three are unequivocally, in my mind, equivalent,

hip and knee arthroplasty and spine, from a pathophysiologic candidate population standpoint. From a pathophysiology standpoint, all three of those involved are fairly significant dead space, if you will, that is either the implant -- fundamentally, it's the implant, okay, whether it be cobalt chrome and polyethylene, whether it be just spine implants, that sort of thing. They are occupying space within the body; the body no longer has circumferential access, so to speak, to that bacteria, and they also provide a scaffold for the bacteria to put their biofilm. Okay, so the pathophysiology of that is a very special condition.

When you start beyond that, spinal laminectomy does not involve placing any implants. Other spine procedures, there are some with implants, some not. Joint fusions typically have an implant, but they're often used as an internal splint, so to speak, so there's not as much dead space; in fact, we're trying to use minimal plating as much as we can. And that also gets you into a fracture category, which is a different population of patients as well.

So I don't want to go through the entire list, but then you get to the other side, you've got the point that he made about carpal tunnel, you don't need any prophylaxis there. Many people don't use it for arthroscopy. There's ligament reconstructions that are soft tissue that don't involve that dead space, and so that's a huge difference in the

pathophysiology of an infection and the -- or excuse me, the incidence of those infections is way lower. For example, in an ACL reconstruction where you have two screws, it's almost nonexistent when you compare that to, you know, a knee replacement, for example, which would be the same joint. So it's really very different to say all of orthopedics.

DR. EDWARDS: Dr. Blackstone.

DR. BLACKSTONE: Great. If you hadn't said that, that was one other thing I was going to try and indicate because we have the same issue in cardiac surgery where, you know, there's a big difference between opening the whole sternum, the mediastinum having stuff in there and having wound infections where you are going after a vein or something.

But I do have a question of Pfizer, and that is I understand very well the idea of a Phase II study in an enriched population that has higher infections, find out a bunch of stuff that you folks have talked about over there about the immunology and all that kind of stuff, and then you're asking us to assume that the study achieves all of its objectives.

What I don't know is, at the very beginning of this study, what you had thought would be the next study to actually get approval for this vaccine. I'd normally think that you'd have a Phase III study. There must have been something in mind. And then what has triggered this, hardly at midpoint, to turn

the Phase II into a Phase III?

DR. EDWARDS: Is that a question that -- go ahead.

DR. B. GRUBER: Yeah, I think it was a question directed to Pfizer, so is it okay, Dr. Edwards, if I answer? So, again, Bill Gruber, head of Vaccine Clinical Research and Development at Pfizer.

So we described this a bit in the briefing document. When we actually started out with the STRIVE trial as a Phase IIb study, we actually thought that the attack rate was going to be significantly higher because some of the published literature had suggested that was the case. As we looked in databases and began to gain experience, it became apparent that the attack rate was lower.

So that afforded us the opportunity, then, to say all right, even though we planned the study originally to de-risk a Phase III study, that now we were going to be compelled to enroll subjects that would allow us to get within range with a safety database of 3,000 subjects in the study to satisfy safety criteria, so we could actually use the study as Phase III. Had we actually had a higher attack rate, in all probability, we might have either decided to, you know, essentially expand the study or do an additional study that essentially allowed us within about 6,000 subjects to get the necessary safety database.

So it was really driven, in part, by the fact that we now

are in a position to meet criteria where we can demonstrate efficacy with a lower bound of the confidence interval greater than 20% with 6,000 subjects. For the purpose of the license, we would have potentially ended up there, anyway. This is just now recognizing the attack rate using the existing study to do that.

DR. EDWARDS: Dr. Kirkpatrick.

DR. KIRKPATRICK: I'd just like to comment on that issue because I've heard it a couple of times. I have approximately 20 years of experience on FDA panels, mostly in devices, combination products, and now in vaccines. At many of those panel meetings, we have had to ask the sponsor why didn't you ask this before, because they've tried to come in and expand their indications at the approval meeting. And I see this, actually, as a very refreshing and an excellent move by Dr. Gruber and his team to open that discussion with the FDA early on so that they don't get to the end of the table and get sent back to square one; they instead are trying to be proactive and with the FDA, get the most safe thing for our patients. So I think this is a great move for them to actually be entertaining this question during their approval process.

DR. EDWARDS: Mr. Toubman.

MR. TOUBMAN: Yes, my questions are only for the FDA, and they're mirror questions I had for Pfizer this morning. Notwithstanding the well-said comment just now about how it is

refreshing, good point, there's also, in terms of the basic questions here, it's not a yes or no. We could answer the questions by saying premature: so yes, we agree, it should be generalized; no, it shouldn't be generalized; or it's too soon and it should wait until the normal process.

But this question is for FDA, first question, is it was made clear, in response to my question, that they are threatening to terminate the STRIVE study if the answer is either no, it can't be generalized, or punting and waiting; they have threatened that. And my question for FDA, maybe not you but somebody else in the room, is, is that even permissible? Based upon all the communication so far between the FDA and the company, is that even permissible? Maybe there's a lawyer from FDA in the room, whatever. So that's my first question.

The second question is, assuming that this group was -- focusing particularly on Dr. Kirkpatrick's comments about the difference, orthopedic procedures are very different, if the FDA were to -- or this Committee were to suggest, and the FDA were to agree, that there should be at least one other study involving one other orthopedic procedure and again, using Table 6, which I urge everybody to look at, from their presentation, there are several other procedures that could be done that have similar incidence of infections in terms of *Staph aureus* infections generally.

If the FDA were to conclude that, could it require, as a condition of getting a yes answer to these questions, that yes, you can use it generally in orthopedic procedures, could it be conditioned upon them doing one more study of one other orthopedic procedure?

DR. MONGEAU: Do you want to pull up the questions again or --

DR. M. GRUBER: Can I comment on that?

DR. EDWARDS: Please. Please, Dr. Gruber.

DR. M. GRUBER: Yeah, Marion Gruber with the FDA.

DR. EDWARDS: The FDA Gruber.

DR. M. GRUBER: Yes, the FDA Gruber.

DR. EDWARDS: Not the Pfizer Gruber.

DR. M. GRUBER: So I think, if I understand your -- understood your first question correctly, is it permissible, I think you're referring to Pfizer potentially stopping the further clinical development of this product pending the outcome of these discussions or any further considerations. There is nothing that prevents them from doing so. I mean, they are at liberty to decide whether to advance clinical development of a certain product, whether to stop it, whether to go to another national regulatory agency instead of us, so that is nothing that we have any influence. That's not a question about is it permitable or not to the FDA.

The other -- do I have an echo here? This sounds -- I

hear myself. Yeah? Okay. The other point that you were making, I think we've discussed this question, whether it is okay to extrapolate from a spinal fusion surgery to other elective orthopedic surgical populations. With Pfizer, I don't know, for the last several years, so this is not a question that is -- that came up last month or 6 months ago. So we decided it is a very complex topic to discuss, and that's why we decided we'd take it, you know, to our panel, including some of the experts here.

So depending on the outcome of what you've been discussing -- and we intentionally didn't phrase this as a "yes/no" question because we wanted to really, you know, encourage and entertain sort of a very frank, very open exchange of pros and cons, if you want, and then, of course, if the outcome is well, you know, you can extrapolate, that's one answer.

But if it is you can extrapolate to a certain point, the possibility of, you know, doing another study, maybe for safety reasons, maybe for, you know, efficacy reasons, is something that is not going to be excluded at this time. So this would be still on the table and something to be discussed with the Applicant.

MR. TOUBMAN: I really appreciate both of those answers. I guess my first question was premised upon the idea that the STRIVE study was developed, as I understand it, with extensive

discussions with the Agency, and it was developed with a lot of thought, and I was just wondering if they're -- given all that investment on both sides, it was permissible, and I guess the answer is yes, they can just take their marbles and go home.

On the second thing, there's both safety and efficacy, and I sort of said twice now, without having gotten any responses from anybody, that maybe we can look at just total *Staph aureus* infections and see how similar they are in other surgeries besides this one we're talking about and to suggest that, you know, we could look at that.

In terms of safety, I believe, unless I'm missing something, that would be a perfectly valid study, equally valid to spinal fusion, to look at that, because you're going to have the same issues either way.

DR. EDWARDS: That may be a little bit more complex in terms of the different pathogenesis at the various infections, pneumonia and sepsis, and so I think we'd need to probably stay focused on the orthopedic questions for this, yeah.

MR. TOUBMAN: No, I was saying -- I'm sorry, I was talking orthopedic. I was just suggesting that it would be, if you look at other orthopedic procedures, you could do a valid test for safety without having to have it be invasive infections.

DR. EDWARDS: Yes, Dr. Blackstone.

DR. BLACKSTONE: Could I ask, is splitting a sternum an orthopedic procedure? Because it is not there, but it is

similar.

DR. EDWARDS: Well, I guess it's not done by the orthopod, right?

DR. BLACKSTONE: The question is why not?

DR. EDWARDS: Well, it seems --

DR. BLACKSTONE: Because this is one of --

DR. EDWARDS: -- doesn't it --

DR. BLACKSTONE: -- the primary things that we worry about. So, you know, we decolonize this very close -- the nose is very close to the sternum and so on, so this is a huge problem that we've had to adjust to.

DR. EDWARDS: It does seem that this is for orthopedic surgery, so I guess the FDA could clarify for us whether that is included. I would think probably not, but --

DR. KIRKPATRICK: Excuse me. I actually function as an oral examiner for the board, and they would not consider sternal osteotomy as being an orthopedic procedure. That is my perception. I'm not representing the board, but that's kind of how I think they'd come down on it.

DR. EDWARDS: Dr. Stephens.

DR. LEVY: This is Ofer. Dr. Edwards, just let me know when it's okay to ask a question.

DR. EDWARDS: Sure. Dr. Stephens is --

DR. LEVY: I have just a comment.

DR. EDWARDS: Sure. Dr. Stephens is going to say

something, and then you can speak, Dr. Levy.

DR. STEPHENS: So while it's not an orthopedic procedure, I must agree that -- and having seen some horrific complications of *Staph aureus* in sternotomies and open heart surgery, this is a real issue, in my view, and why can't you simply -- if you're extrapolating to all orthopedic surgery, why do we have to kind of -- if it's not done by an orthopedist, I understand that, but there's wires, there are other foreign bodies that are associated with those kind of infections, and it is a major issue, and so I'm asking, just kind of, why not? Why aren't we talking about other potential benefits of such a vaccine?

DR. EDWARDS: Dr. Levy.

DR. LEVY: Hi, this is Ofer Levy. Firstly, I'd like to commend Pfizer because they selected a very important topic here. There's no doubt that the burden of disease is great, and there hasn't been a good vaccine, so kudos to them.

In terms of the discussion topics, which really center around generalizability, I think a lot of what we heard in the first half of the day is that our knowledge regarding the host immune system and *Staph aureus* continues to evolve, and I'm thinking very much of the information presented about how -- which elements of the immune response are going to be so relevant, most relevant, to vaccine-induced protection are still being sorted out and that maybe antibody is not going to

be the be-all and end-all here and the T-cell responses are going to be likely important.

And then on the bacterial side, Dr. Otto pointed out the tremendous variation between different *Staph* strains, the toxins produced, the antibiotic susceptibility, the encapsulation, etc.

So to me, I think we're still in a phase where we don't know what we don't know, and with that as a backdrop, I am a little hesitant about making broad generalizations from any one study. I think there's still going to be a lot to learn. I certainly hope this is a successful study and that the data look really good, but I would think that FDA would want to be very thoughtful about ensuring that more information was gathered in a systematic way, including as much information as possible about the bacteriology. It's not just whether there's a *Staph* infection or not; are the studies designed to determine what strains are causing the infections? And not just the antimicrobial sensitivity, but you know, the PVL toxin and other toxins expressed or other parameters that might be relevant, small colony variance, etc. And similarly, not just measuring antibody, but on the host side, also looking at the T-cell response.

So I think there's still a lot to be learned here, and I would be a little loath, based on one study, to generalize it across a broader population without learning more. That's my

thought.

DR. EDWARDS: Thank you, Dr. Levy.

Yes, Dr. Roberts.

DR. ROBERTS: Jeff Roberts from FDA.

It seems like we're veering into the discussion topics really solidly.

DR. EDWARDS: Yeah, that's --

DR. ROBERTS: And I guess I'd just like to ask if we have any other clarifying questions with regard to our presentation, and then we'll haul out Dr. Mongeau.

DR. EDWARDS: Yeah, thank you. That was what I was going to say, too. Right.

Dr. Long.

DR. LONG: A clarifying question for the FDA. It is said in our Pfizer confidential briefing document on page 12 that in 2014 the FDA granted fast-track designation to SA4 antigen for adults 18 years of age and older who are undergoing elective surgery. Can somebody clarify exactly what that fast-tracking means?

DR. MONGEAU: Yeah, I can speak to that. So we have specific criteria for products that -- clinical development plans that we consider for fast-track, and one of those involves whether or not the indication covers a serious condition or disease, which we agreed invasive *Staph aureus* post-op infections are, and whether or not there are data to

show that the clinical development plan is adequately designed to address showing that proposed -- or meeting that proposed indication, and that can involve early, early phase clinical data. And so by giving that fast-track designation, it's sort of showing our commitment to working with the sponsor in terms of moving that clinical development plan along.

DR. LONG: But it doesn't mean, as it did with meningococcal B vaccine, that this could be licensed without efficacy data in this case?

DR. MONGEAU: No.

DR. LONG: It's different for every fast-tracking? There's fast-tracking and there's fast-tracking?

DR. M. GRUBER: I mean, in this very case, the Sponsor is proposing a clinical endpoint efficacy study so -- and that's what they're doing. So we have -- no. At this point, you know, we're going by these premises that, you know, assuming the safety and efficacy is established and efficacy by, you know, looking at prevention of these *Staph aureus* infections as the primary endpoint we're spelling out, that, you know, would be the basis by which efficacy is demonstrated and not based on an immune parameter. So that's very different in this scenario.

DR. EDWARDS: So I think we do need to go to our discussion topics. The first one will be: Assuming that the ongoing study of four-antigen vaccine achieves its pre-

specified primary efficacy objective in a population undergoing elective, posterior approach, instrumented, multilevel spinal fusion surgery, please discuss the reasons why efficacy should or should not be generalized to other elective orthopedic surgical populations.

Dr. Greenburg, would you like to start?

DR. GREENBERG: Sure, thank you.

I want to give the perspective that it's very, very difficult to develop new vaccines for healthcare-associated infections in general. We all talk about the tremendous burden of disease and the economics on a national scale, if not a global scale, but when you drill down to a study population for which you're trying to find the efficacy for licensure, it suddenly becomes very, very difficult, like where are all those, you know, thousands and thousands of cases?

In this case, I think Pfizer identified a cohort to which they could enroll and randomize and do a precise study with just an estimated 1.4% rate of disease. So, therefore, based on the sample size calculation, 70% assumed efficacy with a lower bound greater than 20%, that suddenly becomes, you know, for an event-driven study, 6,000 individuals. It's not a few hundred, it's -- you know, it's 6 and -- and on top of that, it is extremely difficult to enroll the right patients into this type of study. I mean, you already heard it, you know, they contacted hundreds of potential clinical sites. They were able

to work with those who are, you know, most likely to enroll the right kinds of patients. Even when one does that, it still becomes extremely difficult for reasons that were discussed. Patients are a lot more concerned about their spinal surgery than they are about an experimental vaccine.

So, actually, I think they've done a tremendous job, and you know, when they're asking for a broader indication than the narrow population that's being enrolled, I don't think it's unreasonable if the Committee thinks that the pathophysiology, the organisms that are infecting these patients, infect the orthopedic patient, other orthopedic patients, that the pathophysiology has a lot of similarities, that it's as likely for the vaccine to work in these broader populations than just the spinal surgery.

My opinion is that it meets all of those. Is it perfect? No. I don't think it would be unreasonable for there to be either a small study in a broader orthopedic population, not an endpoint, a clinical endpoint outcome, but maybe, you know, basic safety and immunogenicity to help bridge. And then, of course, there's post-licensure work and, you know, I think any manufacturer expects there to be post-licensure work in populations that are beyond, you know -- or include some part of the indication that might not have been studied as extensively as it could have been in the pre-licensure work.

Pfizer didn't discuss cost, but I can tell you, these

studies, like this one, in this narrow population, tens to hundreds of millions of dollars. So to do the same study in -- you know, in hip replacement and knee replacement, you're just simply -- you're spending even more money because the incidence is lower.

So that's my perspective, that I think that the concept is reasonable, the rationale is reasonable, and the information that we have about the infections and pathophysiology meet it. And then I think, then, there could be discussions down the line, probably not today, about what other studies might be reasonable to keep a broader indication.

DR. EDWARDS: Thank you very much, David.

Mr. Toubman.

MR. TOUBMAN: Thank you.

My comments will be similar to my questions that I raised. Obviously, I can't -- because of having no medical background, I can't possibly weigh in on the generalizability in terms of those issues, but I did hear concerns from the gentleman on the phone whose name I forgot, already expressed the comment that, I think, there's too many open questions to generalize at this point.

But what I'm looking at, as a layperson, is Pfizer's own rationale, which appears at page 37 of their briefing document and where they say they considered opening the current STRIVE study to enroll other elective orthopedic surgical populations

with infection rates at the lower end of the incident range. And I would note again, if you look at just total infections, it's -- there were other surgeries that are about the same.

However, a clear interpretation of the study of efficacy could be put at risk because lower numbers of cases driven by lower infection rates in these additional populations would be more likely to lead to a Type 2 error, false negative result for this added subset, and it goes on to say the small number of cases with undifferentiated or adverse -- could lead to erroneous assumption about efficacy for the added elective orthopedic surgical populations. I read that in conjunction with their statement that they -- what they're asking for is a stamp of approval that says if this works out in terms of safety and effectiveness for fusions, spinal fusions, then, automatically, generalize and approve, on the label, for all orthopedic surgeries without knowing the real story in terms of, you know, knee replacements, without knowing for sure, but we should just go ahead and assume that.

Yet here, the concern expressed is that, well, we shouldn't study it because if we study it, it might not come out the way we want it to come out. And I understand the problem of having too small a sample, but that could be explained. That doesn't explain a reason not to even look. So it really is disturbing to me that that's part -- like, very clearly, part of the rationale and was stated orally as well.

So I guess I would say it is -- I would use the word "premature" to give them a stamp of approval on generalizing to all elective orthopedic surgical populations.

And one other thing I wanted to point out about the recruitment issue, I understand that's a real problem, and I believe that's the issue they've had, but part of that was spinal serious surgeries. People in great pain will have -- you know, really are facing a really serious surgery. Perhaps recruitment is not quite as difficult in some of these other procedures, so you could -- and I would support the comment by Dr. Greenburg, there are ways of fashioning studies that I don't understand, but there are ways of fashioning studies that could, in a more limited way, look at some of these other procedures. Thank you.

DR. EDWARDS: Thank you.

Dr. Stephens.

DR. STEPHENS: So I think there is no question that we need a *Staph aureus* vaccine. It's a huge clinical need and an unmet clinical need, and there's no question. We need, however, a vaccine, given the two previous trials, that does show efficacy and does work.

And I continue to be concerned about some of the fundamental science, and whether antibody alone is the right answer with these particular antigens, I don't know. So the assumptions that this is going to work, that's what we're asked

to judge on, and I still have grave doubts, or doubts about the fundamental mechanisms of protection, and have we really captured that with this particular vaccine?

I think, again, it could be broadly applicable to other conditions. We've mentioned cardiothoracic surgery as an example, but there are other conditions where an effective *Staph aureus* vaccine would be needed. I am concerned about the kind of issues around the study in a sense that there are a huge number of sites, there are lots of variables, it's a complex study.

But, again, the question is assuming that it achieves the primary objective, is it then generalizable to other elective orthopedic surgical populations? I must thank my colleague to my left that it's probably not generalizable to all orthopedic procedures, and I think it would be a mistake to use this in that particular setting without other evidence that it is not only efficacious, but makes sense in terms of prevention of infection.

So regarding the safety issue, I probably would come down on No. 2, I'd probably come down and say yes, safety data in this population with this vaccine could be generalizable to other uses of this particular vaccine.

DR. EDWARDS: Thank you.

Dr. Kirkpatrick.

DR. KIRKPATRICK: Thank you.

I'd like to take a moment just to thank the FDA presenters, and I know you had a lot of support working with this, as well as the Pfizer presenters. That was a great education effort for me, and I appreciate it very much, and you put together great presentations on both sides, not that you're opposing, but as two separate groups.

I appreciate the fact that you put the questions back up because what I heard in the presentation was "all other elective orthopedic surgical procedures" and what I see here is not generalized to "other elective orthopedic surgical populations," which implies that you would also like us to define what other populations would we think of considering.

And when my colleagues brought up the cardiac effort, when I was doing cardiac surgery, which was many years ago and don't call me current, full disclosure, okay, we used to take an artery that's on the inside of the chest, called the internal mammary artery, can bypass it to the heart. Unfortunately, we discovered that that led to a much higher incidence of these terrible *Staph* infections, mediastinitis, needing debridements and plastic surgery to fix it and all this kind of stuff, and that was because we basically made the sternum a dead space, like I reported to you earlier. So that kind of surgery may indeed be an exception. I'm not the expert to tell you that, but I'm thinking about it enough to bring it up for the FDA and the Sponsor to consider as maybe that is a rationale to expand

to that one specific indication, because if you have a big dead space, that bacteria can just grow in it.

Now, as far as what other orthopedic elective surgical populations I would include, I clearly would include joint replacement: total knee, total hip. They have a very similar patient population, they have very similar kinds of concerns with the pathophysiology, and so I had a no-brainer with that coming here. It makes a lot of sense.

Now, what other orthopedic areas should be considered, I disagree with the opinion of Dr. Gruber that you should license everything and then we let the medical team figure out what it is because, unfortunately, the medical team doesn't police itself enough to stop using things that are approved that don't work. And so I would much rather side on the FDA taking a stance and saying, okay, the things that have a valid scientific rationale that pass the reasonable assurance of safety and efficacy are reasonable to consider for this, and reasonable assurance may be like this, okay, somebody saying these populations are a lot alike and it makes sense to try, okay?

That also fits into the least burdensome, which, as we heard our colleagues say, 100 million dollars for studies, that's a lot of money, that's a lot of burden. And so, you know, we don't want to overtax them, but at the same time we want to give them some, you know, some oversight.

So on the other populations, I think there's no question about joint replacement.

I would suggest that, like another colleague mentioned, the post-approval is different here. We've heard from both sides that this is a dynamic biological organism. I don't know how they are going to assure me, as a consumer, eventually, that when we approve it with a 70% efficacy in 20 -- what do you think, 2020, maybe you'll get the studies done? Is it going to be the same organism in 2025 and have the same efficacy? So my concern is that to try and find that out might be an overly burdensome post-approval study to try to make sure they maintain that efficacy because it's not going to be studied once it's approved. So that summarizes my concerns.

DR. EDWARDS: Thank you very much.

Dr. Follmann.

DR. FOLLMANN: Thank you.

I'd like to echo some of the previous speakers who complimented the presenters today. I learned a lot, and I think it helped us all to try and understand the questions.

So I want to start by not really addressing this question, but just -- I guess the FDA and Pfizer are in the middle of discussions on how to create this Phase III study. I think it's worth thinking about trying to broaden the inclusion criteria to get people outside of the fusion surgery indication, some other groups that are risk stratified, so they

also have a high risk, so it doesn't take forever.

The idea that we won't get -- that we're at risk for a Type 2 error, that is, we won't have enough events in this study to really identify a true signal, I think, is not really correct because this will be a study that goes to 48 cases. So if we broaden the inclusion criteria, it might take a little longer, it might take less because maybe we could get more than 10 a year at a particular site, as was discussed earlier. So anyway, you know, since the Phase III study hasn't been defined yet, I would mention that as a possibility.

So anyway, so Question 1 is really saying how would we interpret STRIVE if it's efficacious and has roughly 70% efficacy in terms of generalizing these other populations. And what I would want to do is to basically look at the data and see can I create someone who has -- who looks like a hip surgery patient, for example. So within the dataset we have, there will be variation in the incision size, there will be variation in the duration of surgery, there will be variation in age and health status and so on.

And so from those predictors, I'd like to, as an example, let's take the incision size, look at the median incision size in the study, and then look at the vaccine efficacy separately, those with longer incisions than the median and the vaccine efficacy with those shorter incisions than the median.

I would look to see if those are similar or not. If they

are similar, then I'm more comfortable generalizing to the more general surgical population. So I'm not going to, like, separately test the vaccine efficacy in those two groups; it would be pretty underpowered. I'm going to look for similarity of vaccine efficacy in those groups. So there are many different ways to do that, I just gave one for illustration, but I'm sure the statisticians at the FDA and Pfizer can think up more sophisticated ways of doing it.

The other thing, you know, along with that thought is we're sort of limited by the number of cases. If we have 48, we'll have 24 for values lower than the median and 24 infections for values greater than the median. So how can we get greater power to try and look at clues? And so for that, I would recommend that they look at additional outcomes.

So it was mentioned earlier that severity of disease might be something that the vaccine could improve, so look, you know, does the vaccine improve severity of the disease for those general surgical-type populations, is the vaccine efficacy similar? But it's more inclusive of a broader endpoint for which we should have greater power, and then we'd be more comfortable that, in fact, we could generalize.

Some examples of that might be, like, superficial infections, duration of hospitalizations, do you have to open them up again and so on, and I'm sure you'll have other ideas about that as well. Possibly you could look at Day 90 to 180.

I was uncertain why, in the study, which is following patients up to 180 days, why we stop at Day 90. Was it because we thought they'd be rare? Was it because you thought the vaccine efficacy would not be so great? But anyway, I think that would be another thing that you'd want to look at.

Along that line, I guess, of broader endpoints, it -- well, it would be very hard, I suppose, to do a study with this severe infection endpoint in these populations with -- where the attack rate is so low. Maybe it's more feasible to do a study with a severity or broader -- a less severe endpoint, maybe we could add more power, and maybe a second study could be done in a population like that where we have a severity easier-to-achieve endpoint that wouldn't require as many patients to get another signal, at least some data in that population.

And then a final comment: I, too, was -- I had, I guess, a moment of edification when my colleague to the right mentioned all these different surgeries and that why -- that the joint replacement surgery seems similar to the fusion surgery; the other ones could be very minor and so on. If the approval is given for all of those, it seems like the benefit to cost would be very different in these tendon surgeries or somewhere the risk, I would imagine, of a *Staph* infection is exceedingly low. And so in terms of relative benefit, maybe it's large, but maybe in terms of absolute benefit it would be

vanishingly small and, you know, maybe shouldn't be given there. So that's about it.

DR. EDWARDS: Thank you.

Could the people that aren't speaking turn off the microphones?

Karin. Dr. Bok.

DR. BOK: Hi. It's fascinating, first of all, to discuss these kind of studies when they're getting so much more complex and the design of the study is so different from what I'm used to, just preventing hepatitis, meningitis. This gets into a much more complex study design, and I want to congratulate FDA and Pfizer for undergoing this kind of study.

Now, keeping in mind we are assuming that this vaccine is going to be efficacious and safe, and that's something that I'm struggling to just turn off that part of my brain, I think the medical need is serious, and it's very important that it will be very beneficial for us to have a *Staphylococcus aureus* vaccine. I think that, certainly, from my point of view, if the vaccine is efficacious, it could be generalized to other procedures with similar attack rates and similar risk factors, like the length of the surgery or the type of incision or the use of foreign materials into the surgery. So if you have not only certain orthopedic surgeries that we mentioned, but also -- I'm not an expert, but the sternum surgery where the *Staphylococcus aureus* infection risk is significant, I don't

see why, from a pathogenesis point of view, why a vaccine like that would not be efficacious.

And also assuming that after ACIP is going to discuss the data again and make a recommendation, there's going to be other Phase IV studies or other follow-up studies to bridge the kind of information that we're all going to have after the Phase III study.

Now, we also have to keep in mind that doing a study with an attack rate of less than 1% is very difficult, so I just don't see a way of requiring Pfizer to do that right now without just giving them the right to generalize to certain surgeries that are very similar to the one that's in the study.

And from the safety point of view, I have no doubt that if the vaccine is safe in 6,000 individuals and even in the study that they're going to do to control for the log variations, it should be safe in anybody else.

So thank you.

DR. EDWARDS: Dr. Blackstone.

DR. BLACKSTONE: Yeah. So, again, it was nice to be on a very different panel. You're not discussing implanted LVAD devices and that sort of thing, so this is a little bit different. So thank you for, also, the education about these bugs because we have similar problems with endocarditis, particularly with invasive endocarditis. So there's a lot of crosstalk that you could imagine there.

I'll just remind us of one fact, and that is the effective sample size for this study is 48, so that's the challenge. If you think about a study of 48, there's going to be, you know, wide confidence limits, as it were, there's going to be -- there's not many things that you can adjust for and so on and so forth.

So one of the things that I thought about before coming here is, is this the ideal Phase III study? Let's say you meet the halfway point as Phase II. A Phase III study, although we have said it could be extremely extensive, it doesn't need to be extensive. So in my field there are studies of 70,000, 100,000 patients and the like in which we do simple studies, and in fact, NHLBI talks about simple pragmatic trials where you are, instead of having an 800-page CRF, you have one sheet that has just the specific endpoints that you're after, and I could see a Phase III study here that focuses on sort of short-term infections. We don't need all of the fancy stuff that you do need for a Phase II study, and you'll have 3,000 of those, and then have it broader.

And again, I would put it, as John has said so well, in those specific procedures in which there's this dead space and often various, you know, be it sutures, be it plates, be it other things that are filling cavities that normally don't have a bunch of bugs in them.

DR. EDWARDS: Dr. Wharton.

DR. WHARTON: Thank you.

So several of the previous speakers have commented on the special point in time we are where we're looking at a vaccine for a subset of the population, and it's a small subset. It's for, apparently, short-term protection for an elective surgical procedure, and it's actually wonderful to be able to have a conversation about how to protect people from *Staph aureus* infection as a complication of surgery. And yeah, it's hard. It's a hard thing to study. It's raised all kinds of interesting and challenging problems, and of course, our scientific knowledge about pathogenesis and other factors related to *Staph aureus* infection are not complete, but we are where we are.

There was a question in the FDA presentation about whether or not the study represents a stringent evaluation of vaccine efficacy, and it seems reasonably stringent to me, but it also seems pragmatic, understanding I'm using the word differently than you just used it, that in order to make an assessment in a clinical study about whether or not a vaccine is efficacious, there needs to be some uniformity in the population studied, there needs to be some predictability in the expected rate of the outcome, and it seems to me that by focusing on this particular subset of elective orthopedic surgical procedures where the infection rates are higher than they are for other procedures is a completely appropriate strategy.

And it is hard for me to believe that if the vaccine indeed is effective in preventing *Staph* infections in what are these relatively high-risk procedures, that it would not also confer protection for procedures where the infection rate risks were not quite so hot. So I am comfortable with generalizing. That doesn't mean, of course, that the vaccine should be used for all orthopedic procedures, and I think that's where we get to the question about what is the underlying risk of infection in procedures.

And there's a lot of reasons why in the different procedures, why that would vary and it -- and one would expect that the clinical groups that make recommendations for vaccine use could address some of the nuances that might not be addressed in product labeling.

Regarding the safety question, I think I'm --

DR. EDWARDS: Some have addressed safety, and I thought we could -- they could go ahead --

DR. WHARTON: Okay.

DR. EDWARDS: -- and then if you haven't addressed -- go around for that. But go ahead.

DR. WHARTON: So regarding safety, I think the -- there's no particular reason to think that the safety profile would vary based on the type of procedures unless we're concerned that the risk has to do with the underlying risk of invasive staphylococcal infection associated with that procedure. But

still, if you have that outcome, you would expect the safety profile to be the same. So I think I'm comfortable that we can generalize from the safety information.

DR. EDWARDS: Okay, thank you.

Well, I think that this has posed a number of fascinating questions, and certainly, there are still a lot of questions that exist. I do worry a bit about -- certainly, I like the fact that the population is well defined, but I do worry a bit about the nuances of the various people and the management of their various patients and various populations.

And I also worry a little bit about if it's so difficult to enroll the patients, are those patients that are enrolled reflective of the entire population of the patients that are undergoing this? So I think that's going to have to be looked at very, very carefully and dissected out.

If, however, given those caveats the vaccine efficacy does look good in this population, then I think that, at that point, then one could extend it to some very specific things, and certainly, what John had suggested in terms of the joint replacement seems like a very good step. But as David suggested, I think it would have to be coupled with very, very good postmarketing assessment; it would have to be coupled with very careful assessment of those patients for that as well.

So I do have a concern, also, that maybe the biology may not -- this may not contain enough antigens, but that's really

not the question either, and if the vaccine does prove itself to be efficacious for the prevention, I think it will be very exciting. And then in that particular approach, then other populations could be looked at with postmarketing surveillance and looked at in very careful ways.

Janet.

DR. ENGLUND: Thank you. I'm Janet Englund. It's great that everyone's said what I was going to say, so I'll be relatively short.

In addressing specifically the questions asked by the FDA, whether this should or should not be generalized to other elective procedures, populations, I feel very strongly that "other" is too broad. I could deal with replacing "other" with "similar" or "similar pathophysiologic" or something, because I do not think, and it's been said, tendon surgeries and other relatively minor -- more minor procedures with less risks of infection and certainly shorter time duration should not be included in this application. I think the company should be hearing it from us that we don't consider them all the same. So that's number one.

Number two, I do view this as being a complex study, but I think to establish efficacy, we need to have a complex study with a narrow population. The *Staph* vaccines have failed so many times. We want something to work, and we need to do it in an organized fashion that gives it a chance for showing if

there is potential efficacy. So I don't particularly want to extend the efficacy studies. I think things could be extended in a Phase IV postmarketing surveillance.

However, where I would like to just be really, really clear is on Question 2 about safety. I feel that doing safety assessments in a total 5- or 6,000 people in a very high-risk complicated patient group with all kinds of underlying neurological, cardiac, diabetic -- I mean, these are difficult patients. I don't have to -- as a pediatrician, I don't have to deal with all of those problems at once.

I really think we need more safety data, and I feel strongly that that can be separated, as has been said, that could be separated in another study in some other, you know, in some of the -- you know, knee replacement or some of the other studies where we don't really need to have a positive *Staph aureus* culture as an endpoint.

So I think, number one, I feel similar surgeries, not just others, and number two, I want more safety data. And I've been on the Committee, and I'm leaving now, but specifically, I want safety data on the population for which the vaccine is going to be used. We have had time after time where it's not been used in the older people or in the minority people or obese people, so we really want safety data in the population for which one would perceive this to be used.

Thank you.

DR. EDWARDS: Thank you, Dr. Englund.

Dr. El Sahly.

DR. EL SAHLY: In addressing the first question, whether -- the reasons why the efficacy should or should not be generalized to other orthopedic surgical population, for the reasons stated previously, there may be reasons to believe that the efficacy can be extended to certain orthopedic surgical procedures where there would be a foreign body. The location is very -- subject to trauma, like knee and hip where *Staph aureus* can build a niche from which it grows. So some orthopedic surgical procedure, there's possibility to generalize.

But the downside is -- the downside would be is that if we do not do those studies in the other -- no, let's put it that way. If we -- yes, if we extend the efficacy to those populations, then we are missing an opportunity to study, in those populations, if it's -- because if a vaccine is licensed, let's say, for a narrow indication, the barrier to enrolling volunteers into a subsequent study will be much lower because the experimental part, it's still experimental, but it's much more acceptable.

So I would imagine there will be only a fraction of the resistance remaining in potential enrollees there, so it may be easier than presented to do such a study.

Having said that, I do understand the burdens, the

financial burdens, you know, entailed.

The issue of safety, 6,000 people followed for this amount of time would be good, but there would be a lot of post-licensing work to be done.

DR. EDWARDS: Thank you.

Dr. Kotloff.

DR. KOTLOFF: Yes. I think that this is a very important vaccine to have available for patients to try to eliminate some very serious infections. And I applaud Pfizer and the FDA in picking a prototype group that exemplifies a lot of the factors that are associated with *Staph* infections. So these are large -- you know, these can be large incision, prolonged operations with ICU stays and bacteremic infections, etc., etc.

So I think that they've taken a challenging prototype, and we'll be able to learn a lot for that, and I think it presents quite a challenge to a vaccine to be able to prevent disease in such a complex population.

Unfortunately, I don't think, from an efficacy standpoint, that I, as a pediatric infectious disease doctor, not an orthopedist, have heard enough information that would allow me to say whether or not the information from that one group can be generalized to other groups and what criteria I would use to know whether those other groups could be -- the results could be applicable.

So I agree with Dr. Englund that I think that the

recommendation should be somewhat vague in saying that it can be generalized to similar groups, and then I think what happens is it puts the burden on the people who make policy recommendations to try to evaluate the risk-benefit, and I think that's going to be challenging, especially when there is a low-risk group.

I agree, for efficacy, that we should do our best to have closed licensure evaluations in subgroups to try to inform these decisions and to try to understand the efficacy in other populations so that we can more wisely make recommendations about who should get this vaccine.

From a safety standpoint, I think the biggest issue that I see -- I mean, if it looks perfectly safe in this population, then I think you could probably generalize it to other populations. But what if there are certain risks and then you have to weigh risk-benefit, and I think that actually would be even more challenging to understand when you don't really know efficacy, especially in lower-risk populations, then how can you balance safety and efficacy and risk and benefit? And that's going to be challenging, and I think, again, postmarketing surveillance will be important in that regard.

And I actually, also, again agree with Dr. Englund that perhaps a more expanded pre-licensure safety-only assessment would be worthwhile doing to look at other populations in that way.

DR. EDWARDS: Thank you.

Dr. Levy. Ofer?

(No response.)

DR. EDWARDS: Okay. Okay, why don't we go ahead to Dr. Lynfield and then we'll come back to Dr. Levy.

DR. LYNFIELD: One of the joys, I guess, of being on this side of the room is that a lot of the discussion has already transpired, and I do agree with what my colleagues have said. I do like the term "generalized to other similar orthopedic surgical populations." I think that makes sense. I think the examples that have been given, knee, hip, perhaps sternal -- I don't know about that; that wasn't considered orthopedic but could be a consideration. That makes sense to me.

I am concerned that we would be including high-risk people amongst the population in terms of their adequacy of an immune response as well as potential safety issues. I think that the post-licensure studies would help with that. I do like the idea of perhaps having a larger group to look at safety, ensuring that we do get representation of higher-risk groups. Although in one of the prior vaccine trials the issue was infection having a higher case fatality rate, and so, you know, there are things that we may not be able to observe until it is the population that is having the surgery and being exposed to that risk. Nevertheless, I think that would be a useful thing to do.

DR. EDWARDS: Dr. Long.

DR. LONG: I think that the case scenario in the population that's been chosen is the most difficult worst scenario to look for vaccine efficacy, large implants, large surgery, all of the things that you've said, so that I would be absolutely comfortable if this works, is effective in those patients, that it would be effective in lesser surgeries, and I would not limit the -- to any way the other elective orthopedic surgical population.

Just having taken care of a child who had a tendon lengthening who got a terrible deep staphylococcal infection and, you know, lost the ability to use that limb in a patient who -- usually those are done on patients who don't have a lot of leeway. So anyhow, I do not have any concerns about the efficacy in other populations if it works in this one. And I'm glad that they've asked this up front, and I wouldn't -- they can't change the study after they've enrolled it first, and I wouldn't want to enter other patient groups because then it would lose the cleanliness of does it work in the population you most want to use it, which is this population.

As far as safety is concerned, we -- and then others would, as we do with vaccines, Dr. Kirkpatrick, we have completely separate recommending bodies; we have lots of vaccines that aren't recommended in exactly the ages in which they have been licensed, so that happens with vaccines. It

doesn't happen so well with drugs and maybe devices, which are still up to individuals.

As far as safety is concerned, it's a little bit harder. I think 6,000 is enough to answer the question in this risk population, for sure. If we get to lower risk number needed to vaccinate to help the number needed to vaccinate to harm, we have completely different questions. So the questions of safety for the lesser orthopedic procedures, I think, would be harder to answer with a single study.

DR. EDWARDS: Thank you.

Dr. McInnes.

DR. McINNES: Sure, hello. Can you hear me?

DR. EDWARDS: Yes, we sure can. Thank you.

DR. McINNES: I'm sorry I can't be there with you. I recently have had orthopedic surgery on my right foot, and I have spent the last few hours looking at my foot and speaking to any *Staphylococcus aureus* in the vicinity, daring it to come near.

I am really impressed with the conversation that we've had today, and I don't have much to add in terms of the efficacy and safety parameters. My colleagues have, I think, spoken much of what I would say. I have two points to make.

I'm wondering whether all the juice has been squeezed out of the lemon with regard to microbiological endpoints and thinking about the concordance of the genotypes and nasal and

surgical site infection isolates and how much thought was given or still could be given to, perhaps, secondary endpoints that are microbiological in nature because we've had other vaccines that we've been able to demonstrate that with, and I wonder why there was not more emphasis placed on that.

And then the second issue is on the -- I was quite taken by the comment this morning about the surgeons who are largely used to participating in complex efficacy trials around devices and the bearing of an operational question or a systems question into this trial where recruitment, retention, and endpoint analysis is so important, and it seems like this is a golden opportunity to try to actually bury a question, an operations-based question into this trial.

Those are my comments. Thank you.

DR. EDWARDS: Thank you, Dr. McInnes.

Dr. Monto.

DR. MONTO: Being, I think, the absolute last gives me very little to say that hasn't been said before. When I first heard about the large number of sites and knowing what is done at different sites in terms of preoperative care, I did have that concern about small numbers at each site, and I think our Chair has articulated that very, very succinctly.

I really am in favor of a specific but broad definition, and I do think it should be as specific as possible but should be broad enough so that we can get some of the postmarketing

information because you're not going to get very much post-marketing information if it's not used for those specific outcomes. And I do think we do -- we have to worry about safety, given past history. I applaud the investigators, the Sponsors, for doing a study of this length. I do also hope they can keep their teams, etc., in place over this long period of time using the same criteria for evaluating various events as they take place. And I do think we still need to keep an eye on the safety issue because we do have the past history.

DR. EDWARDS: Thank you very much. I think that perhaps those of you on this side of the table weren't able to express your concerns about the safety issue, so why don't we just start with David and go down. And I think this side of the table did that and so did Melinda.

So safety concerns: Assuming that this demonstrates safety in this population, do you think the safety could be generalized to other orthopedic surgery procedures, population?

David.

DR. GREENBERG: Sure. Well, as I mentioned before and echoed by others, we didn't spend a lot of time on the safety data in the prior studies; they were relatively small, but we didn't spend a lot of time on that. I don't have any reason to think that the safety would be different in a broader population, but I also support collecting safety information in some broader population. If it's other specific orthopedic

procedures, it would make sense. I think anyone who's going to use the product would want to know that it's been tested in the target population, the indicated population.

DR. EDWARDS: Mr. Toubman.

MR. TOUBMAN: I should also do what I didn't do before; most of the people thanked the folks at Pfizer and FDA for the excellent presentations and being here and answering our questions.

My answer to that on the safety is similar to my answer to the other thing, which is we really need to look at other populations. Maybe it's not as great a concern, the safety point, but it seems to be something that has to be done and that can be done, I understand it -- as I understand it, more efficiently.

I do have one question or comment about the safety data, and this is sort of a general comment; it's not specific to this particular study, but on Slide 26, where the patient demographics are presented and risk factors, it lists male; it doesn't list female. While generally you could do the opposite from 100, but not entirely. But more concerning is it says white, and then everybody else is miscellaneous, I guess, and I think it's really important to break that down because that could be really relevant for safety. So I urge Pfizer and any other sponsors to be much more specific in the data. And as in the past, we've seen the data is inadequate, meaning if it's

totally a poor representation of certain minorities, we need to know that.

Thank you.

DR. EDWARDS: Dr. Stephens.

DR. STEPHENS: I also want to thank Pfizer and the FDA, and I think I did address this in the sense that I think the safety could be generalized more broadly.

DR. EDWARDS: Dr. Kirkpatrick.

DR. KIRKPATRICK: I think they took a relatively vulnerable patient population, and in my understanding, that means that people that are younger, healthier, nonsmokers, all that kind of stuff, would probably have less chance of having an adverse effect, so I think the safety is generalizable.

DR. EDWARDS: Dr. Follmann.

DR. FOLLMANN: I would say my comments on efficacy with the idea of trying to identify someone who is elective, orthopedic surgeon, characteristics would apply to safety, as well, so you'd look at the safety profile for someone within the study who could be similar to what you're trying to generalize to. The only other thing, I guess, is -- I guess this almost goes without saying, but you should be looking at baseline IL-2 levels in this study.

DR. EDWARDS: Dr. Bok.

DR. BOK: I think I commented on safety a little bit, but just to clarify, I agree with Dr. Englund. I would be more

concerned not about testing it on someone that undergoes a hip replacement, but to include demographics through percent demographics and comorbidities in the safety study to make sure it is tested in the people that it's going to be indicated for.

DR. EDWARDS: Dr. Blackstone.

DR. BLACKSTONE: Yeah, I'd echo what was said over here, and that is the lower the risk of the infection, the higher the risk of safety being more of a problem. And also, cost-effectiveness being an issue in these days when we're all worried about cost, it may not end up being cost effective in these low-risk groups.

DR. EDWARDS: Well, I'd certainly think that the last several meetings at VRBPAC we have looked at populations that are normal/not normal healthy infants, and the fact that we're looking at older individuals and individuals with more comorbidities makes it much more complicated.

So I think that the safety numbers here are a little on the low side, and I think that coupling them with additional studies, maybe in immunogenicity or coupled with studies in the joint replacements, would be helpful to get a broader array, and certainly, postmarketing safety studies would need to be done.

So, okay, Dr. Levy, are you on?

DR. LEVY: I am on.

DR. EDWARDS: Thank you.

DR. LEVY: There are two things. One, I wanted to say a word about correlates of protection; these are really important, and we're still in the early days of *Staph* vaccines and understanding what will induce a protective immune response. So I think this company and all companies, through FDA, should be encouraged to have a broad -- to cast a broad net in terms of immunogenicity and move beyond just measuring antibodies, but also looking at T-cell responses. I think some of the introductory talk this morning emphasized that. And also innate responses.

I'd also say, in terms of safety, that there are surprises and some of the information reviewed this morning, the published *JAMA* study, were the worst outcomes with a particular *Staph* vaccine.

So, again, I think that, given it's early days, given that -- I'm not sure any information was presented indicating that we know, you know, that it's the exact same range of strains that are causing this -- these kinds of postoperative infections after each type of surgery, I would be a little reticent or hesitant to quickly say that it's all comparable with regards to safety. So I guess I'm striking a conservative tone.

DR. EDWARDS: Okay, thank you.

Well, certainly I would like to mirror the compliments of the FDA and of Pfizer and the presentations and also for the

insight of the Committee members and help in terms of addressing these questions. So if there are not any other questions or comments from the FDA, then I think we will adjourn and have everyone -- Dr. Gruber? The FDA Gruber.

DR. M. GRUBER: Yeah, I have -- so I have a concern. So we heard a spectrum of, you know, opinions, and what I really wanted to -- well, I wanted to make a point.

We've heard, you know, there is some concern about -- by some members, that one could not easily extrapolate safety because of, you know, issues that were discussed, different strains that may play a role.

But there were also comments made about, you know, looking at or gathering safety information in subpopulations, you know, different groups, groups with comorbidities.

I mean, I think there was one thing that we tried to point out this morning in Dr. Roberts's introductory remarks, and that is the feasibility even to do these type of studies, and you're looking at subpopulations, you're looking at people who undergo elective orthopedic surgery. Of course, there is a fair number. We saw, you know, 10 million over the next decade for spinal, you know, surgery. But by and large, the -- I mean, I was surprised to hear that studying 3,000 subjects which would get the investigational vaccine is not enough because we're not, you know -- and then, you know, extending this to studying subpopulations, I mean, I'm struggling with

the concept on how we -- you know, how this can be accomplished reasonably in, you know, a pre-licensure setting, and I wanted to -- Janet, you made that point and others, you know, to expand on this a bit.

DR. ENGLUND: Well, I'm willing to do that because I am willing to bet money that the minorities and subpopulations that have already been enrolled are not representing the U.S. population, and perhaps I'm wrong, so I don't know. But having done studies, it's very, very difficult to recruit all of the same population in a study; especially in a time of need, it's just very difficult. Those people in my center refuse to be in the study even when I try.

And then if you have to have special languages, like, you know, languages that -- not Spanish, but other languages, to deal with that, and yet we want to have representation. And I think there is a potential benefit for some of the knee surgery, and I think you could have a sub-study that is based on safety, and I think you could do it to fulfill, to get the African Americans and some of the Asians and whatever minorities, you could do a safety study. It has a potential benefit; it could be one of these pragmatic two-page forms at the end with a couple blood draws and safety.

DR. M. GRUBER: But Janet, if the concern is past history, as some of the Committee members expressed, wouldn't you need a *Staph* infection to really get the full picture of what the

safety profile looks like? And then it becomes really very difficult.

DR. ENGLUND: I agree that would be best, but I don't -- I understand, if you had a *Staph* infection, too, then that is going to incredibly increase the sample size. So I am not -- no, I'm not looking for a *Staph* infection; I'm looking for an unintended or unobserved vaccine reaction.

I just really think we need confidence when we approach our patients that the vaccine appears to be safe, and perhaps I'm in the minority, 3,000 getting -- it's not 6,000 getting the vaccine; it's 3,000 getting the vaccine because half are getting placebo, and that's a pretty small number to be given to a vulnerable population.

DR. EDWARDS: Dr. Bok.

DR. BOK: Yeah, I just -- because I also echo Janet's comment. I was coming from the point of view of assuming that, with an infection, I mean, there's no risk in the placebo group like it was in the Merck trial. So assuming that the vaccine is safe, then after that, what I was thinking is well, Kathy said, in the last meetings, we've been discussing these complex populations like in the zoster or hepatitis trial where sometimes we've commented on the need of having representatives of all demographics and people with certain comorbidities to make sure the vaccine is safe. But that is only -- I mean, we're not going to know that until we know the safety of this

trial, I think, you know?

DR. EDWARDS: The postmarketing issues can be very important ones as well.

So any other comments? FDA?

(No response.)

DR. EDWARDS: Okay. Thank you very much, the meeting is adjourned.

DR. McINNES: Kathy, this is Pamela. Can I say something?

DR. EDWARDS: Please.

DR. McINNES: I think this is a very different population than we are used to talking about in terms of vulnerability. I mean, we're normally -- if we think about it, we're normally dealing with healthy populations with vaccines, by and large, and we accept the comorbidities that go with a so-called mass population approach. I think these patients that we're looking at here are not in the way we think about vulnerability, so I think we have to moderate our thinking about the safety database on this. These are actually people at significant risk for infection, and I think the risk-benefit ratio is altered with this population. So I just wanted to put that on the table. And the benefit, the risk -- the risk piece is mitigated by the potential increased benefit.

DR. EDWARDS: Thank you for your wisdom, Dr. McInnes. Thank you.

I think now, after the third try, that we're ready to

adjourn.

(Laughter.)

DR. EDWARDS: Thank you.

DR. LEVY: Thank you, Kathryn and everybody. Bye.

(Whereupon, at 3:31 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

150TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

November 7, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

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TOM BOWMAN

Official Reporter

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