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Drug Development Considerations for the Prevention of Healthcare-Associated Infections

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DATE: Tuesday, August 30, 2022

TIME: 8:30 a.m.

LOCATION: Client Managed Remote - DC
WebEx
Washington, DC 20001

REPORTED BY: Janel Folsom, Notary Public

JOB No.: 5073521

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PROCEEDINGS

DR. JOHN FARLEY: Good morning, everyone and welcome to this virtual public workshop, Drug Development Considerations for the Prevention of Healthcare Associated Infections. My name is John Farley and I am the director of the Office of Infectious Diseases in the Center for Drugs at FDA.

So innovation in drug development to prevent healthcare-associated infections will be critical to reduce morbidity and mortality and address antimicrobial resistance. Our colleagues at CDC and the team at FDA have partnered to host this workshop. This is one -- this is what we hope will be the first of a number of public dialogues to address drug developmental -- development challenges in this space. And special thanks to our CDC colleagues, the national thought leaders, and industry development leaders that are able to join us today and are here. Next.

So just an overview of today's program. Session one will focus on background and epidemiology. The team has put together a state of the art review of prevention science and the major healthcare-associated

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infections, and I think we're all going to learn a lot from that this morning. We have patients to provide their perspective and impact statements and we have an opportunity for formal public comments.

We'll then turn our attention to the regulatory perspective and trial design challenges and considerations and there are a number of regulatory considerations, first of which is that there really are a number of different products that are under discussion. So there are drugs, there are drugs that are regulated as antiseptics, and there are microbiome-based therapeutics which are often biologics, and each of those has unique considerations and we do have some speakers today to provide a good overview of those issues.

There are a lot of clinical, statistical, and operational considerations to talk about and we'll conclude the day with a moderated panel discussion focusing on some important questions as well as discussing next steps and a way forward.

So there are a number of crosscutting regulatory considerations that I just wanted to

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introduce early as we begin to think about the data. I think it's important that we also keep those in mind. So the first has to do with endpoints and endpoints form the basis of labeling claims. And there are clinical endpoints, endpoints that describe or reflect how an individual feels, functions, or survives, a concept developed early on by the Institute of Medicine and ultimately formally codified by the FDA and its accelerated approval regulations.

Clinical endpoints are not the same as surrogate endpoints. Surrogate endpoints are used as a substitute for a direct measure of how a patient feels, functions, or survives and are thought to predict such effects. Now in terms of approval pathway, there is -- pathways, there is accelerated approval which can be supported by trials establishing an effect on a surrogate endpoint reasonably likely to predict clinical benefit.

There's also traditional approval usually supported by trials establishing an effect on a clinical endpoint, but can also be supported by trials establishing effect on a validated surrogate

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endpoint. Now a validated surrogate endpoint has very persuasive data demonstrating its ability to predict clinical benefit. That takes a fair amount of work and data synthesis and a good example of that is HIV-1 plasma viral load which is a validated surrogate endpoint. Next slide.

Now in terms of accelerated approval which would be based on a surrogate endpoint, I just wanted to highlight one part of the regulations for you, that approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcome.

So what this translates into is that for Subpart H approval or approval based on a surrogate endpoint, there is a requirement to continue to study the drug further to demonstrate an effect on a clinical endpoint. Usually sponsors do this by simply continuing the clinical trial that initially was evaluated based on the surrogate endpoint and they

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continue that. Next slide, please.

So we're going to be talking a lot about use of decolonization this morning and use of decolonization as a surrogate endpoint in clinical trials would have pros and cons. So in addition to other endpoint regulatory requirements, sponsors would need to discuss the data with the agency that supports that the endpoint is reasonably likely to predict clinical benefit for this particular pathogen and clinical situation.

And if there's accelerated approval, sponsors would need to discuss with the agency the plan to verify the clinical benefit. So I just wanted to highlight that this morning. Heidi Smith this afternoon will be going into the regulatory considerations in more detail. Next slide, please.

I also think it's important that we consider bundles in this space or prevention strategies that usually involve these bundles or evidence-based practices that are implemented collectively. So for a new product that's part of a bundle, data will be needed to understand the

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contribution of the new product to the benefit demonstrated in the trial. And as others will point out today, a consideration in this scenario is that standardization between study sites needs to be addressed in terms of these other evidence based practices. Next slide, please.

And then lastly, there are some other design considerations. Ed Bein this afternoon is going to talk us through some of the unique statistical issues for cluster-randomized trials. And it's important that these be discussed with the agency as a trial is being designed because there's actually quite a bit to wrap your head around and I think this will be the beginning of a dialogue around some of these issues.

For example, the cluster level risk difference may not be equivalent to the individual level risk difference and that individual patient benefit is of course going to be a review consideration. So lots to think about and we're probably just going to start that process today. So I want to thank everyone for joining us today and for

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your commitment to prevention of healthcare-associated infections.

I think we'll now have some introductory words from our colleagues at CDC.

MICHAEL CRAIG: Thanks so much, John. I'm Michael Craig. I'm director of Antimicrobial Resistance at the Centers for Disease Control and Prevention. We are very excited to be with you today and really want to appreciate John and the rest of the FDA team for co-sponsoring this meeting with us today.

This is something that is very important to us at CDC and something that we think really holds a lot of potential in terms of saving lives and importantly addressing the challenges of antimicrobial resistance that we face, not only in the United States but around the world.

And so from our perspective, and I think the bottom line for us, is that we -- this day to us is focusing on drugs that could potentially prevent transmission of deadly pathogens, especially those that are antimicrobial resistance. These pathogens are often found in healthcare settings like

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hospitals and nursing homes, and I think the challenge that we see is that increasingly transmission is driving the movement of infections and the movement of these pathogens around the world.

So that's -- wanted to give that sort of big picture context and then I'll pause here for our moderators to introduce ourselves and then I'll dive into my talk.

DR. HEIDI SMITH: Hi, good morning. This is Heidi Smith from FDA. I'll be moderating session one along with Timothy Benson from FDA. I'll be introducing the speakers for the first half of the session, while Tim will be handling the second half of the session. He'll introduce himself at that time. In the interest of time, we'll get going with our first speaker who is Michael Craig who now is going to be talking about Prioritizing Prevention and Diversifying our Patient Safety Toolbox: Decolonization is a Missing Tool We Need.

Michael Craig is director of CDC's Antibiotic Resistance Coordination and Strategy Unit and leads coordination of CDC's $180 million

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crosscutting antibiotic resistance portfolio. He is the CDC's representative on the President's Advisory Committee for Combating Antibiotic Resistant Bacteria, align public health activities and related antibiotic resistance across multiple federal agencies. Michael, look forward to your talk.

MICHAEL CRAIG: Thanks so much, Heidi. And as I noted at the outset, this is very important for us today, and one theme that you're going to hear throughout the day is really prevention and the challenge of stopping or limiting, reducing the transmission of some very deadly pathogens. So why don't we get started. Next slide.

I have nothing to disclose. And the problem. So this is the big picture that, you know, I'm not going to go into all the data on this. I think a lot of you are familiar with it, but when we talk about some of these deadly pathogens we're talking about antimicrobial resistance pathogens which have a high burden in the United States. When you include the burden of C. diff, that's even higher.

We're talking about healthcare-

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associated infections. We're talking about sepsis. And all of these things were problems even before the pandemic, but the pandemic has increased and made all of these issues worse. So we've seen an increase of 15 percent of the number of antimicrobial resistant infections and deaths in hospitals because of the pandemic. And so these are challenges where we feel like we need new prevention tools to better address them. Next slide.

And the challenge that we face is really only getting worse, and what this slide really represents is the fact that antimicrobial resistance is really accelerating and that we have more difficult to treat pathogens every day and fewer effective treatments. And we have some challenges with the drug pipeline that we need to overcome, and I want to highlight we're very supportive of new antibiotics to treat some of these infections, but we also want the conversation to be talking about what we can do to prevent them as well. Next slide.

And the thing that we want to underline is that it's not about just preventing an infection,

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but it's really that we've come to rely upon effective antibiotic treatment for a variety of things. Modern medicine and our healthcare system is really predicated on it. And we've made incredible advancements in all of the areas that you see on this slide, including many others, but those advancements and that longer lifespan that we have because of those advancements is really predicated on the efficacy of antibiotic therapy.

And as that declines and as we see more prevention of very deadly pathogens, so too we're going to lose the innovation and the and the extra years saved by many of these innovations in our country. Next slide.

And so where are we today? Next slide.

So, one thing I want to underline is that we're, you know, still dealing with COVID and there are some prevention lessons that I think that are important to bear for this conversation. One is that importantly, we cannot treat our way out of a pandemic, an epidemic, or an outbreak. We need to have treatment options, but we also need to have

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prevention therapies or prevention modalities that can really stop the spread of infectious diseases and deadly pathogens.

The other thing that I want to underline is that we get what we pay for. I think this is very much evidence by the pandemic when there was a lot of advancement and a lot of investment that went into the development of the vaccines that we then later accelerated for development for the pandemic.

And because of that previous investment, we had those ready to go and I think that's the thing that we want to underline here is that, as John said, we want to start this conversation and we want to bring attention and resources and time to bear on these problems so that when we need these, which I would say we arguably already need them, but when these problems get even worse, we have some of these potentially ready to go and that we can use and deliver to fight these problems, especially if we're in the situation where we're fighting those pathogens again in the middle of another pandemic. Next slide.

This is to illustrate really the

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challenge that we face. So Boxes 1 and 2 really underline how we address these issues today, and Box 3 sort of underlines what's missing. So we have the ability to detect when someone is colonized with one of these deadly pathogens. So that means that the pathogen is living in them, on them. It's not necessarily causing infection but it increases their risk of infection, and we have ways to reduce the potential transmission and the potential risk to that patient.

A lot of these are very familiar. They are infection prevention and control, they are hand washing. They're the bread and butter that you see and that we stress so many times by the CDC in terms of prevention of infections. They are good, but they are not perfect and they cannot eliminate the risk to the individual and they cannot eliminate the risk of transmission.

And so what we would like is we would like to add additional modalities, additional potential drugs, or other things that could be brought to bear so that we could further reduce and maybe even

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eliminate the risk of that colonization becoming an infection in an individual or that colonization spreading to others and being transmitted in sites like nursing homes or ICUs. Next slide.

And I think the thing that we want to note is a prevention approach we know works. So this slide already notes to you that when we've used some of these steps before, even without drugs, we have been able to show that a prevention approach can have success against these bad bugs. The one thing that we would also like to underline is that from the patient perspective, the best infection is really the one that never happens, and that's what we want to go for.

Prevention ultimately saves lives, reduces -- and infections, and I think the thing to also note that is very important for some of these conversations especially when we're talking about antimicrobial resistance, is that prevention reduces our need for antibiotics and antifungals to treat these. So if you prevent the infection, you don't have to worry about whether the antibiotic or the antifungal that you have is going to work or not. So

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it reduces a lot of that pressure.
The other thing to note that I think often goes overlooked is that even if someone survives an infection, they can sometimes have lasting and long term consequences and these could be related to the antibiotic use, the antifungal use, or they could potentially be related to sepsis or whatever happened during the course of that infection. Next slide.
So from the CDC perspective, the thing that we want to really highlight is that we want to have a prevention mindset related to some of our drug development and what can happen. So we want to focus on treatment, but we also want to focus on prevention and how do we use potentially these drugs to reduce that pressure of transmission and to reduce some of what we're seeing in terms of antimicrobial resistance spreading in some of these settings.
So we need evidence, as John noted, and I think he very articulately noted many of the challenges that you're going to hear more today in some of the discussions, and we need to figure out how we can do this also without accelerating antimicrobial

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resistance. And I think that's an important point that we want to make is that we don't want to use any drug to treat transmission, but we don't want that drug to exacerbate the problem in another way.
So these are going to potentially be unique products that have unique qualifications and you're going to hear some of those considerations later, but we think it is important to focus on whether we can bring these to market and whether we can use them in our patient populations.
The other thing that I would note is that there's a lot of challenges that we see in the drug pipeline and some of the issues are whether there's a market for new antibiotics. The thing that I think we see as a potential positive benefit and a consideration is that if we talk -- start looking at the number of people who are colonized, it's potentially a much greater market and potentially a much greater engagement with the private sector to bring something to market.
So the number of people who are colonized versus infected with some of these is five

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to ten times those that are affected. If you look at specific cohorts at risk, as you can see here, we have five million patients admitted to U.S. ICUs. We have 1.3 million people in nursing homes. These are cohorts of people where we know they are potentially at risk because of colonization and transmission and where we have a lot of engagement.
And lastly, I would just note, is that we know the resistance problem goes well beyond the United States and that the burden of this is increasing globally with an enormous burden around the world. Next slide.
This is just a note to you that this is again not a flash in the pan consideration for us. This is something that is important for CDC and important for FDA and something that we want to make sure that is a part of our national action plan and would note that this is in fact something that we put in our national action plan in 2020, and as John said, this is really what we see as a kicking off a conversation with you all about how we can best do this to protect patients and individuals from

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transmission of these pathogens. Next slide.
So I'm going to highlight briefly what we need, but you're going to hear from some fantastic CDC colleagues later about -- that go into more specific pathogen areas, but the things I want to note for you is that we really want to prevent recurrence and do more than decontaminate. So we want to protect and potentially restore the microbiome because we think that this will have long lasting positive benefits both to the individual as well as to cohorts in reduction of transmission.
We want to reduce pathogen burden and/or eliminate pathogens completely. And it's even better if that has a targeted application body site. And you're going to hear later from some patient advocates, and there are communities out there, specifically the cystic fibrosis community where, you know, decontaminating the lungs and reducing the burden on that community from these resistant pathogens would be a major game changer and a major benefit in terms of giving them more quality of life and longer life. And those are some areas that we'd

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like to see if they have potential for targeting.
The other thing that we want to note is that sub-bullet there, is that we do not want these products to drive or increase antimicrobial resistance and we want to make sure that we're using them in a way that is effective at reducing transmission and reducing the problem and not adding to the problem.
Finally, as John noted, we want to consider both benefit for the individuals as well as populations that they may be a part of. We appreciate, as you can see on the right side of this slide, that there are some challenges with this and that's why we want to enter this dialogue with you and see what we can do to overcome these challenges.
These are things that, you know, we don't take for granted and we appreciate that this is some out-of-the box thinking, but we also think that it's critically important for the way we address antimicrobial resistance and healthcare-associated infections moving forward, and if we can come up with development pathways and prove this and overcome some of these challenges, we think that this could be a

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major game changer in our ability to address these threats in the United States and beyond. Next slide.
And so we just want to note to you our objectives today and I think these are in some of the materials that you've seen and I think John gave a great overview of this to begin with, so I won't belabor it. It's really to talk about where we are and where we could go and again start that dialogue with you and start the conversation, talk about some of these challenges, and see what we could potentially do to address them.
For discussion, these three questions are going to be part of a moderated panel with all of our speakers at the end of the day that myself and Peter Kim will be moderating and we really look forward to active engagement and dialogue with everybody. Next slide.
And with that, I will close and turn over to the moderator for additional presentations for today. And I again want to thank you on behalf of the Centers for Disease Control and Prevention.
DR. HEIDI SMITH: Thank you, Michael.

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So our next speaker will be John Jernigan who will be talking about Rationale for Decolonization as a Strategy for Preventing Antimicrobial-Resistant Infections. Dr. Jernigan serves as the chief of Epidemiologic Research and Innovation Branch in the Division of Healthcare Quality and Promotion at CDC. He has 30 years of experience in clinical infectious diseases and healthcare epidemiologic research. Thank you, John.
DR. JOHN JERNIGAN: Thank you very much. Next slide.
In this presentation, after reviewing some definitions, I'll cover some important observations about the epidemiology of healthcare-associated infections or HAIs. I'll discuss the role of colonization in the pathogenesis of HAIs, the role of transmission in driving antimicrobial resistance, and finally the potential role of decolonization as a prevention strategy. Next slide.
First, a few definitions that will be helpful for our discussions today. Colonization simply refers to the presence of a microorganism

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living on or in a host, but not causing disease or symptoms. But there are some nuances that are relevant for today's discussions. The duration of colonization is often prolonged and colonized body sites such as mucosal surfaces can serve as a source of transient contamination of another body site such as the skin.
In addition, the burden or microbial load of colonization can be dynamic over time. For example, the microbial load of a resistant organism might increase with antibiotic exposure. Finally, colonization can and does transition to infection through various routes or mechanisms. Next slide.
Decolonization, by its strict definition, refers to complete elimination of the colonizing microorganism, but for the purpose of our conversations today, I invite you to think about decolonization in a slightly broader context to include pathogen burden reduction or reduction in microbial load of the colonizing pathogen.
And even further, I invite you to think about how even transient reduction in microbial load

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might be beneficial, especially if it is strategically designed to correspond to a relatively short period of increased infection rates, such as during a period of high risk healthcare. You will hear Dr. McDonald's presentation, how this principle is already being used to some extent in some antibiotic prophylaxis applications. Next slide.

Now to the epidemiologic principles that underpin the rationale for decolonization. First, we know that colonization is important in the pathogenesis of HAIs. Patients in healthcare are often subjected to interventions that provide opportunities for colonizing pathogens to invade sterile body sites. Examples include surgical incisions and use of various indwelling catheters. In addition, a disrupted microbiota such as that of the large intestine can create a niche where pathogens can proliferate and find their way into sterile body sites either through contamination of invasive devices and incisions or through translocation directly from the gut. Next slide.

So let's review some evidence that

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colonization plays a role in pathogenesis. First, we know that HAIs are usually caused by pathogens that colonize the patient prior to the infection onset. This slide provides a sampling of evidence. For the sake of time, I won't go through all of these but will highlight that greater than 80 percent of staph aureus bacteremia and surgical site infections are caused by pre-infection colonizing strains and similar observations are described for a wide variety of pathogens in a variety of healthcare settings. Next slide.

Although studies -- these studies demonstrate an association between colonizing and infecting pathogens, does colonization by a pathogen actually increase the risk of a subsequent infection? There's growing evidence that it does. In the Swedish cohort study results shown on the left, individuals colonized with extended-spectrum beta-lactamase producing Enterobacterales had a 32-fold increased risk compared to the general population of incident bloodstream infections caused by the same organism over the six-year observation period.

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And on the right, in a study of patients undergoing colorectal surgery, colonization by ESBL-producing organisms was independently associated with a twofold increased risk of surgical side infections and infections caused by ESBL producers was four times more likely in carriers than in noncarriers. And although the references aren't shown here, colonization with ESBL producers has also been found to increase the risk of infection following transrectal prostate biopsy and also liver transplantation. Next slide.

There's also clear risk with staph aureus colonization where preoperative carriage risk increases risk of postcardiac surgical wound infection by a factor of ten. And importantly, there's also evidence that the risk of infection varies with the microbial load of colonization. In a prospective study of residents of long-term acute care hospitals, the relative abundance of carbapenemase-producing Klebsiella pneumoniae colonization was predictive of subsequent bacteremia caused by this organism.

Similarly, in stem cell transplantation

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patients, intestinal domination by enterococcus defined as greater than 30 percent of sequences in the microbiota was associated with a ninefold increased risk of VRE bloodstream infection. Next slide.

Another epidemiologic underpinning for decolonization as a resistance prevention strategy is that transmission is an important driver of resistance burden. In other words, transmission between individuals either directly or indirectly increases the number of people who become colonized and infected with resistant organisms. To help make this point, let's review how antibiotic resistance usually emerges in bacteria. Next slide.

Oftentimes when an individual is exposed to an antibiotic, they're already carrying bacterial strains having resistant strains, but those strains may be present in small clinically or epidemiologically insignificant numbers. How did those strains get there in the first place? By one of three mechanisms: one, random genetic mutation; two, through acquisition of resistance genes from other bacteria; or three, through transmission from other

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people or the environment.

The first mechanism, random genetic mutation, is often a very rare event for some of our most prevalent resistance problems and so transmission plays a critical role in determining the ultimate burden of resistance.

Once a resistant strain is present in or on an individual, exposure to antibiotics confers a selective advantage, increasing the proportion and total burden of resistant organisms which increases risk of onward transmission of resistant strains to others and may also increase the risk of horizontal transmission of resistance genes to other bacteria, some of which may already possess characteristics making them quite adept at transmission and causing infection.

An acquisition of resistance genes by such bacteria may result in creation of a new and more dangerous resistant pathogen, one that is highly fit for spread. Next slide.

It is the case that some of our most serious resistance problems have been driven largely

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by transmission of highly fit clonal strains. Some examples of this include MRSA colonial groups USA100 and 300, which account for the lion's share of healthcare- and community-associated MRSA respectively; group ST258 carbapenemase-producing Klebsiella pneumoniae, helping to drive international spread of carbapenem resistance; rapid growth of ESSBL-producing E. coli associated with clonal group ST131; and rapid emergence of ribotype 027 C. difficile. Next slide.

Transmission of highly fit strains may have been a particularly important driver of antimicrobial resistance in healthcare settings, where there exists a confluence of factors that favor transmission of resistant organisms such as high risk patient populations, intense antibiotic use and dense contact networks involving close interaction among patients, healthcare workers, and the environment. Next slide.

This graphic depicts a simple illustration of how burden of colonization in patients may drive transmission. In the pink box, you see a

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colonized patients who can serve as a reservoir of transmission to the healthcare workers who care for them and who in turn can transmit to other patients in their care. The patient can also contaminate the environment, which can also serve as a reservoir of transmission. The thickness of the transmission lines in this graphic denotes the magnitude of transmission risk. Next slide.

Under conditions where the patient's microbial load of colonization is high, there's more shedding and increased risk of downstream transmission. Next slide.

Infection control practices such as hand hygiene, use of gowns and gloves, and environmental cleaning create barriers that reduce the risk of onward transmission, but their effectiveness is not 100 percent. Under conditions of high microbial load colonization and high shedding, there may be substantial residual transmission despite infection control barriers. Next slide.

Under conditions where the microbial load of colonization is low, the same proportional

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decrease in risk attributable to infection control will likely translate into a substantially lower absolute residual risk in comparison to their use of conditions of high colonization burden. Theoretically, therefore, reducing microbial load of colonization may work synergistically with traditional infection control precautions to prevent transmission in healthcare. Now, is there any real world evidence that reducing colonization burden translates into less transmission? Next slide.

In this study, Dr. Weinstein and colleagues examined the effect of daily chlorhexidine bathing of ICU patients on burden to VRE transmission and colonization. After implementing chlorhexidine bathing, they demonstrated reduction of VRE on patients' skin, decreased VRE contamination on environmental surfaces and on the hands of healthcare workers, and most importantly, decreased acquisition of VRE colonization by patients.

You'll see similar data showing the relationship between colonization burden and transmission for other resistant pathogens in

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subsequent talks by Dr. Walters and Dr. Sexton. Next slide.

Prevention of colonization is important intermediate outcome, but is there evidence that decreasing colonization translates into decreased infections? The answer is yes, and quite a bit of it. Here, for example, are six randomized trials all showing significant reductions in infection attributable to decolonization strategies in various patient populations. I'm not going to review these in detail. You'll hear more about some of these in Dr. Ham's talk a little later. Next slide.

It's important to examine more closely the mechanisms of action by which decolonizing agents can provide benefit. First, they can reduce risk of transitioning from colonization to infection in colonized individuals who were treated. We refer to this as direct benefit. Second, they can reduce risk in uncolonized individuals and the surrounding population, even if they are untreated, through decreasing shedding and transmission from the treated colonized individual. We refer to this as indirect

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benefit.

A third mechanism occurs in settings where decolonizing agents are used in all members of a population, regardless of known colonization status, for example, daily chlorhexidine bathing in ICU patients. In this case, the intervention might further reduce risk of acquiring colonization in uncolonized individuals who are treated. Let me give a simple illustration of the concept of indirect benefit of decolonization. Next slide.

Imagine a patient gets admitted to a healthcare facility and is colonized with a resistant pathogen, colonization depicted here by the yellow color. Next slide.

And let's assume colonization progresses to infection in this patient, depicted by the change to red. Next slide.

And that the infection results in death depicted by the X. Next slide.

Let's also assume that before death, the patient served as the reservoir of transmission to two additional patients. Next slide.

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And each of these colonized patients transmitted to two additional patients. Next slide.

And these in turn also transmitted to others. Next slide.

And so on, so that the index patient was the original source of transmission to 30 additional patients. Next slide.

And let's assume that of these 30 additional colonized patients, nine of them progressed to infection, resulting in a total of ten infections, including the index patient. Next slide.

Again, for the purposes of illustration, let's assume the mortality of infection given the decreased effectiveness of existing infection treatment drugs due to resistance is high at 40 percent. Therefore, four of the ten infected patients including our index patient die. How might new treatments have impacted the outcomes here? If the pharmaceutical industry were to produce a novel treatment drug that reduces mortality of infection by half in comparison to existing therapy this would, by current standards, represent a significant advance in

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therapeutic options. In our scenario, using the novel treatment agent -- next slide -- would bring the mortality down to 20 percent, meaning we would have seen only two deaths rather than four.

In other words, two lives were saved by the novel treatment. Note that no infections were prevented. Next slide.

On the other hand -- next slide.

On the other hand, what if the pharmaceutical industry provided a novel and effectively colonizing agent? If such an agent had been used by the index patient at the time of admission -- next slide -- it would have had the direct effect of preventing the index patient from not only becoming infected but also subsequently dying. Next slide.

But in addition, it would have also prevented the index patient from becoming a source of transmission, thereby preventing 30 colonizations, nine infections, and the two deaths that occurred despite use of the new and improved treatment agent. This additional benefit resulting from prevention of

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transmission is again referred to as indirect benefit. Next slide.

These simple graphs summarize and compare the benefit of the two novel agents. Direct benefit is depicted in blue and indirect benefit is depicted in yellow. In the graph on the left, you can see that the decolonizing agent prevented twice as many deaths as the infection treatment agent, and most of that benefit was indirect. From the right, you can see that the novel infection treatment drug prevented no infections while the decolonization agent prevented 10 infections, again mostly attributable to indirect benefit.

Now obviously this is an oversimplified demonstration designed to emphasize the theoretical importance of indirect benefit. Well, what would such benefit look like in real world use? To gain some insight, let me present some evidence from mathematical modeling. Next slide.

These are results from a mathematical transmission model developed by Damon Toth and colleagues at the University of Utah designed to

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quantify the effect of a hypothetical decolonizing agent targeting carriers of carbapenem-resistant Enterobacterales or CRE and long-term acute care hospital in-patients or LTACHs. The model was parameterized rise using a study of Chicago area LTACHs which provided real-world observational data on rates of CRE transmission prevalence, clinical detection, and bloodstream infection rates.

Using this model, they estimated the number of CRE bloodstream infections that would be prevented if an effective decolonizing agent was used for all known CRE carriers as detected through routine clinical culturing. And then they extrapolated to national estimates based on the number of LTACH beds and annual discharges nationally. These findings were based on it a presumed admission prevalence of 1 percent.

The green bar depicts the number of CRE bloodstream infections prevented by direct effect, while the blue bar depicts CRE bloodstream infections prevented when considering both indirect and -- indirect benefit. You can see that the number of BSIs

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prevented increases by an order of magnitude when the indirect effect is considered. Or another way to look at it, studying the benefit of decolonizing agents are likely to be dramatically underestimated if only direct benefit is measured. Next slide.

This graph represents work by Dr. Prabasaj Paul and Hannah Woolford at CDC who modified and extended Dr. Toth's model to include not just LTACHs, but U.S. acute care inpatient facilities and skilled nursing facilities or SNFs. Their model also accounted for interfacility CRE transmission by patient transfer and examined three different decolonization strategies.

Green portions of the bars represent CRE BSIs in LTACHs and ventilator-capable SNFs, while blue represents infections in acute care facilities and non-ventilator capable SNFs. Each bar represents annual national incidents under a specific decolonization strategy. From left, the first bar estimates annual incidents of CRE BSIs if no decolonization therapy is used. The next bar represents incidents of decolonization if it's used --

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in all incidents of CRE BSIs if decolonization is used for all CRE-colonized patients, again as detected through routine clinical cultures in both LTACHs and ventilator SNFs.

The third bar represents incidents when decolonization is used for CRE-colonized patients in all facility types. And the fourth bar represents a strategy similar to the third bar, the exception being that for LTACHs and ventilator SNFs, all residents were screened for CRE colonization, rather than relying on routine clinical cultures to detect carriers, and therefore all CRE-colonized patients were treated in these facilities.

According to the model, this approach would result in prevention of greater than 9,000 CRE bloodstream infections annually in the U.S. compared to baseline, a 64 percent reduction. Note that the model suggests that at steady state a reproductive number or R0 would be reduced to less than one, meaning that CRE transmission and the risk of CRE BSIs would be essentially eliminated. Next slide.

Dr. Paul also calculated the number

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needed to treat with decolonization therapy to prevent a single CRE infection. You can see that the values for the number needed to treat are around one representing substantial public health benefit and return on investment. Next slide.

To summarize, I tried to demonstrate that colonization by antibiotic resistant pathogens increases risk of infection as -- and is an important driver of antibiotic resistance, particularly in healthcare. Therefore, reducing colonization may be a potent antibiotic resistance prevention strategy. Furthermore, because of their potential for indirect benefit, efforts to produce and improve and approve novel safe and effective decolonizing agents are likely to prevent substantially more harm from antibiotic resistance than can be prevented if we focus drug development solely on drugs that treat infections. Next slide.

We're hoping that today's discussion can encourage more research and development for agents designed to reduce or eliminate colonization by pathogens and also spark conversation about a roadmap

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for regulatory approval for such agents. We think there's still a lot of wisdom in the old adage, an ounce of prevention is worth a pound of cure. Thank you for your attention.

DR. HEIDI SMITH: Thank you very much, John. We're going to move on to our next speaker who is Clifford McDonald who's going to be speaking about Decolonizing Approaches: Current State and Future Needs. Dr. McDonald is currently associate director for science in the Division Healthcare Quality Promotion at CDC. He's published extensively in healthcare-associated infections, especially C. difficile infections and antibiotic resistance and has led efforts of his division to explore application of microbiome science to public health. Thank you. Dr. McDonald.

DR. CLIFFORD MCDONALD: Good morning. I will be speaking to you today about decolonizing approaches, including current state and future needs. Next slide, please.

I have no financial disclosures and the findings and conclusions of this presentation are mine

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and do not necessarily represent the official position of the CDC. Also I will be speaking today of some non-FDA approved drugs that are currently under development as well as off-label use of FDA approved drugs. My take home messages are that decolonization and pathogen reduction are already widely used for prevention in some forms of antimicrobial prophylaxis.

Second, we can learn from unfolding failings of antimicrobial prophylaxis. From what we learn, we can propose certain attributes that future decolonization strategies should ideally possess. Current and future products span various compositions and modes of action and there is a central role for the human microbiome in colonization resistance that should be considered in all decolonization and pathogen reduction strategies.

A tolerable safety margin is impacted by local versus systemic body site distribution and -- of a drug and target versus risk-based implementation strategies. Finally, to achieve effectiveness, it is important to tailor the intervention and its timing to the duration and timing of maximum risk of infection.

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Next slide, please.

First, decolonization and pathogen reduction is already widespread in some forms of antimicrobial prophylaxis. When we think of antimicrobial prophylaxis, we often think of surgical antibiotic prophylaxis but in practice it involves any localized or systemic administration of an antimicrobial to prevent infection through a range of mechanisms.

These include decolonization and pathogen reduction but also various combinations of prevention of invasion or translocation and prevention of attachment involved in establishing infection. Next slide, please.

I begin with examples where decolonization and pathogen reduction or pilot pathogen reduction are most clearly their mode of action, as these are also examples of the effectiveness of approach to the point that some are incorporated into evidence-based practice recommendations.

Chief among these is the preoperative

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application of nasal mupirocin to prevent staph aureus infections following cardiac and orthopedic surgery. This appears in WHO guidelines as well as relevant U.S. professional society guidelines. Another is preoperative administration of non-absorbed antimicrobials along with mechanical bowel preparation to prevent surgical infection and anastomotic leaks following bowel surgery. Again, this is recommended in WHO and relevant professional society guidelines.

There are also recommendations to prevent secondary cases of meningococcal disease using oral antibiotics. Finally, another other form of antimicrobial decolonization or pathogen reduction is the use of selective digestive decontamination and oral decontamination to prevent infections and reduce mortality in intensive care unit or ICU patients. This is currently a nationally recommended practice in the Netherlands. Next slide, please.

Here's a diagram that outlines the use of selective digestive decontamination and the types of agents used. These are administered from the first day of admission to an intensive care unit in any

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patient expected to stay longer than two to three days during which they are expected to receive ventilator care. Systemic antibiotics included in the regimen consists most commonly of a third generation cephalosporin continued for four days. The idea behind both the topical and systemic antibiotics is that these regimens have relatively little impact on the largely anaerobic microbiota of the large intestine and oropharynx.

I would refer the audience to the narrative review referenced here to read more about the evolution of this practice. Based upon this review, I have prepared my first two supplementary slides to assist the audience in understanding some of the issues encountered in studying this practice, as well as evidence for the practice from cluster randomized trials. Next slide, please.

The conclusions of the authors of this narrative review is that the practice of selective digestive decontamination is consistently associated with less resistance and improved patient outcomes in settings with low prevalence of antibiotic resistance

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such as the Netherlands. However, in settings with moderate to high resistance such as other parts of Europe, the benefits are less clear.

I would note that the main negative study that led to the second sentence was a multisite European study in which the systemic cephalosporin was not administered over fear that it might drive infections with gram-negative bacteria possessing extended spectrum beta-lactamases which were prevalent in many of the study locations. Again, I refer the audience to my supplementary slides about the measured impacts of this practice on resistance.

There has also been one in vitro study demonstrating the colistin use as part of the decontamination regimen can drive microevolution of resistance. There has only been one study to date of the microbiome of patients receiving these regimens which did, not unexpectedly, demonstrate a degree of microbiome disruption relative to healthy controls. However, the status of microbiome disruption relative to usual ICU care has not been studied.

Before moving to my next slide, I will

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note that my third supplementary slide highlights examples of antimicrobial prophylaxis with currently little role for decolonization and pathogen reduction and ask the question whether these may be missed opportunities for future advanced methods of decolonization and pathogen reduction. Next slide, please.

Let's now turn our attention to two areas where there are unfolding failings of antimicrobial prophylaxis and in which decolonization and pathogen reduction plays a variable role. Both involve the use of fluoroquinolones and are shown on this slide. The first is use of oral systemic fluoroquinolones to prevent infections following transrectal biopsies. The fact that some studies indicate improved prevention with administration beginning one day before the procedure provides some evidence the fluoroquinolone alone acts in part through decolonization and pathogen reduction.

Regardless, there are now recent worldwide increases in breakthrough post-biopsy infections with intestinal colonization by

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fluoroquinolone-resistant gram-negative pathogens increasing the risk of these breakthrough infections. The other unfolding failing after a long period of successful use is the systemic use of fluoroquinolones to prevent bloodstream infections in neutropenic patients.

There are now increasing reports of clusters of breakthrough infections and in subsequent slides I will provide evidence how these reflect the role of decolonization and pathogen reduction as well as how fluoroquinolone were poorly designed for this purpose. Next slide, please.

First, we have heard previously of the phenomenon of intestinal domination when a single species or group of species over grows the microbiome, most commonly that of the lower intestine or gut. Here we see results of a study in which 113 hematopoietic stem cell transplant recipients underwent serial stool sampling and microbiome analysis, associating results of these analyses with various exposures and subsequent bacteremias.

In this study domination was defined by

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greater than 30 percent of the composition of gut microbiota and as highlighted by the red box on the slide, domination by gram-negative pathogens of proteobacteria, but bacteria was a predictor of subsequent gram-negative bacteremia. Although not highlighted, you can also see that enterococcus domination was a predictor for vancomycin-resistant enterococcus or VRE bacteremia. Next slide, please.

Also from the same study, we can see how receipt of fluoroquinolones was normally protective against intestinal domination caused by gram-negative bacteria or proteobacteria with a hazard ratio of 0.09 shown in the right columns. Next slide, please.

Finally, from another study of 234 hematopoietic stem cell transplant recipients, 17 or 31 percent of the 54 who were colonized with fluoroquinolone-resistant Enterobacterales developed gram-negative bloodstream infection despite fluoroquinolone prophylaxis, compared to only two or 1 percent of the 180 who were not so colonized. Next slide, please.

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So in summary, intestinal domination by gram-negative pathogens is associated with subsequent bloodstream infection and fluoroquinolone prophylaxis normally reduces the risk of intestinal domination by gram-negative pathogens and colonization with fluoroquinolone-resistant gram-negative pathogens increases risk for breakthrough infection. Therefore, the protection from fluoroquinolone prophylaxis is mediated at least in part through pathogen reduction and fluoroquinolone resistance leads to breakthrough infections through breakthrough intestinal dominance. Next slide, please.

So what can we learn in here about possibly improved approaches? Fluoroquinolones were developed for short-term treatment of local infection through systemic administration and not specifically for decolonization or pathogen reduction. Some key characteristics make them well suited for the former use and not so well suited for the latter. First, fluoroquinolones are highly absorbed following oral administration and have excellent body site distribution and tissue penetration. Reflecting this

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tissue penetration, fluoroquinolones have increasingly recognized toxicity. Despite their high absorption, they do achieve high fecal levels. However, resistance when it develops commonly leads to relatively high minimum inhibitory concentrations or MICs that likely exceed fecal levels.

Finally, although initially thought to have little impact on anaerobic microbiota and the gut microbiome, the selection of resistance in key anaerobes and microbiome disruption are both now increasingly recognized. Next slide, please.

This brings us to what may be specific attributes that future decolonization should possess. First, direct acting agents such as small molecules should have a narrow microbiological spectrum targeted to specific pathogens or groups of pathogens and limited body site distribution. Together these attributes may improve drug safety and reduce collateral damage to the human microbiome. Examples include non-absorbable narrow-spectrum agents for enteral, topical, or other local applications.

Second, agents and strategies should

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have favorable pharmacokinetics to reduce emergence of resistance through local evolution. For example, applications should achieve high drug levels relative to the minimum inhibitory concentration or even the bactericidal concentration.

Ideally, agents should be unlikely to evoke cross resistance to clinically important antibiotics used for treatment of infection usually through markedly different mechanisms of action. For example, antiseptics are generally less likely to evoke cross resistance to therapeutic antimicrobials, although co-selection may still occur.

We will want to say more about leveraging colonization resistance afforded by the human microbiome, and finally we need to think about the durability of effect beyond duration of application. For example, phage or live biotherapeutics may expend -- extend duration of decolonization or colonization resistance through their replication. Next slide, please.

Current and future product categories are listed here along with some examples. These span

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various compositions and modes of action. Mupirocin is an example of a small molecule agent, as are the agents used for gut decontamination. Bacteriocins are proteins produced by bacteria that inhibit or kill pathogens and along with local application of monoclonal antibodies can be quite narrow in spectrum.

Lysostaphin is an example of a bacteriocin that has been studied over the past 20 years with several notable development advancements, but yet to be made clinically available. Topical antiseptics or decontaminating agents such as alcohol or chlorhexidine are used in combination with other agents to decolonize. There are various drugs under development that act indirectly to decolonize or prevent colonization by protecting the microbiome from antibiotics, for example, an activated charcoal product to absorb antibiotics or beta-lactamase enzyme to destroy antibiotics that may make their way into the GI tract.

In addition, there are microbiome restoratives such as fecal microbiota transplantation or FMT which is currently in clinical use for

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recurrent C. difficile infection under FDA enforcement discretion. However, this enforcement discretion does not extend to FMT use specifically for decolonization or pathogen reduction. Under development are drugs such as pathogen reduced or otherwise processed FMT or derivatives, also more defined microbiota consortia.

Finally, phage is a promising avenue for decolonization given its potential to be relatively narrow spectrum and propagate, possibly extending its duration of action. Next slide, please.

There is a central role for the human microbiome and colonization resistance that should be considered in all decolonization strategies. The microbiome resist colonization by pathogens via several mechanisms shown here, including the direct inhibition via naturally produced molecules such as bacteriocins and metabolites.

Metabolites and protein messaging from the microbiome assist the host by maintaining the mucosal barrier that prevents invasion and participate in cross talk with the host to favorably modulate the host immune system. Finally, the normal microbiome

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utilizes nutrients in the microenvironment, denying the pathogen's use of those same nutrients. Next slide, please.

The powerful effect of the human microbiome in providing colonization resistance may be grasped from early data such as this, comparing patients who had their recurrent Clostridioides difficile infections managed via fecal microbiota transplantation versus usual antibiotics. Though this was a prospective observational study, it was not randomized. However, propensity matching was used to make the cohort more comparable.

As highlighted in the red boxes on this slide, in the 90 days following FMT or antibiotics for management of recurrent C. difficile infections, patients treated with FMT were much less likely to develop bloodstream infections, had shorter hospitalizations, and overall improved survival. Next slide, please.

This suggests that whatever methods are used to decolonize or pathogen reduce, they should either replicate essential components of the natural

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functions of the microbiome or spare, protect, or restore the microbiome. I will further point out that the human microbiome is part of a larger microbial ecology and we at CDC are very aware of this. I encourage the audience to read about this at the link shown to the bottom of this slide and listen for Dr. Cal Ham's comments later this morning about how we have considered this in regard to increasing chlorhexidine use. Next slide, please.

Finally, just a few notes on how a tolerable safety margin may be impacted by local versus systemic body site distribution of a drug and targeted versus risk based implementation strategies. Obviously, local versus systemic body site distribution limits and end-organ exposure to potential toxicities. However, the tradeoff is that the locally acting agent may have a slower onset of action, for example, waiting for GI motility to bring a non-absorbed antibiotic to the active site in the large bowel.

Meanwhile there are targeted versus risk-based strategies to apply decolonization and

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pathogen reduction. Targeted application involves rapid screening for colonization and directing decolonizing and pathogen reduction therapy based on that. The results in -- this results in a generally smaller population being exposed to the decolonizing therapy.

In contrast, risk-based strategies focus on specific patient risk factors to minimize the population being decolonized. While targeted application would appear to be favorable from a risk-benefit standpoint, there can be serious implementation challenges to screening for colonization. Next slide, please.

In addition to tailoring interventions to safety considerations, one needs to tailor to achieve effectiveness. Here, one needs to think about the onset of action in the intervention and will it be fast enough to protect the patient as they experience increased risk. If it is to be a targeted application and the patient has increased risk during the screening process, the turnaround on that screening needs to be also considered.

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Still, some decolonization strategies may have inherently slower onset. For example, when selective digestive decontamination was extended to a multi-country study across Europe, its effectiveness may have been compromised by the removal of the third generation cephalosporin from the regimen that normally protected patients while the oral agents transferred to the gut and began to protect through direct decolonization and pathogen reduction.

Finally, one needs an intervention that is durable for the duration of increased risk and overall we need more durable decolonization strategies. Although not an example of HAI prevention, the main reason that prepartum decolonization versus intrapartum antibiotics was historically not pursued as a means of Group B strep prophylaxis of early onset neonatal bacteremia is because durable decolonization strategies were not available. Next slide, please.

So this concludes my comments to you today. Although many of these take home points can be made into standalone presentations, I've tried to span

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a broad horizon of our current state and future needs in decolonization strategies. Thank you.

DR. HEIDI SMITH: Thank you for that presentation. Our next speaker will be Maroya Walters who is going to be talking about Multidrug-resistant Gram-negative Bacilli, Epidemiology and Decolonization Considerations. Dr. Walters is an epidemiologist and leads the antimicrobial resistance team in the Prevention and Response Branch in the CDC Division of Healthcare Quality Promotion. Her interests include strategies to prevent the spread of multidrug-resistant bacteria, especially carbapenem-resistant gram-negative bacilli, and outbreak response. Dr. Walters, thanks for your presentation.

DR. MAROYA WALTERS: Good morning. Next slide, please.

I am leading off four pathogen focused presentations that will each cover epidemiology, asymptomatic colonization, and decolonization and pathogen reduction approaches for an organism or group of organisms. Before delving into the details of multidrug-resistant gram-negative bacilli, I want to

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emphasize key areas of need for prevention. These include developing novel approaches for decolonization and pathogen reduction, primarily focusing on the gastrointestinal tract but potentially including other sites and high risk population, and symptomatic evaluation of these approaches to understand their impact on colonization, infection, and transmission.

Among decolonization and source control measures currently under investigation, the heterogeneity and how decolonization approaches are assessed and in what populations, the use of different endpoints to establish decolonization, and the lack of control groups in some studies compromises our ability to evaluate these approaches and move forward. Next slide. Next slide.

Gram-negative bacilli encompass a large number of organisms that cause a diverse array of infection. They are responsible for approximately one-third of all healthcare-associated infections reported to the national Healthcare Safety Network. Among these, most infections are associated with Enterobacterales species and the lactose non-

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fermenters, pseudomonas and acinetobacter. Next slide.

Today, I will focus on the four healthcare-associated multidrug-resistant gram-negative bacilli listed by CDC as urgent or serious threats. These are carbapenem-resistant and extended-spectrum beta-lactamase producing Enterobacterales which are enteric organisms and multidrug-resistant Pseudomonas aeruginosa and carbapenem-resistant Acinetobacter, which are non-enteric organisms.

I want to note that Enterobacterales is a taxonomic order that represents over 70 different genera. Some of the genera most often identified in clinical microbiology laboratories are listed on this slide. Next slide.

And although they represent a diversity of organisms, these MDR gram-negative bacilli have several common characteristics. They are opportunistic pathogens that can colonize multiple mucosal surfaces such as the gastrointestinal tract, lung, and wound, contributing to the variety of infections with which they are associated. In

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healthcare settings, these are transmitted by a direct and indirect contact with infected or colonized individuals or the contaminated healthcare environment. And finally, horizontal transfer of resistance elements plays an important role in facilitating spread of these organisms. Next slide.

There are also important epidemiological differences among these organisms, including between ESBL producing and carbapenem resistant Enterobacterales. ESBLs are endemic in the United States and approximately half of cases occur in community dwellers who have not had recent hospitalization, long-term care stays, or invasive procedures. Risk factors in the community include recent antibiotic therapy and international travel, and food and water are increasingly recognized reservoirs.

In contrast CRE are still emerging in the United States. CRE primarily occur in patients who have extensive healthcare exposures. Indwelling devices, severe underlying illness, long-term care facility admission, and antibiotic exposure are all

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associated with CRE acquisition. Patient to patient transmission accounts for the majority of CRE acquisitions, although environmental reservoirs such as healthcare facility wastewater plumbing also contribute. Next slide.

A distinguishing feature of MDR-P. aeruginosa and carbapenem-resistant acinetobacter is the ability to form biofilm, which contributes to colonization of indwelling medical devices, persistent wound and respiratory tract colonization, and the contamination of shared medical equipment. Risk factors are similar to those for CRE.

Infections occur almost exclusively in patients with substantial healthcare exposure, including in patients with chronic underlying conditions resulting in dysbiosis, such as cystic fibrosis. And although I won't address cystic fibrosis patients specifically, I want to note that they are an important group to include when discussing P. aeruginosa colonization and infection, as shown on my supplementary side, and we will hear from Dr. Whitney Brown of the CF Foundation later this morning.

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Intrinsic resistance of these non-enteric gram-negatives combined with the remarkable ability to acquire new resistance mechanisms means that there are limited treatment options despite the many new antibiotics for gram-negatives that have recently come to market. Next slide.

Overall, how common are MDR gram-negative bacilli? This graph shows the number of clinical cultures with MDR gram-negative identified in hospitalized patients in 2019 and the 90-day attributable mortality. Case numbers vary substantially from 6,000 cases of carbapenem-resistant acinetobacter to over 194,000 cases of ESBL producing Enterobacterales.

The number of cases should not be confused with relative importance as these organisms are in different stages of emergence and the carbapenem-resistant gram-negatives are associated with limited treatment options and higher mortality relative to the total number of cases than ESBLs. Also, these cases are just the tip of the iceberg because most individuals with gram-negative bacilli

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are colonized, not infected. Next slide.

Carbapenem-resistant gram-negatives have been the focus of targeted public health detection, response, and prevention efforts in healthcare settings. Perhaps in part due to these efforts, during 2017 to 2019, cases of carbapenem-resistant acinetobacter among hospitalized patients remained steady while cases of CRE and MGR-P. aeruginosa declined.

In contrast, ESBL-producing Enterobacterales increased, illustrating challenges in controlling spread once these pathogens move into community settings. Since ESBLs and CRE encompass the same organisms with spread driven by mobile resistance elements, the trajectory of ESBL Enterobacterales could presage the future for CRE in the absence of new approaches to prevent transmission. Next slide.

And this is especially important in light of case trajectories during the COVID-19 pandemic during which we observed increases in carbapenem-resistant acinetobacter cases and halting of prior declines for CRE and MDR-P. aeruginosa. Next

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slide.

Now let's look more closely at the characteristics of colonization. The gastrointestinal tract is the primary and Enterobacterales colonization site, although MDR Enterobacterales can also be found elsewhere on the body of colonized patients including on the skin. Estimates for the duration of colonization vary. Factors that contribute to this variability include differences in patient populations, decolonization criteria, and laboratory testing approaches.

Despite the heterogeneity in the exact estimate, colonization is generally prolonged, with one meta analysis estimating that 35 percent of colonized individuals remained colonized with ESBL Enterobacterales or CRE one year after initial detection. Median time to decolonization or negative culture in three exemplar studies ranged from 144 to 295 days. In general, community dwellers are found to be colonized at higher rates and more rapidly than those admitted to healthcare setting, possibly owing to more rapid restoration of a healthy microbiome or

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reduced risk of becoming recolonized.

And some strains and organisms are associated with increased duration of colonization, including certain strains associated with epidemic spread such as ESBL producing ST131 E. coli. Next slide.

Colonization with MDR Enterobacterales is strongly associated with increased risk of infection with the highest risk among intensive care unit patients. In studies of ICU patients, those who were CRE colonized at admission had two- to tenfold higher risk of infection than those who were not colonized.

In another study, 95 percent of ESBL Enterobacterales infections in ICU patients occurred in those with a history of colonization. The risk of CRE infection among colonized hospitalized patients is substantial. In a meta analysis, 16.5 percent of CRE colonized patients were estimated to develop subsequent CRE infection. The mortality in patients who develop infection is over 30 percent. As Dr. Jernigan described earlier, not just the presence of

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the organism, but the abundance plays a role in pathogenesis.

Among long-term acute care hospital patients colonized with KPP producing Klebsiella pneumoniae, a type of CRE, higher abundance in the gastrointestinal tract was independently associated with increased risk of bacteremia with this organism, reinforcing the concept that reducing organism burden even without complete eradication has potential benefit. Next slide.

In contract to MDR Enterobacterales, there is no gold standard screening site for MDR-P. aeruginosa or carbapenem-resistant acinetobacter. These bacteria can colonize the skin, upper and lower respiratory tract, wounds, and digestive tract. The figure illustrates the wide range of reported sensitivities for detection of carbapenem-resistant A. baumannii at different body sites.

Similar to MDR Enterobacterales, colonization can be prolonged. One study found that 17 percent of patients with a prior carbapenem-resistant A. baumannii clinical culture remained

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colonized after six months, although as the author stated, this is likely an underestimate due to the low sensitivity of screening methods used.

Among hospitalized kidney transplant patients, carbapenem-resistant P. aeruginosa colonization persisted for a median 42 days. Next slide.

Like for MDR Enterobacterales, colonization with acinetobacter and pseudomonas typically proceeds infections with the same strain with higher risk of infection and higher acuity patients. ICU patients with carbapenem-resistant A. baumannii bloodstream infections were colonized with the same strain prior to developing infections, and among patients colonized with P. aeruginosa at admission, 23 to 43 percent developed infection during their hospitalization and their risk of having a clinical culture with P. aeruginosa was six times higher than those who were not colonized at admission. Next slide.

Colonization is not only a risk for infection in the colonized individual, but a risk for

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transmission to other patients, as Dr. Jernigan so nicely illustrated. In a study of long-term acute care hospitals in Chicago, which had achieved a greater than 30 percent reduction in KPC-producing Klebsiella pneumoniae prevalence and infections after implementing a bundle of prevention intervention that included active surveillance, daily chlorhexidine bathing, contact isolation, and healthcare personnel education, a 1 percent increase in colonization pressure was associated with a 2 percent increase in acquisition risk.

The figure shows that if colonization pressure increases, so do the odds of KPC acquisition, even in settings where intensive infection control measures have been implemented. Next slide.

These characteristics can lead to very high prevalence of patients colonized with multidrug-resistant organisms, especially in high acuity, long-term care settings. This is a schematic of the ventilator unit of a skilled nursing facility in which each circle is a resident. The purple circles represent patients colonized only with the yeast

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Candida auris, which Dr. Sexton will cover later this morning, and the other colors represent residents colonized with different combinations of carbapenem-resistant organisms, some of whom also carry C. auris.

Note the high prevalence which leads to sustained transmission and creates a reservoir that, through patient sharing, can amplify spread throughout healthcare facilities in a region. Next slide.

Multiple products have been assessed for pathogen reduction or decolonization of MDR gram-negative bacilli and I have attempted to summarize them in this table. However, there are currently no FDA approved decolonization agents for these organisms. Skin antisepsis with chlorhexidine, abbreviated CHG on the slide, has been found to reduce skin concentrations of CRE and may also reduce the skin burden of carbapenem-resistant acinetobacter, which theoretically can prevent infections and reduce transmission.

In the next presentation Dr. Ham will highlight the success of chlorhexidine bathing for preventing gram-positive infection. However, it's

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important to note that substantially higher concentrations of chlorhexidine are needed to reduce the growth of gram-negatives compared to gram-positives, and these may be difficult to achieve in clinical practice.

This may be in part why in two meta analyses of chlorhexidine bathing in ICU patients, this practice was not found to impact gram-negative infection. The use of non-absorbable oral antibiotics for selective digestive decontamination during periods when patients are at high risk of infection such as in the ICU was described by Dr. McDonald. Across multiple randomized controlled trials, SDD reduced the gastrointestinal carriage rate of ESBL Enterobacterales, CRE, and carbapenem-resistant acinetobacter.

The effect is temporary, suggesting that this may serve more to suppress these organisms than to eliminate them from the gut. SDD fails to meet several of the specific attributes of a decolonizing agent through its use of therapeutic agents, typically polymyxins and aminoglycosides, with

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the potential to both evoke resistance to these therapies and to disrupt the intestinal microbiome.

The next two approaches, probiotics and fecal microbiota transplant are intestinal microbiome restoratives. By restoring the natural colonization resistance of a healthy microbiome, these modalities could potentially protect against colonization with MDR gram-negatives or function as decolonization or pathogen reduction agents.

Among two randomized controlled trials in which a probiotic was administered to hospitalized patients, MDR Enterobacterales acquisition and loss were not altered. Similarly, randomized controlled trials to assess decolonization of MDR Enterobacterales carriers did not show reductions in carriage after probiotic treatment.

The current evidence for fecal microbiota transplant assessed across multiple case studies and primarily uncontrolled case series is more optimistic. A meta analysis of three studies estimated that one month post fecal microbiota transplant, 46 percent of patients decolonized

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antibiotic resistant organisms which included both VRE and MDR Enterobacterales. A small number of reports in case series have documented decolonization of carbapenem-resistant P. aeruginosa and acinetobacter following FMT, suggesting that this strategy may not be limited to the enteric gram-negatives.

However, more well controlled studies including randomized controlled trial with clearly defined endpoints for decolonization or pathogen reduction are needed. Finally, the literature contains several case reports of successful treatment of acinetobacter, P. aeruginosa, and Enterobacterales infections with bacteriophage under compassionate use, including cure of wound infections and eradication of P. aeruginosa from cystic fibrosis patient lungs. This may be a promising approach for decolonization due to the narrow spectrum and durability of phage action. Next slide.

So where do we go from here? First, let's recap where we are. These are highly resistant organisms with limited treatment options. Colonization increases the risk of infection and

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creates a reservoir for transmission to other patients. Current infection control methods slow but do not stop transmission, as illustrated in our LTACH example.

Therefore, MDR gram-negative decolonization or pathogen reduction has the potential to positively impact both the individual and the population by reducing infections and preventing transmission, but there are currently no FDA-approved agents for these purposes.

Hence there is a critical need for novel approaches that satisfy the specific attributes of decolonization and pathogen reduction agents and to systematically evaluate these approaches including randomized control trials in order to understand their effect on colonization, infection, and transmission. Thank you.

DR. HEIDI SMITH: Thank you for that presentation. And so we're going to move on to our last presentation of the first half of this session. Cal Ham is going to be speaking on Gram Positives: Staph aureus and Vancomycin-resistant Enterococci.

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Dr. Ham is the deputy lead of the Antimicrobial Resistance Team in the Division of Healthcare Quality Promotion at CDC. He serves there as a subject matter expert on antibiotic-resistant gram-positive bacteria. He oversees a broad portfolio of projects focused on the prevention of antimicrobial-resistant pathogens in the healthcare setting. On to your presentation, Dr. Ham. Thanks.

DR. CAL HAM: Good morning, everyone. Thank you very much for that introduction and I am pleased to be speaking with you all today about decolonization and pathogen reduction for two important gram-positive bacteria, Staphylococcus aureus and vancomycin-resistant Enterococci. I have no financial disclosures to report.

So as with the previous talk, I will begin today with the description of key areas of need for prevention. For Staphylococcus aureus, decolonization and pathogen reduction strategies have proven effective as demonstrated by a number of large clinical trials; however, despite these excesses, there remains work to be done first in evaluating and

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expanding decolonization and pathogen reduction strategies for staph aureus to additional settings and high risk populations, and second in the development of additional products and novel approaches that can be incorporated into our prevention arsenal.

In contrast, while we have seen great successes in decolonization and pathogen reduction for staph aureus, for VRE there are currently no approved decolonization products. As such, there is a great need to develop and investigate promising and novel agents with the potential for large impacts on patient outcomes. Next slide, please. And next slide, please.

So staph aureus is a common cause of infections in both community and healthcare settings. We categorize staph aureus based on resistance patterns into two types: methicillin susceptible staph aureus or MSSA and methicillin resistant staph aureus or MRSA, which is commonly resistant to many commonly used first line antibiotics.

When MRSA first emerged, it was primarily identified in patients with healthcare

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exposures. However, transmission of a highly fit clone, USA300 in the community subsequently led to large increases in infections among those without healthcare-related risk factors in the United States.

Staph aureus also remains a major cause of healthcare-associated infections, with it being the number one cause of surgical site infections and overall the second most common cause of HAIs in hospitals. Next slide, please.

Diving a little bit deeper into the epidemiology of MRSA, in 2020 there were an estimated 279,300 MRSA infections among hospitalized patients in the United States, representing a significant burden of disease. And as with other HAIs, the COVID-19 pandemic had a major impact on hospital-onset MRSA infections.

This table is taken from a recent publication and shows national estimates of hospital onset MRSA bacteremia by quarter in 2020 compared to respective quarters in 2019. You can see that in quarter one 2020, hospital onset MRSA bacteremia estimates were down 7.2 percent compared to quarter

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one 2019.

However, this dramatically changed beginning in quarter two 2020 with increases noted in each subsequent quarter compared to their respective 2019 quarters, highlighting the need for continued prevention efforts to combat the increases we have seen in these invasive infections. Next slide, please.

Continuing with some background information, staph aureus is transmitted by direct or indirect contact with infected or colonized individuals or contaminated surfaces. The primary site of colonization is the nares, but it can also colonize other anatomic sites including the axilla, groin, perineum and pharynx.

It is estimated that approximately one-third of the population is colonized with staph aureus and about 1 percent with MRSA; although, this MRSA estimate is based on older data and may be higher now, particularly in certain high risk groups such as long-term care facility residents, healthcare personnel, and individuals with extensive healthcare exposures.

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The duration of colonization by MRSA is highly variable, but can be prolonged. Reports in the literature range from weeks to years; however, one systematic review that I reference here reported a median duration of MRSA colonization of 88 weeks.

And finally, as has been mentioned in previous talks, colonization is a driver of transmission but also increases the risk of developing an infection. In fact, among hospitalized patients who are newly colonized with MRSA, about 15 percent will progress to clinical infection. Next slide, please.

Next, I'll provide some background information on VRE which like staph aureus is a common cause of HAIs. In 2020, there were an estimated 50,300 infections caused by VRE among hospitalized patients in the United States. VRE is also spread by direct or indirect contact with infected or colonized individuals or contaminated surfaces; however, I do want to highlight that environmental contamination plays a much greater role in VRE transmission than for staph aureus. Next slide, please.

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Unlike staph aureus, the primary site of VRE colonization is the gastrointestinal tract and it can occasionally colonize the urinary tract. VRE colonization among hospitalized patients is common and one meta analysis found that the prevalence of colonization at time of admission to an ICU was 12.3 percent among U.S. patients.

Similar to MRSA, the duration of colonization for VRE is highly variable but ranges from weeks to years with a median of 26 weeks. And risk factors include prolonged healthcare exposures, invasive devices, antibiotic receipt, and long-term care residence.

As with MRSA, colonization by VRE can drive transmission but also increases the risk of developing an infection. Certain groups at high risk for progression to clinical infection include cancer patients where an estimated one out of eight who are colonized go on to develop a VRE bloodstream infection, and ICU patients where rates of progression to clinical infection may also be very high. Next slide, please. And next slide, please.

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So for MRSA, we are fortunate to have a number of different decolonization and pathogen reduction agents available. Decolonization or pathogen reduction is typically done using an intranasal anti-staphylococcal agent in combination with a topical antiseptic. For intranasal agents, mupirocin, which is an antibiotic, has been most commonly investigated, but there is also iodophor or povidone iodine and alcohol-based agents that have been employed.

For topical antiseptics, chlorhexidine gluconate is the most commonly used and is applied directly to a patient's skin. I did want to note that a mupirocin and chlorhexidine decolonization regimen has been shown to be superior to an iodophor chlorhexidine based regimen for staph aureus prevention based on results from the Swap Out Trial.

And while there have been reports in mupirocin resistance in the literature which bears careful monitoring, no significant increases in mupirocin resistance were observed in a large clinical trial for decolonization, the reduce MRSA trial, which

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I'll talk about more in just a minute.

We have also investigated chlorhexidine resistance in collaboration with academic partners and in a convenience sample of just over 500 antibiotic-resistant isolates, we did not observe increases in chlorhexidine MICs over time from 2005 to 2019.

In a separate evaluation at healthcare facilities with longstanding chlorhexidine patient bathing, no increases in chlorhexidine nonsusceptibility or deleterious changes to microbial ecology were identified in the chlorhexidine bathing period compared to the pre-chlorhexidine bathing period.

Now the existing intranasal agents listed on the slide have a broad spectrum of activity which can affect the entire nasal microbiota, but are there ways that we can be more targeted with nasal decolonization? One potential class of decolonizing agents that are often narrow spectrum are bacteriocins which are antibacterial peptides that are produced by competing bacteria, including in the nears.

One of these, lysostaphin, targets

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staphylococcus species including staph aureus and has shown promise in animal models. Other approaches such as phage therapy and monoclonal antibodies targeting staphylococcus protein A also show promise and have narrow spectrum activity that is likely to have minimal impact on the nasal microbiota.

In addition, further study of the nasal microbiome itself and how other bacteria compete with staph aureus in the nares may yield additional decolonization targets. Next slide, please.

So next I'm going to spend a few minutes talking about the evidence supporting decolonization and pathogen reduction for staph aureus to give you a sense of how successful these approaches have been. One of the seminal trials that I'll go into a bit of detail on is to Reduce MRSA Trial and you'll hear more from the study's lead author Dr. Susan Huang later today.

This study was supported by CDCs Prevention Epicenters and was a cluster randomized trial of 74 adult ICUs that involved three arms: Arm 1, which is what I'll call the routine care arm where

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patients were screened on admission to ICUs and MRSA carriers were isolated; Arm 2, which was a which was a targeted decolonization arm where they screened patients on admission, isolated MRSA carriers, and decolonized those who were MRSA positive with intranasal mupirocin and chlorhexidine bathing; and finally Arm 3 or the universal decolonization arm where there was no screening on admission, but rather, they decolonized all ICU patients with intranasal mupirocin and chlorhexidine bathing as well as isolating previously known in MRSA carriers.

It is important to note that practices in Arm 1 where the standard of care during the baseline period for all arms and therefore results from this arm are an indication of the secular trend. Next slide, please.

Now, getting to the results which are presented as reductions in outcomes observed during the intervention period relative to the baseline period. Statistically significant reductions are noted by an asterisk. You can see that for the routine care arm, there were no significant reductions

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in MRSA clinical cultures or all cause bloodstream infections. However, for the targeted decolonization arm, there was a 25 percent reduction in MRSA clinical cultures and a 22 percent reduction in all cause bloodstream infections, both of which were statistically significant.

And for the universal decolonization arm, there was an even greater impact with a 37 percent reduction in MRSA clinical cultures and a 44 percent reduction in all cause bloodstream infections, both of which were statistically significant. These large reductions, particularly those in the universal arm are truly remarkable and demonstrate that decolonization is one of the most effective prevention tools we have available for staph aureus. Next slide, please.

Now, in addition to REDUCE MRSA, there are several other studies which have evaluated the impact of decolonization and pathogen reduction interventions for staph aureus in various patient populations and in the next two slides, I'll summarize some of the key findings. While I can't discuss each

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of these in detail, the main takeaway I want you to have is that these interventions have proven successful in reducing infections across a number of different populations.

These included hospitalized patients outside the ICU with indwelling devices, as shown in the ABATE Infection Trial, MRSA carriers following hospital discharge from Project CLEAR, nursing home residents in the Protect Trial -- I've included some updated results from that trial here -- surgical patients as seen in studies from Bode et al. and continuing to the next slide, the MARS Study and STOP SSI, and finally neonatal ICU patients.

Again, the results from these studies as well as several others, point to how impactful decolonization and pathogen reduction strategies for staph aureus can be, particularly for high risk patients during high risk periods, such as during an ICU admission, when indwelling devices are present, or when undergoing high risk surgeries.

They have resulted in national recommendations from both CDC and the Society for

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Healthcare Epidemiology of America or SHEA, and these strategies have been widely implemented in acute care hospitals with 37 percent of U.S. hospitals in 2021 reporting routine use of an intranasal anti-staphylococcal agent in combination with chlorhexidine bathing. Next slied, please.

Now, for VRE, we have a very different story. As I mentioned earlier, there are currently no approved products for VRE decolonization. Now, chlorhexidine bathing can be effective for pathogen reduction, but will not impact colonization of the gastrointestinal tract. Several other approaches have been investigated and generally fall into the categories of antibiotics, repurposing of other drugs with activity against VRE, gut microbiome-modifying therapies, or combination approaches.

In general, these have been small case series or trials that have yielded mixed results, had limited follow-up time, and commonly reported colonization rebound. Next slide, please.

Now, on the next two slides, I'll highlight just a few findings from the literature for

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these different approaches. First, the use of antibiotics for VRE decolonization has shown mixed results with reports of poor tolerance and gut microbiome disruption. Oral bacitracin is one of the more commonly investigated and one review article reported here -- sorry -- reported between 43 and 100 percent initial clearance. However, only 33 to 53 percent of individuals remained decolonized at three weeks.

Another antibiotic, rampolanin, was investigated in a small randomized control trial with 68 participants which showed 85 percent clearance at day seven in the treatment arms compared to zero present in the placebo arm. However, there were no significant differences between treatment and placebo arms at day 21.

In terms of repurposing other drugs with activity against VRE, ebselen, a synthetic organoselenium compound, has been demonstrated to have potent activity against enterococcus in vitro, in a mouse model reduced VRE fecal burden by 99 percent. However, clinical trials are still needed to determine

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its effectiveness. Next slide, please.

Next, it is known that certain commensal bacteria inhibit VRE growth in the GI tract, such as Barnesiella species which prevent intestinal domination by VRE and may reduce the risk of subsequent infection. As such, probiotics have been investigated for MDRO decolonization including for VRE.

These studies have shown mixed results and I'll highlight one small randomized control trial assessing VRE clearance following the use of Lactobacillus rhamnosus GG, which showed 100 percent clearance at four weeks in the treatment arm compared to just 8 percent clearance in the control arm. I will however note that another recently published study showed no effect of Lactobacillus rhamnosus on VRE clearance.

Finally, fecal microbiota transplantation or FMT is a promising new approach that may prove effective. However, as with other approaches to VRE decolonization, many reports on FMT have been case series and have shown mixed results.

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One that I'll highlight here came from France where they successfully decolonized seven out of eight carriers during a hospital outbreak of VRE. Next slide, please.

So to summarize, decolonization and pathogen reduction for MRSA carriers has proven successful with several large trials among different populations demonstrating effectiveness which have resulted in national recommendations. Universal approaches such as universal decolonization of ICU patients as was done in the REDUCE MRSA Trial also have the potential to impact MSSA infections as well. These decolonization and pathogen reduction strategies play a major role in the prevention of staph aureus infections.

However, as I pointed out earlier, we still have more work to do both in terms of expanding the use of these in populations where they have proven to be effective, but also in evaluating their impact in other high risk populations or settings. There is also the need to investigate the effectiveness of other agents for staph aureus decolonization, and

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pathogen reduction and some promising new approaches including bacteriocins, phage therapy, and the use of monoclonal antibodies may add additional tools to our prevention arsenal. Next slide, please.

For VRE, there remains a major need for effective decolonization and pathogen reduction regimens. While several strategies have been investigated with mixed results, we need a more systematic approach and larger clinical trials to determine the effectiveness of these agents as well as the development and evaluation of other novel products.

Given the burden of VRE infections among hospitalized patients, the development of effective decolonization and pathogen reduction regimens truly has the potential to greatly impact patient outcomes in the United States. Next slide, please.

Thank you very much, and I will turn it back over to the moderators.

DR. HEIDI SMITH: Thank you very much, Dr. Ham, for that presentation. And I want to thank

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all the speakers for the first half of session one for some great presentations and also for staying on schedule. So we are on time to take a break. We will be taking a break now and we'll be back at 10:25 for the second half of session one. Thanks very much and see you then.

(Break)

TIMOTHY BENSMAN: Welcome back everyone. My name is Tim Bensman from FDA and I'll be moderating the second half of the morning session.

We're going to begin with Dr. Joe Sexton who will present on the topic of Candida auris colonization and the implications for public health. Dr. Sexton is a microbiologist and a team lead for the Mycotic Disease Branch Laboratory at CDC. Dr. Sexton has specific subject matter expertise in the detection and control of Candida auris including diagnostics, colonization, transmission, and environmental control. Dr. Sexton, the floor is yours.

DR. JOE SEXTON: Good morning, everyone. Thank you so much for tuning into this talk and workshop. My name is Joe Sexton and I'm the team

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lead for the Mycotic Diseases Branch Laboratory at CDC. I'm really grateful to be here today and have fungi be included in this important conversation.

Like many bacterial pathogens, we're also really concerned about increasing antimicrobial resistance in fungi and healthcare-associated infections. Today, I'm going to talk to you about Candida auris, an emerging fungal pathogen of increasing public health concern. Next slide, please.

Candida auris was first reported in 2009 but has rapidly spread across the globe and USA. Using whole genome sequencing, we've learned that this is not simply recent detection, but is true emergence and essentially the spread of just a few highly clonal groups or clades. Unlike most fungal pathogens, Candida auris has proven to be unique in its ability to heavily colonize patients' skin and cause outbreaks in healthcare settings that are hard to control.

To date, there are no decolonization or pathogen reduction strategies for Candida auris. In 2019, Candida auris was identified as an urgent threat in CDC's 2019 AR Threat Report. Next slide, please.

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I'd like to highlight that much of what we know about Candida auris right now in the United States is thanks to the AR Lab Network, seven highly specialized public health laboratories who have the unique capacity to provide C. auris colonization screening which is performed by testing ESwabs collected from the axilla, groin, and sometimes interior nares. The AR Lab Network also performs antifungal susceptibility testing and plays an important role in helping us track AR. Next slide, please.

So why are we concerned about Candida auris? I'm going to go through three main reasons. First is antimicrobial resistance, high rates of antimicrobial resistance, and for a little bit of context I think it's important to appreciate that because fungi are eukaryotic organisms like ourselves, it is challenging to find unique drug targets that can hurt the fungal pathogen without having side effects on us. And for this reason, we really just don't have a lot of antifungals to work with in the beginning and that really makes antifungal resistance highly

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concerning to us.

Just to paint a picture of what we're seeing with Candida auris, we're seeing that over 80 percent of isolates are resistant to one class of antifungal. Over 25 percent of isolates in the United States are resistant to two classes and we're really concerned to now see isolates popping up that are resistant to all three classes of antifungals that are currently available.

Colonization also amplifies the problem. We're learning that 5 to 10 percent of colonized patients go on to develop invasive infections and of those we're seeing over 45 percent mortality within the first 30 days. Candida auris also causes large outbreaks in healthcare settings that are hard to control and we see colonization prevalence go very high. In some cases, it can -- in some units it can be equal to or even greater than 70 percent of the patients are colonized by Candida auris. Next slide, please.

Unfortunately, Candida auris cases are increasing. This figure shows case counts from data

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generated by the AR Lab Network as well as other sources showing colonization screening cases in green and the clinical cases in blue. I'd like to draw your attention to early 2020 that coincides with the start of the COVID-19 pandemic. As you can see, cases have increased substantially during the pandemic. The reasons for this are not fully understood, but are likely related to increased patient movement during the pandemic as well as other logistical challenges experienced by healthcare facilities such as PPE shortages, turnovers, and other challenges just doing the work that they're trying to do. Next slide, please.

So who gets colonized by Candida auris? Known risk factors are actually pretty similar to other MDROs, things like mechanical ventilation and recent exposure to prior acute healthcare. Antibiotic exposure is also a risk factor as well as systemic fluconazole, a commonly used antifungal that C. auris is typically resistant to. Next slide, please.

It's important to highlight that providing healthcare for patients colonized with

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Candida auris is not easy under even normal circumstances. Caring for colonized patients requires increased resources to adhere to transmission based precautions, enhance communication across units and between other facilities, and investing in enhanced IPC practices across the board.

One example includes special attention to disinfectants. We learned early on that many hospital disinfectants with general fungicidal claims are often not effective against Candida auris. This prompted a collaborative effort between CDC and EPA to generate additional data and clarified guidance. This resulted in the release of List P which is an easily referenceable list of disinfectant products that have met EPA's five log reduction performance thresholds for Candida auris. We often get the question, how do we de colonize patients.

It's often dissatisfying to have to communicate that there's really not a lot of options right now, and I think that one of the things that we're concerned about is that we're hearing from healthcare facilities that they're struggling to

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transfer colonized patients out of their unit to the appropriate level of care because some facilities and units will not accept patients known to be colonized by Candida auris. This means some patients are getting stuck at the incorrect level of care, in some cases for prolonged periods of time. Next slide, please.

So what do we know, what tools do we have? I think this is a good opportunity to communicate something a little different between Candida auris and some of the other pathogens we're hearing about, simply because Candida auris is so new. We still have a lot to learn. We don't have a large body of literature to reference, but we have learned certain things that I think are relevant and helpful to this conversation.

One thing we've learned is that environmental contamination can be extensive in the healthcare environment around colonized patients and C. auris can persist on inanimate surfaces for at least weeks. So let's talk a little bit about what we know about Candida auris colonization and how that

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relates to environmental contamination and subsequent transmission. Next slide, please.

First we and others have noted very high concentrations of Candida auris in the swabs we've received for colonization screening. We're talking about millions and even tens of millions of viable cells in a single colonization swab. For those who can't see the Y axis clearly, this figure is in a logarithmic scale going up to 10 to the ninth CFUs per swab. This was surprising to our lab. We actually had to continually revise our laboratory methods to incorporate additional serial dilutions to finally get countable colonies. Next slide, please.

And perhaps not surprisingly, we've also observed that patients with more Candida auris on their skin also have more Candida auris in their environment. Here on the left, you can see a look at environmental contamination on the Y axis plotted against skin colonization burden on the X axis, showing the positive relationship between those two variables.

On the right, you can see individual

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patients organized along the X axis and the concentration of C. auris detected on their left and right handrails of their bed with a horizontal line, showing the average between those two values. What you can see is that the left and right handrails for a given patient have remarkably similar levels of Candida auris contamination, again indicating a common source from the patient shedding to the environment.

So we know that colonized patients can serve as a reservoir and contribute to environmental contamination in the healthcare setting. Next slide, please.

So what else have we learned about Candida auris colonization? This figure highlights a study looking more comprehensively at what body sites can be colonized in a cohort of 57 residents at a ventilated skilled nursing facility that was previously known to have high Candida auris colonization prevalence. This study demonstrated C. auris can colonize many body sites, literally from head to toe.

In particular, the high frequency of C.

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auris colonization in the interior nares observed in this study and corroborated by others, emphasizes the importance of considering the interior nares in any strategy intended to decolonize or reduce pathogen burden. Next slide, please.

One interesting observation in the same cohort of patients, the patients who were not colonized by Candida auris tended to have mycobiome is dominated by Malassezia. Malassezia is another yeast species that is generally thought to be a part of a normal healthy mycobiome. In contrast, in colonized patients, C. auris was really dominating the mycobiome and we saw very little Malassezia.

We certainly have a lot more to learn about what a healthy fungal mycobiome looks like, but these observations at minimum suggest further investigation is warranted and additional insights would be relevant to considerations about how to decolonize or reduce pathogen burden for Candida auris. Thank you.

Unfortunately Candida or is colonization appears to last a very long time and may

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be indefinite without some kind of intervention. To date, there are some patients that have been tracked being colonized consistently for over four years now. It probably can go longer, but this is the longest that we've been able to track people to date. Thank you.

So let's talk a little bit about CHG, chlorhexidine, because again, we're still -- there's still a lot more data to have, but there are patients who are colonized with Candida auris that are receiving CHG bathing as a part of care for other MRDOs or other IPC interventions. However, we don't have a lot of data that speaks to its efficacy against Candida auris specifically.

In this work, CHG concentrations were measured on patient skin and correlated with their colonization status. Although colonization was less common when CHG levels were greater than 625 micrograms per mil, this concentration was rarely observed, suggesting it can be difficult to achieve necessary CHG concentrations in practice. And of course CHG bathing would not be expected to impact

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Candida auris populations in the interior nares. Next slide, please.

I'd also like to highlight that there is some very interesting work happening right now with mouse models and other new model systems including pig skin and other artificial models. This field is still young, but I think it's already producing interesting results. One study by Julie Segre's group shown on the left indicated C. auris may be able to colonize even the base of the hair follicles, which again, is relevant to considerations of what it would take technically to access Candida auris to effectively decolonize or reduce burden.

The figure on the right shows additional data from Mahmoud Ghannoum's group at Case Western demonstrating that they were successful at achieving a stable colonization model and observed pathogen reduction with an antifungal cream. I think just highlighting that they were able to achieve stable colonization is worth noting because that's been a practical challenge for several groups establishing these models.

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Others are also doing really interesting work in this area, so this slide isn't necessarily intended to be comprehensive, but I do want to highlight while both of these studies were done very well in independence, just to point out that they did use different mouse models and for that it's hard to kind of compare apples to apples and I think I'm highlighting that because that's kind of a current need I think in the field.

Whether you're talking about a mouse model, a skin model, or some other artificial model, it will be helpful as the field grows to see consensus develop around common model systems that can be standardized to best support robust evaluations of products before moving to patient populations.

So what do we need? Just to briefly review some of the things and takeaways from today, I hope you guys have learned and come to appreciate that C. auris can asymptomatically colonize patients' skin and that increases their risk of developing an infection and it contributes to environmental contamination and transmission to others.

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Healthcare facilities often ask us about decolonization treatments and it's dissatisfying and disappointing when we have to communicate that there's just not a lot of options right now. Patients colonized with Candida auris are increasingly stuck at the wrong level of care because other facilities refuse to accept them.

And so there's a public health need for decolonization or pathogen reduction strategies that can specifically address C. auris colonization, and I think that further advancing and standardizing laboratory models to help evaluate new approaches will be an important piece of that puzzle. Next slide, please.

And so that -- with that, I'd like to give some special thanks in particular to the AR Lab Network who've done a lot of work to help us keep track of Candida auris. Of course, our colleagues in the Division of Healthcare and -- Quality and Promotion for collaborating with us so consistently on Candida auris, many of which are presenting before and after me.

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And I'd like to thank my home branch, the Mycotic Diseases Branch, for doing a lot of work on this, but also other fungi. We always like to point out that we are a small but dynamic group. We're the only group at CDC responsible for an entire kingdom of life and we couldn't do that without a really strong and dynamic team.

And I'd also like to thank other groups, the Wadsworth Laboratory, Chicago Department of Health, Mary Hayden and Rush University, Julie Segre and NIH, Susan Huang and UCI, and others that we've collaborated with on these special studies to learn what we've learned.

With that, I want to conclude with one of our mottoes is think fungus and save lives. And thanks again to the organizers for including fungi in this important conversation. And with that, I will conclude my talk and turn it back over to the moderators. Thank you.

TIMOTHY BENSMAN: Wonderful. Well thank you Dr. Sexton and a very nice presentation. Our next speaker is Dr. Alice Guh who will present on

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Clostridioides difficile: Epidemiological Risks and Decolonization Strategies. Dr. Guh is a U.S. public health service medical officer in the Division of Healthcare Quality Promotion at the CDC. She leads the Clostridioides difficile infection and multisite gram-negative surveillance initiative team within the Epidemiology Research and Innovations Branch in DHQP. Dr. Guh, the microphone is yours.

DR. ALICE GUH: Thank you. Good morning, everyone. I will be presenting on Clostridioides difficile or C. diff, the Epidemiologic Risks and Decolonization Strategies. Next slide, please.

I have no financial disclosures. Next slide.

What we need for C. diff is an effective decolonization strategy to prevent transmission of C. diff from infected patients and asymptomatic carriers and to prevent primary and recurrent C. diff infection. We also need an approved microbiome-based therapeutic for C. diff infection.

There are currently several

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biotherapeutics and clinical trials, some of which I will be highlighting later in my presentation, but first I'd like to provide some background on C. diff and associated colonization risks. Next slide, please. Next slide.

C. diff is an anaerobic gram-positive spore-forming gastrointestinal pathogen. Transmission usually occurs via the oral-fecal route. Clinical spectrum ranges from asymptomatic colonization to severe disease with fulminant colitis and death. C. diff is the leading cause of healthcare-associated diarrhea and is increasingly reported in the community.

It's been estimated that there were 462,000 incident C. diff infections or CDI in the United States in 2017 with an estimated close to 224,000 cases and almost 12,800 associated deaths among hospitalized patients. Next slide, please.

Asymptomatic colonization of C. diff can occur in about 7 to 18 percent of hospitalized patients and 15 percent of long-term care facility residents. Colonization rate can be higher during

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outbreak settings with one study reporting 51 percent during an outbreak involving a long-term care facility.

Among persons in the community, about 2 to 10 percent can be asymptomatically colonized with C. diff. For most healthy individuals with intact microbiota, C. diff carriage is transient but for some they can remain persistently colonized for several months. Next slide, please. Next slide.

In a meta analysis of hospitalized patients, previous CDI, hospitalization in the previous six months, tube feeding, gastric acid suppression, and corticosteroid use in the previous eight weeks were all found to be risk factors for C. diff colonization. Interestingly, prior antimicrobial use was not found to be a risk factor for C. diff colonization among hospitalized patients, but this may be due to the pooling of all antibiotic classes in the meta analysis, which may have diminished any class-specific effect.

In addition, it's possible that even without prior antimicrobial use, a patient's

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microbiome might be disrupted from acute illness or from dietary changes of hospitalization that might predispose the patient to being colonized with D. diff. Among long-term care facility residents, risk factors for C. diff colonization include prior CDI outbreaks in the facility, previous CDI, prior hospitalization, and prior antimicrobial use. Next slide.

It's been shown that 10 to 60 percent of hospitalized patients who are colonized with toxigenic C. diff may develop CDI. The risk of CDI increases with gut microbiome disruption and immunosuppression. The primary risk factor for CDI is antibiotic use which can directly impact the gut microbiome. Other risk factors that can affect the microbiome and/or cause immunosuppression include proton pump inhibitor use, advanced age, and chemotherapy.

Certain strains of C. diff may also be more likely to cause disease. One study found that ribotype 027, which is the epidemic strain and produces more toxin than most other C. diff strains

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was found in 25 percent of CDI cases versus 3 percent of asymptomatic carriers. Next slide, please.

Asymptomatic carriers can transmit C. diff to other patients since they can shed the organism on their skin and in the environment, although to a lesser degree than symptomatic patients. Certain patients who are colonized might be a higher risk of transmission, including those who were recently infected and might still have a high burden of the organism.

In one study, patients with recent CDI accounted for 22 percent of hospitalized asymptomatic carriers. Patients with a higher burden of C. diff colonization might also shed greatly on their skin and in the surrounding environment. Next slide, please.

In fact, several studies have demonstrated the transmission of C. diff by asymptomatic patients. In the study on the left by Curry et al., they found that incident CDI cases among hospitalized patients were as frequently linked to transmission from asymptomatic carriers as from symptomatic patients. They also identify four

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transmission events that may have occurred from environmental exposures where transmission may have occurred from prior room occupants who had CDI or who were asymptomatic carriers.

In a more recent study by Donskey et al., they investigated transmission of C. diff from asymptomatically colonized or infected long-term care facility residents. Using whole genome sequencing, they found that 19 percent of healthcare-associated CDI cases could be linked to long-term care facility residents with CDI or who were asymptomatic carriers.

They also found that almost three-quarters of the asymptomatic carriers had positive cultures of their groin, skin, and/or surrounding environment for toxigenic C. diff, indicating the potential for transmission due to shedding. In fact, among asymptomatic carriers who were linked to transmission, they found a high burden of C. diff with more than 25 colonies per perirectal swab. Next slide, please.

This figure shows the important role of the gut microbiota in CDI development. When C. diff

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spores are ingested, it can remain in the dormant form or they can germinate to form vegetative cells that cause disease. The homeostasis of the gut microbiome is essential in preventing the overgrowth of the vegetative form of C. diff and along with an intact immune system can help keep the patient in a asymptomatically colonized state and not develop disease, although shedding can still occur.

In contrast, when the microbiota is disrupted, C. diff can thrive in the gut causing disease and lead to significant shedding, hence the reason why there is great interest in therapeutic strategies for CDI that can help restore the normal gut microbiota. Next slide, please. Next slide.

Currently microbiome-based therapy for C. diff is primarily focused on the treatment of recurrent disease. They include traditional fecal microbiota transplantation or FMT and novel biotherapeutics. To date, there is a lack of studies evaluating microbiome-based therapy for the prevention and treatment of primary CDI, and as of yet there is no effective decolonization strategy of asymptomatic

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carriers. Next slide, please.

FMT, which you heard mentioned by several of the other CDC speakers, is probably one of the most well studied microbiome-based therapy for CDI. It involves the transplantation of the gut microbiota from a healthy donor to a patient to restore normal diversity and function. It's usually administered endoscopically or through the nasogastric or nasoduodenal tube. Several randomized controlled trials and meta analyses have demonstrated the efficacy of FMT for recurrent CDI.

The first randomized control trial to be published was by Nood, et al. in 2013. They assigned 43 patients with recurrent CDI to receive either a standard course of oral vancomycin, oral vancomycin with bowel lavage, or four-day course oral vancomycin followed by bowel lavage and FMT.

The study was ended early after interim analysis showed that FMT was significantly more effective than vancomycin with resolution of CDI in 81 percent who received FMT versus 31 percent who received vancomycin alone versus 23 percent who

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received vancomycin with bowel lavage. Next slide, please.

There are, however, some challenges with traditional FMT. Although generally considered a safe procedure, there some risks such as possible aspiration and bowel perforation. Most of the safety data that we have come from short-term studies. So far, associated adverse events are generally self-limited and infectious complications have been rarely recorded, although they have included two immunocompromised patients who developed bacteremia from extended-spectrum beta-lactamase-producing E. coli.

More recently, there has Shiga toxin-producing E. coli from a single donor to four patients who developed self-limited diarrheal illness. Another challenge with FMT Is the heterogeneity and its practice. Although we now have stool banks, there is the variability in donor recruitment and screening as well as stool preparation methods. Next slide, please.

Therefore, there's a need for

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standardized microbiome restoration therapies. In recent years there's been a development of several capsule- and enema-based products. Several these products have many potential benefits. For example, they're easier to administer and especially the capsule-based product they're more aesthetically pleasing to patients. And both capsule- and enema-based products are less invasive than traditional FMT.

Many of these novel products are now in clinical trial. They include whole stool or defined FMT as well as a product containing fecal bacterial spores specifically purified firmicutes spores known as SER-109. A Phase 3 double-blinded randomized control trial was completed for SER-109 and the results were published earlier this year.

They had enrolled 182 patients with three or more episodes of CDI to receive either SER-109 or placebo following standard care antibiotic therapy. Twelve percent of the SER-109 group versus 40 percent of the placebo group developed recurrent CDI. A recent meta analysis compared capsule-based FMT with FMT given endoscopically. Both treatments

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showed similar efficacy with a polled cure rate of 92 percent for capsule-based FMT and 94.8 percent for FMT using colonoscopy. Next slide, please.

As Phase 3 clinical trials completed for some of the novel biotherapeutics, there's the potential for an approved product that can replace traditional FMT and be effective in preventing further recurrence of C. diff as well as transmission of C. diff to other patients. Over the next decade or so, we hope to have data from longitudinal follow-up studies that can provide more insight on long-term safety as well as the durability of FMT and other microbiome restoration therapies.

We also need continued advancements in developing defined microbial consortia to help improve the safety of these products. In addition, we should explore the role of FMT for the management of primary CDI. A few years ago there was a proof of concept clinical trial that enrolled 20 patients with primary CDI and signed to receive either FMT or treatment with metronidazole. A full clinical response was observed in 78 percent of the FMT group versus 45 percent of

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the metronidazole group. A Phase 3 clinical trial is currently underway. Next slide, please.

I also want to mention the use of nontoxigenic C. diff strains to prevent recurrent CDI. In a Phase 2 double-blinded randomized control trial, 173 patients with CDI were signed to receive one of three treatments with a nontoxigenic C. diff strain, M3, or to receive placebo. The three treatments consisted of either 10 to the fourth or 10 to the seventh spores of M3 per day for seven days each or 10 to the seven spores per day for 14 days each.

This figure on the slide shows the proportion of patients of positive C. diff cultures from day one of the study through week 26. The shaded color represents toxigenic C. diff and the nonshaded color represents nontoxigenic C. diff. The top lefthand quadrant shows the results of the placebo group. We can see that there was a high rate of colonization with toxigenic C. diff versus the remaining three quadrants each showing the results of one of the three treatments with M3.

You can see that they all had high rate

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of colonization when nontoxigenic C. diff compared to the placebo group. In fact, CDI recurrence was observed in only 11 percent of patients who received the nontoxigenic C. diff strain M3 versus 30 percent of the placebo group. The likely mechanism by which M3 might be preventing recurrent CDI is that patients are colonized with it, thereby decolonizing or out competing toxigenic C. diff strains from the microbiome.

The investigators noted that M3 colonization was likely transient as it was undetectable after week 22 of follow up, possibly due to restoration of the normal gut microbiota. Next slide, please.

To date, there is no effective strategy for decolonizing asymptomatic carriers. This study was conducted in the early '90s and was unfortunately unsuccessful. They randomized 30 asymptomatic carriers to receive either 10 days of oral vancomycin or metronidazole or placebo. This figure shows the percent of positive stool cultures among the asymptomatic carriers.

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Treatment with metronidazole shown by the dashed line and treatment shown by dotted line did not suppress C. diff colonization; whereas, oral vancomycin shown by the solid line suppressed colonization during treatment, but you can see that this effect was only temporary since the carriage rate increased subsequently after vancomycin was stopped. Next slide, please.

And lastly, I want to mention the use of oral vancomycin prophylaxis for primary and secondary CDI prevention. As I alluded to in my last slide, vancomycin has potent activity against C. diff but it can profoundly affect the microbiome resulting reduced colonization resistance to C. diff that can persist for weeks after vancomycin has stopped, potentially increasing a patient's risk for CDI.

There's been at least one randomized control trial that has assessed the use of oral vancomycin prophylaxis. The trial enrolled 100 patients to receive either oral vancomycin prophylaxis while systemic antibiotics or no prophylaxis. Zero percent in the oral vancomycin prophylaxis group

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versus 12 percent in the no prophylaxis group developed healthcare facility onset CDI.

No new colonization of vancomycin resistant enterococci was detected among the oral vancomycin prophylaxis group. However only a portion of the patients had a follow up swab done. A recent meta analysis assessed the efficacy of oral vancomycin prophylaxis for primary and secondary CDI prevention in patients treated with systemic antibiotics. This analysis included 11 studies, including one randomized controlled trial and several studies immunocompromised patients, and they found that oral vancomycin prophylaxis is protective against CDI and that its use was not associated with high risk of VRE.

While these results are promising and more randomized controlled trials are needed, I do want to note that there are some major shortcomings with the strategy namely that vancomycin is an antibiotic and it's used to treat an infection, and as I mentioned earlier it can leave -- it can affect the microbiome leaving it in an even more impaired state and that's failing in an attribute of decolonization

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or pathogen reduction agent, many of these attributes that you heard earlier in Dr. McDonald's presentation. Next slide, please. Next one.

So in conclusion, I'd like to reiterate that for the future of C. diff, we need an effective decolonization strategy that can help prevent transmission of C. diff from infected patients and asymptomatic carriers and prevent primary and recurrent C. diff infection. We also need an approved microbiome-based therapeutic for C. diff infection, which I believe will not be too far off in the future since there are several biotherapeutics that are currently in clinical trials. Next slide.

Thank you. I'd like to turn it back to the moderators.

TIMOTHY BENSMAN: Wonderful. Well thank you, Dr. Guh. We will now hear presentations on patient impact and perspectives. Dr. Whitney Brown will share with us the impact of infection on the lives of people with cystic fibrosis. Dr. Brown is currently at Inova advanced lung disease and transplant program, and helped create the Inova Cystic

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Fibrosis Center.

In July of 2021, Dr. Brown joined the clinical affairs department with a focus on supporting the care center network and the evolving cystic fibrosis care model. She continues to care for adults with cystic fibrosis at Inova which energizes and informs her work at the Cystic Fibrosis Foundation. Dr. Brown, the stage is yours.

DR. A. WHITNEY BROWN: Thank you so much and good morning. Yes, I have the pleasure of speaking today on behalf of people with cystic fibrosis to give us a little insight into the impact of infection on their lives. Next slide.

So as many of you know, cystic fibrosis is really characterized by a lifetime of infections, and I'll be primarily talking about the respiratory tract today but what we can see in this schematic is because of the underlying defect in cystic fibrosis, the result is sticky, dehydrated mucous down in the lungs and that really sets the stage for inflammation and infection and the cycle goes round and round.

And in fact, really repeated or

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persistent airway infection over the course of a lifetime is what leads to progressive loss of lung function in people with cystic fibrosis. And unfortunately respiratory failure is the leading cause of death. Next slide.

So this acquisition of respiratory infections really occurs early in life and what I'm showing you here is a schematic from our 2019 cystic fibrosis patient registry data report. And so what we can see on the X axis is this is the patient age and years and on the Y axis, the percentage of individuals that culture from the respiratory tract one or more of these organisms.

And so early, on by age one and age two, you can see a variety of different colors meaning that even infants have acquired respiratory tract infections and early on it's primarily staph aureus, but as kids aged through adolescence, it becomes more predominant with pseudomonas or staph aureus and pseudomonas in combination. But what you definitely notice is the percentage of the population that escapes respiratory infections is very small at the

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bottom, denoted in gray. Next slide.

So because the acquisition of infections occurs so early in life and because there's repeated exposure to the healthcare system for people with cystic fibrosis, we struggle with antimicrobial resistance. And here again, we have more data from our patient registry, this time from 2020. And I can show you here in the bottom left field, we see the distribution of gray, that's the age distribution, the number of individuals at each age in our registry.

Superimposed on that are the people in 2020, individuals that grew staph aureus. And the subset in red are those who grew methicillin-resistant staph aureus. So clearly -- and we can see that staph is again more prevalent at early ages and decreases and stabilizes later in life.

Likewise, up with pseudomonas, same kind of figure with gray being all individuals in the registry and then we see the distribution of those who grew pseudomonas in the registry from a respiratory culture, and then the subset growing multidrug-resistant pseudomonas. So clearly, we struggle with

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antimicrobial resistance. Next slide.

And we have learned some difficult lessons over time, and this is just to highlight. This is a timeline of reported publications or reports of transmissible strains of, in this case we're focusing on pseudomonas and burkholderia that were published in the literature and made known over time, and this really heightened our awareness that these pathogens don't just come from the environment but there can be patient-to-patient transmission occurring in nosocomial settings as well as in community settings like even the CF summer camps that used to occur. Next slide.

And this -- these events and these reporting really lead to a revamping of our infection prevention and control guidelines for cystic fibrosis. And these were put out in 2013 and are specific to our population. Really, the most fundamental one is the first year that all people with CF are placed on contact precautions in healthcare settings, regardless of what they have grown in the past. And historically, this was gown and gloves, as you see in

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the picture.

Of course, now with universal or almost universal masking in healthcare settings, the mask has been added. And speaking of masks, we've asked our patients to wear masks themselves in healthcare settings since the publication of these updated guidelines and also to keep 6-foot distance between other patients and themselves.

And so this distance is not only in the healthcare setting but also in social settings. So for example, at Cystic Fibrosis Foundation events or other social settings, only one person with CF is usually invited to indoor events to be extremely cautious on this basis. We also have in this reported guideline standards for reducing risk with pulmonary function testing and also for cleaning and disinfecting environmental services. Next slide.

So naturally I think most healthcare providers and patients and families would agree that these guidelines are really for their protection, but I wanted to share some terms or thoughts that have been shared with me from patients over the years in

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terms of really how these guidelines impact their lives.

So as I mentioned, two people with CF can't be within 6 feet of each other, so really that has resulted in a heavy social media presence, lots of virtual friendships. And in the healthcare setting, although there are upsides to getting private rooms with contact precautions, you know, naturally there in some settings is the feeling of isolation and stigmatism, particularly for healthcare settings that are outside of the typical CF team.

And indeed, patients I think complain that procedures and surgeries are often scheduled at the end of the day or postponed unnecessarily in some cases because of this contact precaution status, which results in prolonged fasting. It really can be a problem for those with CF-related diabetes. Next slide.

So what about the burden of getting sick? So we know these bacteria are down in the lungs, and what I'm showing you here is, this is a graph showing us the number of pulmonary exacerbations

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requiring intravenous antibiotic use. So this is the number of times people get sick and need IV antibiotics. And this is a time span from the beginning of 2019 looking at almost to the end of 2020.

And what we see up here in red is for people 12 years and older and the number of monthly exacerbations and down here in blue is 11 and younger. And what we can see at the beginning of 2019 was really there was a high level of intravenous antibiotic use for pulmonary exacerbation treatment each month, a little bit of up and down but high level in those 12 and older.

And then something transformative happened in our community in October of 2019 which was the approval of elexacaftor/tezacaftor/ivacaftor, and this is an oral CFTR modulator medication that helps the CF protein work better in almost 90 percent of individuals with CF. But initially it was approved for 12 and up.

So what do we see in this 12 and up group? We see a marked decline in the subsequent

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months in the need for IV antibiotics in this population, which was very, very encouraging. We don't see it as notably in the pediatric population, because the medication was only approved initially for 12 and up.

Then of course we have COVID coming on the scene in March of 2020, which led to a further decrease in both populations now of IV antibiotic use, and that of course is partially a result of social distancing and more universal masking. Next slide.

And then this slide is just to catch us up on what happened last year. And really last year is a continuation of the really good pattern we saw early in the in the pandemic after the approval of elexacaftor/tezacaftor/ivacaftor, which is only 14 percent of adults needing IV antibiotics last year, only 10 percent of children which are markedly reduced from the rates seen pre-pandemic.

Likewise, we have this chart here. This is based on surveillance respiratory cultures that were done in 2019 and then compared to those done last year, again from our patient registry. And we

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see encouraging trends that there may be less infections being detected with -- in terms of these key bacteria for us and non-tuberculous mycobacteria when you compare the two years.

However, there are two caveats to this, which is our clinic attendance and therefore surveillance culture data has not returned to pre-pandemic levels. So we are -- we have a sampling bias. There are less cultures being collected. And secondly, because of the new medication, many people with CF are living healthier lives, having less cough and sputum, and therefore the cultures that we are getting, they may be more oropharyngeal or throat swabs because patients cannot cough up sputum on command during their visits. So we take these data with a grain of salt, but some encouraging trends. Next slide.

But still, infection remains a deep concern for our community and this -- and many patients express to me that they are afraid that they will run out of antibiotic choices over the course of their lifetime due to resistance and due to repeated

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use of oral, inhaled, and intravenous antibiotics.

So we conducted a survey in quarter three of last year asking the patients and families in our community what they're -- what they saw the CF Foundation's priorities in the field of infection-related research. And not surprisingly, the top one here was the development of new treatments. And again, that's to answer that concern about antimicrobial resistance.

Also optimizing current treatments was notable in the top three, and then again improving detection and diagnosis, which I would argue is becoming even more important now that less individuals are coughing up sputum cultures. Next slide.

So in our research portfolio that we fund at the CF Foundation, we're trying to mirror our community's priorities, and this you can see is the number of studies that we are funding divided up into those in industry, those in academics, and looked at over time and by pathogen type.

And what we can see is that really heavy emphasis, not surprisingly, on the burden of

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pseudomonas also on non-tuberculous mycobacterium, and then multiple organisms accounting for another body of funding. And more recently, really also interested in bacteriophage therapy. Next slide.

So we have many unanswered questions when it comes to the infection landscape in cystic fibrosis, but I hope I've convinced you that during the pandemic time period with the approval of the transformative new therapy, things are looking up for our population. But questions remain and one of those would be with less antibiotic use, if this trend continues, will we see less antimicrobial resistance in our population?

Secondly we're all very concerned about the impact of masking. I think it has had a positive impact on the incidence of pulmonary exacerbations. And we're -- you know, I think it would be quite beneficial to continue masking in healthcare settings for the protection of our community.

And then lastly, with less -- if people are healthier with CF, if they're lucky enough to be on this therapy and are benefiting, they're not

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coughing and having as much sputum. Will their pathogens be as transmissible and will there be a point at which we can revisit infection control practices and allow people with CF to be safely together in person?

These are very provocative questions and really they're going to take time to answer. And to get these answers, we're going to continue to perform surveillance respiratory cultures. We're going to continue to collect clinical data in our registry. And we're going to continue to invest in infection-related research. Thank you.

TIMOTHY BENSMAN: Thank you, Dr. Brown. We'll now hear from Ms. Jeanine Thomas on the aftermath of living with having healthcare-associated infections. Ms. Thomas was the first patient advocate to raise the alarm concerning methicillin-resistant staph aureus and healthcare-associated infections in 2002 and founded the MRSA Survivors Network in 2003. She's a survivor of MRSA sepsis and C. difficile. Ms. Thomas, the floor is yours.

JEANINE THOMAS: First, I would like to

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commend and give gratitude to the healthcare workers who have worked tirelessly and selfishly through the last couple of years to save patients from COVID-19. Your commitment to save patients from COVID is highly appreciated and all the sacrifices that you made from yourself and from your family. We applaud you.

The healthcare system was pushed to its limit and beyond, but now we have more protocols in place that can combat healthcare-acquired infections and so many more patients now know what a nasal swab is and how it can help them from acquiring an infection.

It has been over 20 years since I was infected with MRSA. My story is like many patients who came into a hospital for surgery that should have not been life threatening and ended up fighting for their lives and were forever changed by this experience. The sad thing is that now we have soaring rates of MRSA infections.

My journey started in December of 2000 when I slipped on black ice and fractured my ankle. I had multiple fractures and -- which required a plate

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and two screws. During surgery, I was infected with MRSA and it went into my bone marrow giving me osteomyelitis and later it would be sepsis.

I went home a couple of days after surgery and was recovering, but then I began to feel nauseous but didn't have a fever. I paged my surgeon and he said, come to the ER. And of course, it was a Friday night. When the doctors took my cast off, my - - I was horrified by the sight and smell of my leg. I could not have surgery that night because I had eaten during the day.

The next day, I had surgery and I don't remember it. By then, I had a high fever and was in a lot of pain and sedated. The next few days were also a blur and I had another surgery to clean the wound and I could no longer speak or communicate with anyone. I knew I was gravely ill and I felt that I was dying, and I don't know why the staff didn't realize that because I know sepsis is hard to diagnose.

I was burning up with fever. I felt utterly helpless and afraid, desperate to speak but

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could not. My body was shutting down. I didn't want to die. I still had more -- so many more things to do in life. My culture had come back positive for MRSA, but when I was not given vancomycin, so the broad-spectrum antibiotic was not working on me.

On the fifth night of being in the hospital, I suddenly woke up in the night and the night nurse was checking my temp and laid the box on my chest. I happened to see for a second the digital readout, 105. I thought, oh my God, no wonder I'm burning up. I heard the nurses screaming in the hall to page my doctor and then carts rattling down the hall as they worked on trying to save me. I was near death.

I had a near death experience, the one you had when you were close to crossing over. I felt relieved that I was not burning up anymore and a serene calmness came over me. I saw the nurses working on me and they were very distraught and anxious. I wanted to tell them that I was going to be -- not going to die, that I was going to be okay. It was not my time.

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I was finally given vancomycin. I remember being semiconscious later the next day. I could not open my eyes. Later I could not even see anything. All I saw was dark gray. I did not know if I was alive or in some other space of time or reality. I could hear faintly voices around me. I fought as hard as I could to open my eyes and I was able to for a second. I knew that I was alive but would find out later that I was septic and had the beginnings of multiple organ failure.

The next few weeks were a blur of surgeries and unbearable pain as they tried to save my leg from amputation. I spent Christmas in the hospital and finally my infection stabilized. I went home and did not recognize myself. I had lost over 30 pounds and I had no color in my skin, so sickly looking with excruciating pain and total fatigue.

I had a couple of more surgeries on my leg but was not able to have a bone, muscle, or skin graft. I then developed C. diff which was another trip to the ER and more antibiotics. I was on a cocktail of antibiotics for many months and after a

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year I had the hardware taken out. I was diagnosed and treated with posttraumatic stress disorder and depression. I never had these disorders before.

Over the next couple of years, I would have fevers, more antibiotics and feel like I was just surviving. I would have breakouts and I was constantly vigilant and I was the lucky one, though. I had survived, though the pain was so increased in my leg that many times I wish that they had amputated it. But I was wondering how could I have died nearly from ankle surgery. There was barely any information about MRSA on the internet.

In 2003, I founded my organization MRSA Survivors Network to educate and raise the alarm to the epidemic and we also established the first crisis hotline in the U.S. I worked with former Illinois State Senator Barack Obama to pass the Hospital Report Card Act to mandate MRSA and other HAIs be publicly reported.

It was the first legislation of its kind in the U.S. I was placed on an Illinois State advisory board and saw that more needed to be done and

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initiated legislation, the MRSA Screening and Reporting Act, which passed unanimously in Illinois and enacted in 2007. It was the first in the country and more states followed the legislation.

From this 50 -- the next couple of years, 50 percent of the healthcare facilities were screening high risk patients and infection rates were dropping. My health over the years was never the same and I have to be careful of contracting viruses and if I do, I'm sometimes ill for several months. This is very common with MRSA patients.

In 2015, I had a surgery and contracted staph aureus and pseudomonas. I was devastated and realized that very little had changed for patient safety as SSIs are still very high and contamination in healthcare facilities needed so much more attention, along with other measures.

I contracted COVID-19 in February of 2020 and was seriously ill and had long time -- long COVID for over a year. But I was able to heal myself and have had two more COVID infections since then, and of course I'm fully boosted. I am forever

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immunocompromised.

For many, MRSA and HAIs are a dehumanizing experience and diminishes a person's personal health. I know I felt like a leper. And we also lose our wellbeing, quality of life, and for so many, financial futures. There's still a stigma for MRSA patients and this we've worked very hard at but it still is acquiring this.

If we have learned anything from COVID, the pandemic, it is the screening is essential along with contact precautions, contamination -- decontamination, strict hygiene, and more. More healthcare facilities suspended screening for MRSA and reporting infection rates during the pandemic. MRSA has proliferated into a bigger epidemic in the past two years.

We must remember patient safety should come first. It is time to laser focus needless pain and suffering should not happen anymore. We patients want a desire for superior antibiotics and therapies, not inferior products. So we must invest in the advanced technology, fully staffing of infection

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control, along with continued training.

We can never get to zero, but we can get close to that. So this should be our goal. Remember, prevention saves lives. Thank you. Back to the monitor.

TIMOTHY BEHSMAN: And thank you, Ms. Thomas, for your story. The burden you bear is truly humbling and something I think we will keep with us as we work through this workshop.

We'll now begin presentations by our public comment speakers. Our first speaker is Dr. Michael Woodworth, who will talk about microbiome approaches to treat colonization with antibiotic-resistant bacteria. Dr. Woodworth is an assistant professor of medicine, infectious diseases at Emory University School of Medicine.

Dr. Woodworth's research is primarily focused on the translational study of microbiome therapies like fecal microbiota transplantation to treat colonization with antibiotic-resistant bacteria and leads two microbiome clinical trials as an investigator with the CDC funded Prevention Epicenter

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of Emory. Dr. Woodworth, the stage is yours.

DR. MICHAEL WOODWORTH: Good morning, everyone. My name is Michael Woodworth. I'm an assistant professor at Emory University School of Medicine, and I'm excited to speak to you today about microbiome therapies to treat colonization with antibiotic-resistant bacteria. I'd like to thank the organizers for the opportunity to speak today.

As talks have so clearly elaborated earlier today, antibiotic resistance is a true global threat and this is chiefly due to diminishing numbers of effective therapies. As an infectious disease physician, I frequently see isolates that are resistant to many if not all antibiotics on first round susceptibility testing, and this is a true and present threat.

Others have said earlier that nothing in biology makes sense except in the light of evolution, and I would like to suggest today that nothing in antimicrobial resistance makes sense except in the light of colonization. Simply put, we must increase our focus on colonization to address the

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mounting threats of global resistance.

So then what can be done for patients who are colonized with multidrug or even pan-resistant organisms? And the honest answer is that today, nothing can be done for these patients, because there are no -- as outlined earlier today, intestinal microbial communities are well established as being critical to MDRO colonization resistance.

So to further evaluate the safety and efficacy of directly applying these microbes in a procedure called fecal microbiota transplantation, we conducted a small clinical trial in renal transplant recipients who are colonized with MDROs after infection called PREMIX.

This slide shows you the culture results from the first 11 patients who were enrolled and treated in PREMIX, and on the bottom five rows you can see the participants who were randomized to start with the bowel prep alone without an FMT followed by an observation cycle of visits.

As you can see in the following columns, that all patients who were MDRO positive at

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day 36 by stool culture, proceeded to get an FMT. In this way, everyone in the study was eligible to receive up to two FMTs. What you can see in the observation column, is that five out of five participants who received a bowel prep but did not receive an FMT were still positive at day 36.

Those patients who were randomized to start with an FMT or proceeded to get an FMT after an observation period, you can see that six out of ten of these participants were MDRO negative after one FMT. And of those who proceeded to get a second FMT, two out of three were MDRO negative at day 36.

In a pooled analysis, eight out of ten patients who received at least one FMT were MDRO negative at their last stool culture. Shown in the time to event analysis in a Kaplan-Meier style plot, you can see that in the Y axis, the proportion of patients who had a positive MDRO stool culture. The green trace shows those patients who were randomized to start with FMT and the blue trace shows those patients who were randomized to start with an observation period followed by FMT at a later date.

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And what you can see is patients who were randomized to start with an FMT were those who were in MDRO negative first. Put in a slightly different way, all of those who were in the observation group were MDRO positive until they received an FMT.

Now, because all patients in our study were eligible to receive an FMT, we had to turn to a different cohort of patients at Emory. This large cohort of over 4,000 renal transplant recipients contained 16 patients who would have been eligible for PREMIX, but were not enrolled and did not receive an FMT for any other reason. This group is shown in the purple trace. They're compared to our patients in the PREMIX study in the brown trace on the top, and what's shown on the Y axis is the proportion of agents who are free from MDRO infection.

And what you can see is that the patients in the PREMIX study in the brown trace on top had a much longer time of being free from MDRO infection from the time of their initial eligibility.

Now, this slide summarizes all of the

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studies that have been published to date, evaluating the safety and efficacy of FMT for MDRO decolonization. And what you can see are strong signals for efficacy, but the other signal that you can see in this table is that none of these studies were designed or conducted in the United States and I believe that as a country, we're starting to fall behind.

So then how do we move beyond the crude application of microbes to try to treat or even prevent an infectious disease? Well, you may remember that this was the humble beginning of vaccinology when Edward Jenner applied a live virus to try to prevent small pox in a small boy, and how far we've come in vaccinology since that time, such that we could develop an entirely novel vaccine within less than a year of the emergence of a global pandemic.

So then I had two suggestions for how to accelerate the development of microbiome therapies for MDRO colonization. First, we need to do the studies. We need to design and conduct prospective clinical trials of decolonization as an indication and

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as a primary endpoint.

Second, we must require data sharing and open science for microbiome clinical trials. Almost everything that we've come to learn about the human microbiome, much less interventional studies, had its beginning in the Human Microbiome Project and many of the sub-studies that followed. So much was gained from an open data approach that we need to carry this forward with academic and industry partnerships going forward to accelerate the translation of these therapies.

Finally, in conclusion I would like to point out that it was the boldness of the FDA to exercise enforcement discretion in 2013 that really facilitated and accelerated so much of what we've learned since that time about the use of fecal microbiota transplantation. So much has been gained from secondary study of FMT for other indications since that time. This is another one of these moments when the FDA can again listen to public comment from providers and patients and to facilitate more rapid translation and development of microbiome

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therapeutics. Thank you for your time and attention and for the invitation to speak. Good morning everyone.

TIMOTHY BENSMAN: Thank you, Dr. Woodworth. Our next speaker is Carl Genberg, who will speak about Preventing Biofilm Fouling of Indwelling Medical Devices to Reduce Healthcare-Associated Infections and Antimicrobial Resistance.

Mr. Genberg is a chief scientist and development officer at N8 Medical. Mr. Genberg is involved in the development and commercialization of patented technology designed to prevent bacteria, fungi, and viruses from forming biofilms on medical devices and resulting healthcare-associated infections. Dr. Genberg, the floor is yours.

CARL GENBERG: Thank you very much. Good morning. My name is Carl Genberg. I'm with N8 Biosciences, also known as N8 Medical. I'd like to thank the organizers for allowing me to speak to you this morning. I'll be speaking on three points: HAIs, the role that biofilms play in HAIs, and how we may prevent such biofilm-related HAIs with our

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CeraShield coated medical devices potentially save lives and billions of dollars in the process. Next slide, please.

Just as water may exist in various physical forms, liquid, gas, and solid -- ice -- with dramatically different properties, bacteria also exist in two forms, free living single planktonic cells which are highly susceptible to conventional antibiotics and biofilms which are slime-like aggregates of millions of CFUs of bacterial cells which are highly tolerant of conventional antibiotics. Next slide.

We are losing the war against HAIs. The situation is likely to get worse. Most of the funding efforts to date have gone to develop new drugs to cure infections. We need to invest more technologies to prevent colonization and infection. Next slide.

Twenty years ago, Dr. Bell highlighted the need for a fundamental shift in thinking to focus on biofilm-related infections. New technology, our biofilm-resisting coating called CeraShield, now makes

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that possible. Next.

It has been observed in the recent literature that one factor that's been consistently overlooked in these types of discussions is biofilm. Biofilm fouling accounts for 65 percent of hospital acquired infections. According to the NIH, HAIs add $30 billion annually to the annual healthcare expenditures in the U.S. Next slide.

FDA has also called for a focus on preventing infections and the best way, according to Dr. Gottlieb, to prevent a resistant microbe from becoming resistant was to prevent patients from getting infection in the first place. Next slide.

Biofilms are responsible for over half in some cases 65 percent of all HAI bacterial infections such as VAP, CAUTIs, urinary tract infections, and surgical site infections. The biofilm growth on these medical devices in the case of gram-negative pathogens secrete endotoxin and these endotoxins lead to inflammatory cytokine cascade driven primarily by IL6. This can be prevented along with the adverse events that are associated with this

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type of cytokine cascade. Next.

Dr. Donlan of the CDC's Biofilm Research Center has also opined that biofilm plays a key role in antimicrobial resistance and that antimicrobial concentrations sufficient to inactivate planktonic organism are generally inadequate to inactivate biofilm organisms. Next.

Recent editorial in The Lancet, also focusing on the need to prevent infections in the first place. Next.

Of the various infections, ventilator associated pneumonia is high incidence and high mortality and is the leading biofilm-related medical device infection. Within hours after intubation of the patient with an endotracheal tube, the surfaces of the tube begin to grow biofilm and these biofilm act as a reservoir in infectious disease, leading to VAP in some cases.

A patient who develops VAP spends on average eight additional days mechanical ventilation in the ICU with an estimated cost of $4,000 a day, total estimated cost of $6.4 billion annually in the

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U.S., which may be largely preventable if new technology can prevent biofilm growth on endotracheal tubes. Next.

We've developed a new technology based on insights from research and innate immunity, specifically the role of antimicrobial peptides as a first line of defense in the innate immune system. We have developed a lead compound CSA-131 which is active against all escape pathogens, fungi, lipid enveloped viruses, COVID, and monkeypox.

There's been some very interesting discussion on the role of Candida auris. We co-published a study with CDC's. Dr. Sean Lockhart on the activity of CSA-131 active against all tested isolates including pan-resistant. FDA has designated our device as a breakthrough device. It's already approved in Canada and Brazil and other countries in the near term. We're working with the NCDC in Tbilisi, Georgia for an upcoming VAP study in high risk patients where the VAP rates may exceed 50 percent. Next.

Prevention of VAP is a good first

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target because it can have a dramatic impact on healthcare and expenditures as well. And this is a technology that is available worldwide at a reasonable cost because we'll be saving the share -- share the savings of what preventable cases of VAP lead to. Even in India, LMIC, we're looking at $6,000 added costs for VAP.

Money saved on treating VAP can be used, redirected to develop and purchase expensive antibiotics and to address other critical healthcare concerns. A solution that is only applicable in wealthy countries is suboptimal. We're dealing with an international crisis. Next.

This is a scanning electron microscopy image of endotracheal tubes challenged with a combination of pseudomonas and Candida auris. On the lefthand side, you see dense biofilm. On the righthand side, with our coated endotracheal tube segment, you see clean surface. Next.

Of critical importance is that the active is a mimic of antimicrobial peptides which has been in nature for millions of years. And serial

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passaging studies show that CSA-131 does not induce mutation resistance, even after 30 serial passages, in contrast to colistin who's MICs rise above 300 and close to 400. Next.

We've done a small study in Canada with Professor John Muscedere at Kingston General Hospital. We looked at endotracheal tube aspirates from the mechanically ventilated patients looking at bacterial colonization and we dramatically reduced colonization and of significant importance, not a single gram-negative pathogen was detected. This compared to historical controls from a prior published study, looking at 75 and 80 percent even with a sub-glottic suctioning device. Next.

Ceragenins have broad spectrum activity -- there are over 100 peer reviewed journal articles - - active against all escape pathogens, MDR strains, C. auris, Candida, aspergillosis, and lipid enveloped viruses such as COVID-19 and monkeypox.

When you're dealing with a lipid enveloped virus, the virus mutates, the lipid does not. So we expect that this would be broad spectrum

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in these viruses or the lipid enveloped viruses. We're also developing this active as an inhaled drug. given the presence of biofilm in cystic fibrosis patients with support from the Cystic Fibrosis Foundation.

So this is able to prevent and eradicate biofilm. Prevention on medical devices that is a very low concentration. Also able to bind endotoxin and sequester LPS and most importantly does not induce mutational resistance. Next.

Current drug developments are focused on free living planktonic cells, acute infections. However, more than half the problem is by biofilm and conventional antibiotics are not effective. The only way we can deal with this problem is to prevent the growth on the first place. There's new technology, CeraShield coating that has been developed and can achieve this without inducing mutational resistance.

We're about to start a large 800-patients study in Canada, funded by governmental agencies in Canada with Professor Muscedere as the lead PI, who is the head of the Canadian Clinical

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Trial Task Force for Diseases of the Elderly. Biofilm prevention is highly cost effective and will significantly reduce the need for antibiotic therapy while potentially saving billions. Next.

Thank you. I look forward to hearing from you.

TIMOTHY BENSMAN: Wonderful. Thank you, Dr. Genberg, for the nice presentation. Our last speaker is Dr. Christopher Lehmann who will talk on the topic of Microbiome, Liver Transplant, and Hospital Acquired Infections. Dr. Lehmann is an adult and pediatric infectious disease clinical fellow at the University of Chicago. His research is focused on describing the interactions between stool microbiota and multiple drug resistant organisms, as well as identifying possible microbiome therapies to prevent multidrug resistant infections. I'll now turn it over to you, Dr. Lehmann.

DR. CHRISTOPHER LEHMANN: Yes, thank you for the introduction and thank you to the organizers for inviting us to this presentation and for putting the presentation together. Next slide.

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I have no disclosures to make it this time. Next slide.

Before we get into the microbiome discussion, I just wanted to briefly mention liver transplantation. You know, liver transplantation is often the only curative therapy for many liver diseases affecting many people and hospital acquired infection is a very significant contributor to this course, occurring in up to 25 percent of patients.

These infections are very morbid and oftentimes deadly. Further, these infections are often linked to the microbiome. And then finally, you know, we view this opportunity to study the microbiome in this patient population but likely would be generalizable to other patient populations reaching thousands and thousands of people. Next slide.

So to assess the microbiome in this patient population and its contribution to infection, we performed shotgun metagenomic sequencing of stool samples in the postoperative period and we organized them based on infection and no infection. Each vertical column you see here is a single stool sample

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collected from a patient and each color within each vertical column is a unique organism.

You'll see immediately the dark green color that represents enterococcus. The bright red color that you see represents proteobacteria. This contains the family Enterobacterales, things like E. coli and klebsiella, and then many of the other colors, the pinks, the cyans, the purples, and the browns, these are obligate anaerobic bacteria that are generally regarded as healthy members of the microbiome.

If you look sort of in the middle of the right side, you'll see some stool samples that have sort of a rainbow of appearance of multiple different colors of these anaerobes and these stool samples would be the closest to what we would consider to be normal microbiome.

And then finally at the bottom each one of these colored squares, the green colored squares represents an enterococcus infection and the red colored squares represents an Enterobacterales infection. And to determine the association between

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colonization and infection in this group, we ordered these stool samples based on relative abundance of enterococcus where on the far left you see stool samples that have a normal microbiome essentially completely replaced with a single organism of enterococcus and then gradation from there.

And then if you draw your attention to the enterococcus infection column, you'll see that nearly every single enterococcus infection experienced in our study occurred in patients who have expansion of these enterococci within their stool microbiota. Next slide, please.

We then did the same reordering, but now focusing on Enterobacterales, and we see a similar trend where Enterobacterales expansion sometimes even complete domination of the microbiome occurs and is associated with an infection caused by these Enterobacterales.

The other thing that you may have noticed is there are patients in the no infection group who also experience expansion and domination with these taxa, suggesting that while expansion may

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be necessary for infection, it might not be sufficient raising hypotheses that perhaps other residual microbiota may be preventing infection and defending these patients from infection. Next slide, please.

So to better determine the exact association between the colonization, expansion, and then subsequent infection, we created two receiver operator curves with Enterobacterales and enterococcus colonization and then associating that with infection. And here we see a very strong association with areas under the curve approaching 90 percent and then 80 percent for Enterobacterales.

We then optimized the cut point at the degree of expansion necessary to highest predisposed towards infection, and here we see that an expansion at a level of between 5 and 6 percent is actually associated with that significant increase in risk for infection. While those 90 percent expansions are impressive, perhaps the 5 percent threshold is what's important. And finally at these thresholds we found an odds for infection to be significantly elevated in the expanded patient populations, reaching an odds

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ratio of up to 50 in the enterococcus group, and again, that's a 50-fold increase in risk for infection.

Now these numbers are somewhat disconcerting in terms of risk for infection with colonization, but if you flip this on its head and view this as an opportunity where we can use microbiome therapies to suppress expansion of these taxa down below this 5 percent threshold, we have the opportunity to reduce the risk for infection up to 50-fold in these patients. And again that's a reduction that would be really revolutionary compared to other therapies with much less magnitude for benefit. Next slide, please.

So next steps within our research endeavors is to recognize that these organisms aren't just existing within the colons and the stool of our patient, but that these organisms are active. They're doing things. They're competing with each other and they're interacting with the host.

So here we looked at the microbiome derived metabolites in the stool and you'll see here

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on the top right of this figure, these are metabolites that are enriched in our patients who managed to escape getting infected. And while we don't have time to discuss each of these individual metabolites, we know that they are produced by the microbiome and many of these compounds have been implicated in health. Notably the top five on the right, indole, desaminotyrosine, and tryptamine have been implicated in boosting enterocites mucosal barrier, inducing host production of antimicrobial peptides, and then finally immunomodulation and avoiding excess inflammation within the gut. Next slide, please.

So you know as we move forward on understanding the relationship between the microbiome and hospital acquired infections and multiple drug resistant infections, these questions rise. Who are they? How many? What are they doing? But I think most importantly is how can we return to normal, how can we suppress these pathogens back to low levels and reestablish those anaerobic consortias, and at the University of Chicago, the Duchossois Family Institute, we are currently working on developing a

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discrete healthy microbiome consortia using good manufacturing practices that will engraft into our high risk patients, will restore their microbiota, will reestablish colonization resistance, will suppress pathogen abundance, and will ultimately prevent infection. And with that, thank you so much for all of your time. Next slide, please.

I'd like to thank the Duchossois Family Institute, University of Chicago, my mentor Dr. Pamer, and so many other mentors, collaborators who have helped progress this work and are continuing to work on those future projects. I thank the CDC and FDA for organizing this presentation, this workshop, and to all of the audience for your thoughts and considerations. And with that, I will turn it back to the moderators.

TIMOTHY BENSMAN: Wonderful. Well thank you, Dr. Lehmann for sharing some of your clinical research findings. This concludes this morning's session. Dr. Smith and I want to thank all the speakers this morning for their excellent presentations. They were very comprehensive,

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informative, and thoughtful which is no small feat with the time restrictions you all faced.

It's now time for the lunch break, so feel free to answer the poll questions as it comes up, but do rejoin us at 12:30 for Session 2 talks.

(Break)

DR. JOHN JERNIGAN: -- get started with our first afternoon session which will be covering the regulatory perspective and trial design challenges and considerations. My name is John Jernigan, chief of the Epidemiology Research and Innovations Branch in the Division of Healthcare Quality Promotion at CDC, and I'll be co-moderating this session along with Dan Rubin from FDA and I'll turn it over to Dan now to get it started. Dan.

DR. DAN RUBIN: Good afternoon. My name is Dan Rubin. I'm a co-moderator for this session, and I'm a statistical team leader in the Office of Biostatistics at CDER FDA.

Our first speaker for this session is Heidi Smith. Dr. Smith is a clinical team leader in the division of anti-infectives in the Center for Drug

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Evaluation and Research at FDA, where she is involved in the review and regulation of products intended for the treatment and prevention of infectious diseases. Over.

Heidi, I think you're on mute.

DR. HEIDI SMITH. Thank you. Double muted. We can go ahead and move on to the next slide.

All right, a brief outline of the presentation. So I'm going to start with some context on HAIs and the clinical context of what we'll be covering, standards for approval. We'll delve into the characteristics of adequate and well-controlled trials and then go through some illustrative examples of drugs to prevent surgical site infections, drugs to reduce the incidence of catheter-related bloodstream infections, and then talk a little bit about safety database confederations. Next slide, please.

So as was discussed in much more detail this morning, healthcare-associated infections are broadly defined as infections that develop while receiving healthcare or shortly thereafter, and it includes catheter associated bloodstream infections,

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catheter associated UTIs, surgical site infections, and ventilator associated pneumonia.

And as I've also noted the pathogens responsible frequently develop antimicrobial resistance. The drugs developed to prevent or reduce the incidence of HAIs may have different clinical development pathways. Next slide, please.

So before we talk more details about the statutory standards for drug approval, it sometimes helps to take a step back and recall where these statutes came from. So this photo is actually showing President Kennedy signing the 1962 amendment to the food -- the federal Food Drug and Cosmetic Act, and these were also known as the Kefauver-Harris amendments.

They established the framework that required drug manufacturers to prove scientifically that a drug was not only safe but also effective. I also like this picture because the only woman in the room in this picture is Frances Kelsey, who was the FDA medical officer who was very instrumental in preventing thalidomide from coming to the market in

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the U.S. because she had over its data. Next slide, please.

Okay, so what do these standards state? So a drug's effectiveness must be established by substantial evidence of effectiveness defined as evidence consisting of adequate and well controlled investigations including clinical investigations. And this is generally interpreted as requiring two adequate and well-controlled trials, each of which is convincing on its own.

Now the Food and Drug Administration Modernization Act amended the provisions to add that the FDA may consider data from one adequate and well-controlled clinical investigation with confirmatory evidence. Next slide, please.

So let's talk a bit about the definition of adequate and well-controlled trials. So the purpose of these trials is to distinguish the effect of the drug from other influences, spontaneous change, placebo effect, observational biases, and the Code of Federal Regulations describes the trial design elements that are intended to minimize bias and permit

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a valid comparison with a control in order to affect a drug's effect. Next slide, please.

In the CFR, there's these seven characteristics laid out of adequate and well-controlled trials. These trials have a clear statement of objectives and a proposed method of analysis. They permit valid comparison with a control so that a quantitative assessment of the drug's effects can be made. They have a method of selecting subjects that provides assurance that they have the disease that's being studied or in the case of a preventative treatment, that there's evidence of susceptibility and exposure to the disease to be prevented.

The method of assigning -- assignment to study arm minimizes bias and is intended to ensure comparability between the treatment groups. Measures to minimize bias on the part of the subject, observers, and analysts of the data are incorporated into the trial design. There's a method for assessing treatment response that's well defined and reliable. And the analysis of the results is adequate to assess

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the drug's effect, the analytical methods used, the comparability of the test and control groups, and the effects of any interim analyses.

Next slide, please. Can I have the next slide? Is it an anything on your end, because I'm not seeing -- there we go. Perfect. Thanks. That's the one.

So since adequate and well-controlled trials has control, let's talk a little bit about some different types of controls that we might see in these trials. So, placebo concurrent control is a comparison to an inactive preparation that's designed to resemble the test drugs. A dose comparison concurrent control has a comparison of at least two different doses of a test drug.

A no treatment concurrent control has a comparison of the test drug with no treatment, but it usually still includes randomization and it's usually only used in situations where the outcome measure is objective and the placebo effect is negligible. An active treatment concurrent control is a comparison with a known effective therapy. And this is usually

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used in situations where placebo or no treatment is contrary to the interests of the patient.

It's worthwhile noting here though that with this type of control, the similarity of the test drug and the active control can mean either that both drugs are effective or that neither drug was effective. An analysis of the study should reference the evidence for the effectiveness of the control.

And then finally, historical control of the comparison with experience historically derived from natural history of disease or results from active treatment in a comparable population. This is usually reserved for special circumstances such as diseases with high predictable mortality or studies where effect is self-evident. Next slide, please.

So trial endpoints. So these -- the methods that are assessing the response to the drug should be well defined and reliable and the endpoints should be clinically meaningful. The most common type of endpoint that we're dealing with is a clinical endpoint, as referenced by Dr. Farley early on in the workshop, these are characteristics or variables that

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directly measure a therapeutic effect, the effect on how the patient feels, functions, or survives.

It's important to note in the context of what we're discussing today that medical biologic outcomes are not clinical endpoints.

We can also use validated surrogate endpoints. So these are endpoints that are supported by clear mechanistic rationale as well as critical data that provide strong evidence that the effect on the surrogate predicts a specific clinical benefit. Next slide, please.

So • 03:18:15 a little bit more detail on surrogate endpoints. So as Dr. Farley had mentioned, surrogate endpoints are used as a substitute of a direct measure of our patients feel, function, or survive. So they must be supported by evidence that show that they can be relied upon to predict a clinical benefit.

And in terms of approval based on surrogate endpoints, there's two potential pathways. Traditional approval can be supported by adequate and well-controlled trials that establish an effect on a

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validated surrogate endpoint and this endpoint would have data including some clinical trials and epidemiologic studies that demonstrates its ability to predict a clinical benefit.

Accelerated approval, on the other hand, can be supported by adequate and well-controlled trials establishing an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other evidence or on the basis of an effect on the clinical endpoint other than survival or irreversible morbidity.

Now, in the case of accelerated approval, this requires that the applicant study the drug further, can vary and describe its clinical benefit where there is uncertainty as to the relationship of the surrogate endpoint to the clinical benefit or the observed clinical benefit to the ultimate patient outcome.

The FDA does maintain a public list. Listed in -- the link is in the hyperlink at the bottom of the side of surrogates that have been used

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as a basis of approval. We should note though that the acceptability of these surrogate endpoints for use in a particular drug development program is determined on a case-by-case basis and it is context dependent: the disease, the patient population, the mechanism of action of the drug, and the availability of other approved treatments. Next slide, please.

So trial objectives. The two primary types of studies that we'll be evaluating are superiority trial and this would be a study that demonstrates efficacy by showing that the test drug us superior to control. And generally this provides the strongest evidence of effectiveness.

The other primary type of trial we evaluated is non-inferiority trials and these demonstrate efficacy by showing that the test drug is not effective less effective than the active control by more than a predefined amount or the NI margin, the non-inferiority margin. But these types of trials rely upon the assumption that's not confirmed in the trial itself that the control had its anticipated effect, which is the basis for the NI margin. Next

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slide.

So these are a couple illustrative examples starting with drugs to prevent surgical site infections or SSI. So did a compare and contrast two types of development programs, one for a topical antibacterial for staph aureus nasal decolonization and another for systemic antibacterial for peri-operative prophylaxis.

So for both of these types of development programs, the trial endpoint is likely to be surgical site infection incident. But in the case of a topical antibacterial for staph aureus nasal decolonization, there's inconsistent data on whether nasal decolonization alone results in reduction in surgical site infection. So this is going to require an assessment relative to placebo, because there's no active comparator with demonstrated efficacy.

In contrast, for systemic antibacterial for peri-operative prophylaxis, there's multiple trials demonstrating reduction in surgical site infection when peri-operative antibiotic compared to placebo or no treatment. This allows the

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justification of an NI margin that can be used for an active comparative controlled non-inferiority trial. Next slide, please.

So going into a few more details, starting with the example of a topical antibacterial for nasal staph aureus decolonization. So the published literature regarding the clinical benefit of nasal staph aureus decolonization is not conclusive. Studies to date have not demonstrated a consistent outcome for the prevention of surgical site infection. Most of the studies reporting a clinical benefit have used bundled nasal and skin decolonization strategies so determination of the benefit of the nasal decolonization alone is not possible.

Other limitations have included heterogeneity in the patient populations, differences in the reported endpoints and treatment effect, and variable methodological quality. Next slide, please.

So some of the trial design considerations for the development of a product like this would include the choice of control would likely be a placebo vehicle which could control for the

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physical effects of the topical application of the product as well as blinding. Patient selection considerations would include potential enrichment for staph aureus carriers and surgical population, the highest risk of surgical site infection.

Concomitant prophylaxis measures that should be controlled for would be things like timing and the type of skin decontamination and the use of systemic peri-operative antibacterials. Randomization could be cultural randomization by hospital or by surgical unit or by individual patients.

Clinical endpoints. Primary endpoints would likely be incidence of surgical site infections, incidence of all infections due to staph aureus and/or mortality. And secondary endpoints that could be considered would include hospital length of stay, readmission rates, or reoperation rates. And the endpoint analysis is likely superiority of the treatment to placebo. Next slide, please.

Looking a little bit deeper at systemic antibacterial for peri-operative prophylaxis to prevent SSI, there are multiple trials in the

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published literature that demonstrated clinical benefit relative to placebo or no treatment in surgical procedures with high rates of infection, clean-contaminated or contaminated procedures.

And one example from The Lancet in 1979 is a randomized double blind placebo controlled single center trial where patients undergoing elective colorectal surgery were randomized to IV metronidazole or placebo dosed immediately prior to surgery and then repeated at eight and 16 hours. For both groups, the preoperative, bowel preparation was identical and the endpoint evaluated was the overall surgical site infection incident. They found 34 percent in the metronidazole arm and 77 percent in the placebo arm. Next slide, please.

So there are multiple parenteral antibacterials that have been FDA approved with an indication for surgical site infection prophylaxis in clean contaminated and potentially contaminated procedures such as those listed here. Next slide, please.

So the types of trial design

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considerations for the development of a product like this for a selection of a control, an active control could be used for surgical procedures with established efficacy in surgical site infection prevention. A placebo control might be considered for procedures without a demonstrated efficacy.

For patient selection, considerations would include the type of surgical procedure, the similarity to the population in which efficacy was demonstrated by the comparator, as well as enrichment strategies for patients at highest risk of surgical site infections.

Concomitant prophylaxis measures could include also timing and type of skin decontamination as well as bowel prep. Randomization, again, could be cluster or individual patient. Clinical endpoints, likely incidence of surgical site infection and mortality with consideration of secondary endpoints for length of stay, readmission rates, and reoperation rates.

Endpoint analysis would be superiority to control or non-inferiority to an active control,

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without adequate justification for the NI margin. Next slide, please.

Then looking at a slightly different illustrative example, we could look at an antibacterial to reduce the incidence of catheter-related bloodstream infections. So we could consider an antibacterial, locally administered in a catheter lock solution. So while there are FDA approved catheter lock solutions that include saline solutions that physically occupy the catheter space to provide a hydraulic lock plus or minus an anticoagulant drugs to reduce the incidence of clotting, and antibacterial could be evaluated as an add-on to the catheter lock solution containing saline plus or minus an anticoagulant and compared to a control lock solution that had an otherwise identical composition. Next slide, please.

So the types of trial design considerations for this type of product development could include for selection of control, there's no FDA approved antibacterial catheter lock solution, but once they consider an active control with an FDA

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approved anticoagulant catheter lock solution evaluating the antibacterial as add-on therapy or a placebo control with a saline solution.

Patient selection. So take in account factors such as the catheter type, whether it's a long-term catheter or short-term catheter use, the catheter function -- hemodialysis, nutrition, chemo (indiscernible) -- and enrichment for patients at highest risk of infection such as those who have past history of infection, more frequent access of the catheter.

Concomitant prophylaxis measures to control for would be things like protocols for aseptic technique, whether chlorhexidine-gluconate impregnated sponges or other dressings are used, or standardization of tubing changes.

And then clinical endpoints would be catheter-related bloodstream infection incidence, catheter loss, mortality. Consideration of secondary endpoints to evaluate potential effects of clotting, catheter patency. And then finally endpoint analysis would be superiority to control. Next slide, please.

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Then finally safety database considerations. Approval decisions requires both a finding of substantial evidence of effectiveness and the determination that the drug is safe for its intended use. The benefits of the drug must outweigh its risks under the conditions of use defined in the labeling.

For drugs used as prophylaxis or reduction of incidence of infection, the benefit may only be experienced by a fraction of the treated patients, that subset who would have developed the disease without the prophylactic intervention. And in these cases a larger safety database would generally be required for a drug intended for prophylaxis of a serious infection than a drug intended for treatment of a serious infection.

And then finally, just to sum up what we've talked about, products developed for prevention of healthcare-associated infections can have diverse modes of delivery and mechanism of action. The approval of an indication for prevention of healthcare-associated infection requires demonstration

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of efficacy using a clinically meaningful endpoint or validated surrogate and an adequate safety database to determine whether the benefits of the drug outweigh its risk for the use defined in the labeling. Thank you.

DR. DAN RUBIN: Great. Thank you, Dr. Smith, for that great review. Our next talk is entitled Regulation of Healthcare Antiseptics and will be presented by Dr. Theresa Michele. Dr. Michele is currently the director of the Office of Nonprescription Drugs in the Center for Drug Evaluation and Research at the FDA. Among other drugs, the ONPD is responsible for regulating healthcare and consumer antiseptics. Dr. Michele.

DR. THERESA MICHELE: Thank you so much and good afternoon, everyone. It's really a pleasure to be here today as part of this important workshop on prevention of healthcare-associated infections. Now because topical antiseptics are often considered part of the armamentarium of infection prevention tools, it's useful to understand some of the background on these products when considering development of new HAI

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prevention strategies.

So over the next 15 minutes or so I'll be providing just a very high level overview of the regulation of healthcare antiseptics which is a bit more complicated than the typical prescription drugs. Next slide.

This is the usual FDA Disclaimer.

So when we talk about antiseptics we typically divide them into categories based on indication which the -- with the two largest area is being consumer antiseptics and healthcare antiseptics. So for the purposes of today's talk, I'll primarily be discussing patient preoperative skin preparations which fall under the healthcare antiseptic category. The other products in this category are primarily intended to be used on the hands of healthcare personnel, not on patients.

So despite the indication for use in the healthcare setting, these are all nonprescription drugs; although, the healthcare products are typically marketed to hospitals and to clinicians in other healthcare settings rather than to the general public.

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Next slide.

There are two different ways to bring an OTC drug to market in the U.S.: the new drug application and the abbreviated new drug application or NDA and ANDA process, and then the OTC monograph process. These two processes are quite different. Patient preoperative skin preparations are actually marketed under both processes. So under the NDA process, which is how most prescription drugs come to the market, an application for the drug is submitted to FDA for approval and the application includes information about the safety and effectiveness of the drug, which you just heard about from Dr. Smith.

So the drug can't be marketed until FDA approves that application for the drug. The NDA is specific for a particular drug product including its formulation, its dose, its use, and its labeling. In contrast to the NDA process, an OTC monograph drug can be marketed without FDA approval if the drug complies with all of the requirements in section 505(g) of the federal Food Drug and Cosmetic Act which was added by the CARES Act as well as applicable conditions of its

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therapeutic category-specific OTC monograph. That's a mouthful, and we'll talk about what an OTC monograph is exactly in just a moment.

So except for any final formulation testing specified in the relevant monographs, a manufacturer that's following the OTC monograph does not need to provide safety and effectiveness data of each individual drug product. This is because OTC monographs established conditions including the active ingredients under which an OTC drug is considered generally recognized as safe and effective or GRASE, and does not require FDA approval prior to marketing. Next slide, please.

So what's a monograph? Well, an OTC monograph is kind of a rule book. It lists the conditions of each therapeutic category that describes the active ingredients, the uses or indications, the doses, route of administration, labeling, and testing for an OTC drug to be recognized as GRASE. So drugs that are GRASE and meet other requirements in Section 505(g) of the act can be marketed without a new drug application and FDA premarket approval.

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The monograph remains one of the largest and most complex regulatory programs ever undertaken at FDA. Over 100,000 different OTC drug products are marketed under the OTC monographs in the U.S. These monographs or rule books cover approximately 800 different active ingredients for over 1,400 different uses. Next slide.

This slide compares and contrasts the two systems. I'll give you just a moment to look at this and note that these slides are available on the website after the presentation if you want to read this in more detail. The most important takeaway here is that the NDA process is product specific, while the monograph process is therapeutic category specific.

So in order to qualify for monograph status, a product has to fulfill all of the indications laid out in the monograph in terms of its active ingredients, indication, labeling, et cetera. Now while certain flexibilities are permitted under the monograph such as in inactive ingredients, if a product differs in any way from the prescribed monograph conditions, that product requires a product

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specific NDA or an OTC monograph order request to change the monograph before it can be marketed. Next slide.

Currently for patient preoperative skin preparations, there are six active ingredients that may be marketed under the monograph. These include alcohol, povidone iodine, benzalkonium chloride, isopropyl alcohol, benzethonium chloride, and chloroxylenol.

Only single-ingredient products are permitted under the monograph, and combination products require an NDA. While it's possible to submit an NDA for a product with any active ingredient, currently the primary active ingredient found in most NDA patient preoperative skin preparations is chlorhexidine. Next slide.

Recently the monograph process underwent significant changes. On March 27th of 2020, the Coronavirus Aid, Relief, and Economic Security Act or the CARES Act was enacted and the CARES Act included important statutory provisions that reform and modernize the way over the counter monograph drugs

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are regulated in the United States.

OTC monograph reform changes the process for revising, issuing, amending, and finalizing OTC monographs from the three phase public notice and comment rulemaking process to a new much more facile administrative order process. The administrative order process still involves public comment and is still largely a public process.

Under the CARES Act, OTC monograph healthcare antiseptics can continue to be marketed if they follow the 1994 Antiseptics Tentative Final Monograph, as further amended by the 2015 Health Care Antiseptics proposed rule and other applicable requirements. Next slide.

So currently all monograph active ingredients require additional data to determine whether they are generally recognized as safe and effective or GRASE for use in healthcare antiseptics. And we're currently working with manufacturers to help ensure they provide the data necessary to make a GRASE determination for these ingredients.

It's the manufacturer's responsibility

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to ensure that their products have been properly tested, comply with applicable -- goodness -- comply with applicable regulations and have inactive ingredients that are safe and suitable for use in an OTC healthcare antiseptic. Next slide.

So this is an example of some of the labeling for a patient preoperative skin preparation. Both NDA and monograph products carry similar labeling. I show this to point out that the indication for these products is for preparation of the skin prior to surgery to help reduce bacteria that can potentially cause skin infection.

Note that there are no approved antiseptic products for the prevention of other infections or for repeated use. Also note that the products are intended for external use only on intact skin, not in the eyes and the ears and the mouth and the nose or in any other orifice. Next slide.

So testing for a preoperative antiseptic is based on the labeled indication and use which again is for use prior to surgery for the reduction of bacteria on the skin that can potentially

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cause skin infection. So efficacy testing for preoperative antiseptics includes both in vitro tests and in vivo simulation testing. Testing follows the directions from for use, which I just showed you, and these directions generally state to allow the product to dry completely and do not rinse.

I'll review the required efficacy testing in a moment, and while I'm not going to review the safety data as part of this presentation, I do want to point out that the data that we have and that we have requested to support safety of these agents is limited to this specific indicated use.

It's a common misperception that because these antiseptics have been around for a very long time and that they have a general indication that data supporting approval is extremely broad, which is just not the case. So testing of these products does not currently include viruses, reduction of systemic infections, or prevention of any specific infection, repeated use, use over a large surface area, us in infants and neonates where there are potential issues with absorption, use on other than intact skin, use

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for pre-catheterization or any of a variety of other uses that people use these things for.

This isn't to say that doctors cannot use products in clinical practice for things that go beyond the label. We all know this happens every day, especially with these products. That falls under the practice of medicine, which is not regulated by FDA.

What I just want everyone to be aware of is the limitations of the data supporting approval of these products, so that as we discuss options for developing tools to reduce HAIs we consider what additional information might be needed to provide specific evidence to support drug approval for such use. Next slide.

In vitro efficacy testing for preoperative skin preparation antiseptics is designed to demonstrate the product spectrum and kinetics of antimicrobial activity by looking at the spectrum of activity against recently isolated normal flora and cutaneous bacterial pathogens.

Testing is generally for MIC or MBC testing of 25 representative clinical isolates and 25

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ATCC reference strains followed by time kill testing of each of the bacteria tested in the MIC or MBC. So a complete list of these strains can be found in the healthcare antiseptic proposed rule at the reference listed on this slide. Next slide.

So products that show adequate in vitro testing then go on to clinical simulation efficacy studies. These studies are based on a surrogate endpoint of the number of bacteria removed from the skin rather than on a clinical outcome endpoint such as reduction in the number of infections.

This simulation follows a prescribed protocol with a single application of the product on a dry skin site and a moist skin site such as the groin or axilla which generally has higher numbers of resident bacteria than the dry skin sites. The primary endpoint compares the test product to both a vehicle or negative control and a positive control, and it must demonstrate a superiority margin of 1.2 log reduction over the negative control in both sites after 30 seconds or 10 minutes.

In addition, the bacterial counts may

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not exceed baseline at six hours. The use of the surrogate endpoint of clinical simulation studies to support this particular indication was discussed at a public advisory committee which agreed with the proposal. Next slide.

So this covers a very high overview of the regulation of healthcare antiseptics in general and preoperative skin preparations in particular. Now I glossed over a lot of information so I would encourage anyone who wants to take a deeper dive into this topic to review the rule makings that I pointed out earlier as well as our website on healthcare antiseptics that's listed here. I'll also leave you with some additional resources on related topics that may be of interest, and I thank you very much for your attention.

DR. DAN RUBIN: Thank you very much for your presentation, Dr. Michele. Our next speaker is Paul Carlson. Dr. Carlson is a principal investigator in the Laboratory of Mucosal Pathogens and Cellular Immunity, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and

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Review in CBER, FDA. His researched FDA has focused on infections caused by the enteric pathogens, Clostridioides difficile and vancomycin-resistant. Enterococci species as well as fecal microbiota transplantation and bacteriophage therapeutics. Over.

DR. PAUL CARLSON: Hi. Thanks for the introduction and for the invitation to speak today. I'm not going to be talking about any of my research today. I'm going to talk about regulation of these particular product classes that we've lumped together here to call microbiome based therapeutics. Next slide, please.

Just my quick disclaimer. My comments are my own. Slides are always approved, but anything I say particularly later in response to questions will not -- id not.

Quick outline. I'm going to go over very briefly some aspects of IND or investigational new drug applications that are relevant for these products. And then I'm going to get into CMC considerations for fecal microbiota transplantation or FMT and live biotherapeutic products, both of which

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have been mentioned previously today. Next slide.

And so briefly, IND, as I said, investigational new drug application exempts the investigational drug from premarketing approvals. You can lawfully ship it. Basically, if you want to use a drug that is not licensed in people and as part of a trial or for any other purposes you need an IND. Next slide, please.

Our primary objectives throughout all stages of this review is to assure the safety and rights of the subjects that are part of the investigation and in later phases to also include evaluation of effectiveness and safety. Next slide, please.

All right, so here's one of the key questions that I get asked all the time. Do we need to use CGMP manufacturing practices? Does it have to be full CGMP? Do you have to pay the CMO, you know, half a million dollars to get into Phase 1 and the answers are yes and no. Everything has to be done under good manufacturing practices; however, what that means could change throughout the course of product

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develop.

So again CGMP has to be done because it ensures that the drug is safe, has adequate identity, strength, meets the quality and purity characteristics that it purports or is represented to possess. However, for Phase 1, CGMP is not the same as what it might be for later phases. And really what this means is you have to have some control over how you're manufacturing the product. But can you manufacture your Phase 1 material in a research laboratory? Yes. Can you do it in my research laboratory with enterococcus and C. diff floating around? No.

So, you know, there are ways these things are done and we work with you as part of the IND process and to work on manufacturing and ensure that the product is going to be safe. Next slide, please.

All right. So from here, I'm going to move into CMC considerations for these two product classes, starting with FMT. Next slide, please.

So this is a brief history of FMT at the FDA, noting that I arrived in 2015 so I can't be

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blamed for everything. Briefly here, and in May of 2013 the FDA and NIH called a public workshop that was attended by just about everyone in the field or all parts of the field were certainly represented. And at this particular the workshop the FDA noted the use of FMT and clinical studies to evaluate its safety and effectiveness were subject to the regulation by FDA.

And I've heard a lot of people say in 2013 the FDA decided that no that's not how -- it's always been this way. This is a drug. But this was when it was made clear to everyone that INDs were going to be required or have been required.

Now there were concerns from many people regarding the situation with C. diff and the use for C. diff and the ability to get an IND in and for it to be allowed to proceed at a reasonable pace and in the sheer number of INDS that would have been coming in.

And so in 2013, we issued a finalized guidance issuing a policy of enforcement discretion regarding the IND requirements for use of FMT specifically to C. difficile infections not responding

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to standard therapies. This only applies to C. diff, to treating C. diff that's not responsive to standard therapies and not any other use of FMT.

All other uses still require an IND. This guidance from 2013 is still in effect today and this is still policy that we are functioning under. We issued two draft guidances subsequent to that. Neither of those have been implemented to date. First one would have limited enforcement discretion to situations where the donor is known to the doctor or patient. We received many comments, took those into consideration, and chose not to finalize that guidance.

Additionally, in 2016 we issued a guidance that would exclude stool from enforcement -- product enforcement discretion if the stool was obtained from a stool bank. So enforcement discretion only applies to those not purchasing or obtaining product from an entity that would be considered a stool bank. Again, this has not been finalized to date. Next slide, please.

All right. So how do we ensure the

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safety of FMTs? Imagine that this is -- this is a challenging product to regulate or even to develop. It's going to be variable depending on the donor and the day, and also has potential significant risks associated with it, primarily in terms of infections that can be carried along with the product.

So we look at both intrinsic and extrinsic safety. Our primary handle on safety here is through donor and stool screening. So we need questionnaires to -- and tests to ensure the health of the donor. How often should they be tested?

Should we allow off site donations, is one of the things that comes up frequently and I can say right now we do not allow any offsite donations. One, to ensure chain of custody, and two, to make sure we're getting a full handle on the potential symptoms that these individuals may have, particularly during the COVID-19 pandemic.

Testing of stool. What should we test for? How good our tests? These are both questions we think about all the time and also research questions in my lab. Intrinsic safety is a little harder,

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right? What are the long term effects of these products? And this is much harder to get at and typically beyond the scope of a typical clinical trial.

And then the last thing I have on your side, we characterize these products as we're looking for consistency. Are the organisms or consortia that matter, specific functions that matter, what's a good potency assay. And I can say, I don't think the field knows the answers to all of these things right now and the majority of the potency assays that we see are still CFU per mil or per gram of product, and these are estimates of potency because not everything is going to grow on those plates. Next slide.

I think it's just holding the previous slide. Next slide again, please. One more. Thank you.

All right. So along with the concerns about safety, we have had some safety alerts issued as problems have arisen and infections have occurred. This slide is actually out of date as of last week. We added another one last week. But here you can see,

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had a safety alert regarding the transmission of two ESBL E. coli infections from FMT into two individuals, one of those two individuals did die as a result of that infection and that led to changes in donor screening that now require both exclusion of donors that are at high risk for carriage of these, of various MDROs and also direct testing for them. Previously it had been one or the other.

The next alert after that was one I believe was mentioned earlier also, where we had instances of transmission of enteropathogenic E. coli and Shigatoxin-producing E. coli. The enteropathogenic E. coli, we did -- were not requiring testing for prior to this. We now do, so that was the change that that one pushed us towards. And the Shigatoxin-producing E. coli one, it was an interesting case because of course we require testing for Shigatoxin and for STEC, but now we have to require specific testing because in this case they were testing by EIA and that missed the particular case and so now it's required to be done by nucleic acid amplification testing.

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The next one was a couple of years ago we released the safety alert pertaining to the potential risk of SARS-CoV-2 virus being shed in stool and the potential -- it's known to be shed in stool, but the potential risk of that for FMT products, and so additional donor screening was required there.

And then last week, for those of you who have been following this, we did release an additional safety alert regarding the potential risk of transmission of monkeypox virus after reports the virus being isolated from -- viable virus being isolated from stool of infected individuals and many instances of both rectal swab and stool samples being positive. Next slide, please.

So this is going to be an ongoing and dynamic list as we move through time and as new pathogens emerge, but this is a list of donor screening -- potential donor screening recommendations that we published a couple of years ago. Now you can see in red that about the timing of when this was published, because those were added after. There's a long list of things here. Many of them are always

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going to be required under every circumstance.

Some things like say CMV are going to be required if we have concerns about the patient population. It's a challenging one because many people are seropositive but there are ways around that as well. Again, we added STEC by nucleic acid amplification, EPEC, and COVID later, and we have as of today not added a requirement for monkeypox testing, however I think that the addition of donor screening questions and risk assessment will be important in mitigating that risk. Next slide.

This is just the paper that I mentioned from the table from the previous slide came from. So if anyone wants to learn a little bit more about that, it's just a slightly more extensive version of the presentation I've just given here. Next slide.

So now we're going to move on to live biotherapeutics. Next slide.

And live biotherapeutic for the case -- for this presentation as defined by CBER is a product that contains live organisms such as bacteria, not limited to bacteria, is applicable to the prevention,

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treatment, or cure of disease or condition of human beings -- so it's a drug -- and three, is not a vaccine. Next slide.

So the CMC for these products needs to be such that we have sufficient information to ensure that we know what we're dealing with. We have proper identification, quality, purity, and strength of the drug. And then as development proceeds, we expect that that CMC information is going to increase. The detail is going to be greater and things like assay validations and things are going to be provided later on the process of drug development. Next slide.

So this slide outlines some of the things that should be included as part of the CMC package for this type of drug. You need to know what the strain is that you're working with. Very simple and straightforward one. Where did it come from? Is there any information on strain and passage history, and note there, it says as available.

You don't necessarily have to have this, but it's nice if we can understand where this strain is coming from and what the reason for

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including it the product is, and any relevant genotype or phenotype of information, and ideally you're going to have a full genome sequence of your organism. That's so cheap to do these days that there's really no reason that you wouldn't expect that a sponsor would have that information.

We also need to know the antibiotic resistance profiles for clinically relevant antibiotics both by MIC and potentially looking in the genome to see if there's anything of concern. But in the end, it's really the phenotypic evaluation, so we know what drugs are available to treat these things in the event of a breakthrough infection.

We need information on the cell banking systems. Master cell banks, working cell banks, research cell banks, et cetera. Description of the drug substance and drug product manufacturing processes. In these cases a lot of times one product has many substances. If you have 5, 10, 15, 100 strains in the product, each one of those might be individual drug substance that is then combined into your final drug product.

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We'll need stability data on your product. This is also required for FMT despite the fact that I didn't mention it earlier. We need to know that the product is stable throughout the course of the trial that you are planning and that you're not going to have any issues with, you know, product dying off, right.

Just like FMT, you need a potency assay. Also like FMT, many times the potency assay for these things is going to be a measurement of total viable cells. In this case, you can tailor that assay to the strains that you're working with, perhaps get more accurate numbers. I do want to note there for multi-strain products you will need to be able to enumerate all strains.

And this is an instance of where I'm talking about the CMC information that's required increasing over time. In Phase 1, going to need to show that they're all there and have a big picture measure of overall potency. But as we move into Phase 3, you're going to need to be able to enumerate the individual strains in your product and provide potency

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information on each of them and that can get complicated, admittedly, as the product size grows.

Any additional information on biochemical or physiochemical properties of the product can be provided as part of potency assays and will be reviewed as such. Bioburden testing will be required in these cases. These are done typically under USD Protocols 61 and 62 looking for extraneous undesirable bacteria.

And then additional testing may be required depending on the intended population. They're at high risk for infection for some reason, and any other organisms that are manipulated in the same facility. Again, coming back to my lab as the extreme example, working with C. diff and VRE would not be a good thing for product manufacturing. Next slide.

All right. So we updated our guidance on LBPs in 2016 to account for commercially available products and the challenges that sponsors were having in getting the CMC information. So commercially available products, probiotics, do in fact fit the

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definition of LBPs when they're being used to treat a disease. You might get it off the shelf. They're meant for safe -- or for healthy populations, not for sick individuals. And so in those instances, we need to have an IND and we need to have the information -- sufficient information to product under IND. Next slide.

Because there were challenges getting that information and often, you know, the manufacturer is not going to be the sponsor of these INDs and the manufacturer frequently doesn't have incentive to provide the information that we're looking for, we do have a method for getting a waiver from the requirements for CMC information and I'll outline that in this slide and the next slide here, but -- so if you had an IND that's utilizing a commercial product, you can request a waiver and it will or will not be granted.

If it's not granted, then you have to provide full CMC. If it is, then you just have to provide the label of product. And on the next slide, I will tell you how you get that waiver.

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So the waiver will be granted -- may be granted if all four of the following conditions are met. So the product and the proposed investigational use -- the product for proposed investigational use must be lawfully marketed as a conventional food or dietary supplement. So it's commercially available. Step one.

Step two, the route of administration, dose, patient population, or other factors does not significantly increase the risk. It's a pill and the label says you say one per day, then that's what you're going to do in your trial, then you're probably okay as long as there's no reason to be concerned about your patient population.

The investigation is not intended to support a marketing application of the live biotherapeutic as a drug or biologic product for human use in the future. So this is for research studies, clinical research studies only.

And then finally, the investigation is otherwise conducted in compliance with IND requirements. And then you can get the waiver and

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provide us with the label of the product and your clinical trial plan as well as part of your IND, and then you will likely be able to proceed. Next slide.

All right, and those things are outlined in this paper that was published a few years ago now in Microbiology Spectrum and some more details. It's really a summary of more up-to-date current thinking regarding the things that are in that guidance document. Next slide.

All right. And I will end here with some final thoughts. I think you know this meeting the microbiome and microbiome-based products have been mentioned many times. There are many meetings addressing these things around the country and around the world frequently, so I think it's very safe to say interest in these products is increasing, has increased greatly, and will continue to do so.

And they -- from our perspective, CBER's regulatory approach to these products has been science based and will continue to be science based and we feel that we have allowed and will continue to help sponsors get these novel approaches into the

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clinic to be safely tested and hopefully moved on to be approved therapeutics in the near future. Next slide.

I will just leave this up for a minute. This is just some additional resources. I think the slides are all going to be available after the meeting, too, so you can find these in my slide deck after the meeting. And with that, I'll turn this back over to the moderators. Thank you.

DR. DAN RUBIN: Thank you very much, Dr. Carlson. Our next topic is Clinical Considerations and Operational Challenges for Prevention Trials and will be presented by Dr. Susan Huang. Dr. Huang is professor in the Division of Infectious Diseases at the University of California Irvine School of Medicine and medical director of Epidemiology and Infection control at UCI Health. Dr. Huang has led several large randomized clinical trials involving decolonization to prevent MDRO disease and other HAIs across the continuum of care. Dr. Huang.

DR. SUSAN HUANG: Thank you. Thanks for the opportunity to talk about design challenges

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and operational challenges for HAI prevention trials. Next slide.

So there are some really important common features of HAI prevention trials that are fairly distinctive, and one is a general desire to evaluate what's often a quality improvement strategy. And when this occurs, it often has a group focus; that is, quality improvement is usually applied at a unit level, clinic, hospital, nursing home. Often in this case for HAIs, it is targeting a contagious outcome and it's generally spurred by an urgent common need.

Oftentimes, this is because of national reporting requirements that bands hospitals and units together to try to identify effective solutions and therefore it's often under the jurisdiction of operational implementation and that often means that there are resource constrained funds. Next slide.

Another key distinction between the difference of classical individual randomized control trials and these types of pragmatic trials is that pragmatic trials are targeting populations and they're usually looking for effectiveness. That is, if any

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hospital were to adopt this, any clinic, how would they be eight to be assured that this is a typical response that they would see.

These trials are often minimal risk. That means they employ controls that don't use placebos and many times they will qualify for a waiver of informed consent. Next slide.

One reminder about the difference of these effectiveness types of trials versus efficacy is they're not trying to demonstrate the effect of the intervention under its best conditions. It's actually trying to show what happens under typical conditions, meaning the less selection of a population the better, so everybody that comes into a unit, everybody that comes into the emergency department, everybody that comes into a nursing home.

And for that reason it can sometimes lend itself towards an efficient type of recruitment. You can recruit a number of sites that want to participate and it also can use a lot of things that are already in place. So operational infrastructure, it can use staff that are already in place to produce

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quality improvement campaigns.

It can use compliance tables or reports that are already in place. And often it is trying to adopt learning while doing, so the learning health system rather than a compensated type of trial or a trial where you develop a whole infrastructure with staffing just to conduct the trial. Next slide.

Targets for these types of populations can include, as I mentioned, these types of grouped locations but of course it can also include special populations. So this includes people who undergo surgical procedures, have specific medical devices, including those that have very specific chronic illnesses like people who are going to a dialysis center.

This also applies to those who have multidrug-resistant organisms, so those that are tagged as carriers and of course those that can be followed post discharge for any number of reasons. Next slide.

Often when you think about universal versus targeted populations, there are real pragmatic

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considerations on how to actually roll out the intervention. When you do something in a group, a whole unit, a whole clinic, often it's easier to train and implement. These are changes in protocols and practices that are constantly occurring and usually institutions have a way in which we roll out new protocols and new adopted guidelines.

Often these types of outcomes again are already tracked because many of them are under national reporting. Targeted populations, on the other hand, require either a flag in the medical chart or some sort of detection algorithm to find them. We then require some sort of way to track them to be able to reach them to find out whether or not they've actually had a good outcome, so detailed chart review, and many times if we're looking at longitudinal effects, then we require special sampling. Next slide.

This is just an example of two different ways in which you can study decolonization. You can have a population target that's at a unit level. So this is a population of critically ill

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individuals. You can recruit and randomize ICUs in a cluster randomized way. Those ICUs can just receive standard order sets or standard protocols that adopt a new practice. And usually the unit based surveillance are things that are normally being collected so hospital onset, multidrug-resistant organisms, bloodstream infections.

And on the other hand, you could design a trial that would decolonize MDRO carriers. That is, you would find them with some sort of flag that's in the electronic health record. You then recruit them. You consent them. You randomize them. And then you follow them up on whether they're in the hospital or out for any sort of clearance or infection outcomes. Next slide.

So depending on the question under study you can design your trial to be very, very temporary. That is, you find these high-risk periods. Some of these were mentioned in prior talks, and you can find these high-risk moments like being in an ICU or being in a nursing home, in a dialysis center, and you can focus all of your intervention right at that

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moment.

So when they leave those areas, the follow-up stops. And in those settings, because these areas generally have a high amount of staffing and a high ability to track, usual surveillance outcomes may suffice and may in fact be the actual outcome that is of high interest for changing during a quality improvement endeavor.

On the other hand, you might be looking for something that is long standing. That is, you want to find something that is going to benefit this individual for a very, very long period of time, not just during this temporary high-risk period and then you need to follow them up post discharge in other clinics, sometimes have special home visits, and then of course either sample them, and this could include swabbing or blood draws or any other thing that would be required to demonstrate a benefit. Next slide.

Often when you're doing these types of trials for reducing HAIs, it's really important to have health system partners. This can be important for recruitment. A lot of times health systems have

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multiple sites that can be leveraged to actually have efficient recruitment and often it's actually better if the system leaders reach out and there's a rapport that actually encourages participation in a trial.

It also means that health systems often are asked to make special IT solutions. So they're asked to either build reports to find certain people who might have certain characteristics or certain clinics with certain characteristics. They may be asked to actually implement certain order sets or adherence tracking reports and do feedback. And then of course, system leadership may be very much asked to avoid competing interventions at the time for the duration of the trial. Next slide.

These trials, as I mentioned, often do meet the rules for minimal risk and by both OHRP guidance as well as FDA guidance, and one of the questions that's going to be important when we think about waiver of informed consent is who normally consents in the first place.

For example if we're talking about a soap that a hospital uses or even something as

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significant as what drugs on the formulary, what devices are implanted, what devices are used for intubation, many times these types of things, central lines, are not actually under the choice of the patient.

The facility, the clinic, the hospital actually chooses what they purchase. They have a certain supply and those supplies are then used for implantation as needed during the course of medical care. Next slide.

Controls are really, really important. It's going to be a big complexity as you think about these types of trials that are not typical of the individual randomized trial. If you're looking at these types of group type of studies, that is looking at let's say 30 hospitals, that's a pretty big sizable trial for a group randomized trial, and yet you only randomize 30 different individual sites.

So it's going to be important that you have really important controls. You can imagine that every hospital, every clinic is slightly different. And so it may be particularly wise to have a baseline,

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a baseline before they enter into the intervention period and that particular baseline for every hospital allows it to account for unmeasured confounding; that is, a hospital compared to itself probably has a fairly stable population that they tend to see.

They have a fairly stable set of providers. Those providers interact and prescribe a certain way. They influence one another. So having both a baseline period and then an intervention period can be really, really helpful.

It's also important to have contemporaneous controls. So a lot of times you want controls at the same time as the intervention is happening so that you can account for secular trends, new changes in guidance, and so oftentimes you may want to employ what's called a difference-in-differences approach. That means you have two groups. One is the control group. One is the intervention group. Each of them compares its intervention period performance to its own baseline performance. And those differences are compared across the two groups. Next slide.

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That is one way of course to address confounders, and another way is to make sure that we randomize well. This can be particularly challenging when you're randomizing 30 hospitals instead of 30,000 people. When you are faced with having to randomize that, it's really important that you use the methods that are most unlikely to achieve balance in key variables.

There are specialized approaches to do this. We and others have published on this. We've -- the one I highlight here is called the Goldilocks approach and you basically take a whole bunch of baseline characteristics or outcomes that are present in your particular population, your hospitals, your units, whatever you're going to use, your clinics, and then you use those baseline values and you assign specific weights to them based upon your clinical judgment and then you run a whole bunch of simulations of different ways in which you can randomize and you look at the style of randomization scheme that actually gives you the most likely chance that you will always have balance.

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And so if you use that a lot of times you can push the button once and you can pick a schema that actually maximizes your chance of having a balanced draw. This is also important when you look at analysis. Of course it's going to be important to look at confounders, so in addition to the as-randomized analysis, often as-treated or adjusted analyses are going to be important. Next slide.

This is a particularly important consideration for things that occur in acute healthcare, but also in long-term care and these would be competing interventions. We all know that hospitals, clinics are incredibly driven to always improve, and because of that, there are a myriad of quality improvement activities that are being launched, being maintained, and being dismantled at almost any given time.

Because of that, if you have only 30 hospitals, for example, that are joining into a trial, many of them have entirely different baseline activities that are ongoing and the best way to handle this of course is large scale randomization, which I

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just said it's really difficult. Thirty hospitals is already a huge trial. And the other way is to addresses through a difference-in-differences approach.

Another way though that's really important is to really consider what happens during the trial. And so many of the times it's going to be critical for people who are pursuing HAI trials that they actually have to monitor to make sure that new interventions aren't being unleashed every other week during the course of the trial.

A good example of this is the REDUCE MRSA trial that we did. This is an ICU trial for decolonization. And during the course of 18 months of that particular trial, there were 69 hospital interventions that were proposed during that time and 36 of them directly conflicted with the trial and could not be pursued. So a lot of effort for monitoring, dissuading, and managing dropout is really important. Next slide.

Of course, sample size is very, very important. Not only is it important because it always

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is important, but because of the issue related to competing interventions, these types of trials really favor larger, shorter trials. Most clinics and hospitals and ICUs, emergency departments don't like to be locked out from being able to do other things that could improve care.

So, this idea of constant quality improvement is a really big activity that pervades through healthcare today. Same thing, often because we're dealing with things that may be minimal risk, so minimal trials often don't need a robust safety assessment. They don't need an interim analysis and that interim analysis would actually in fact prolong trial time. Next slide.

Analysis. This is a really key area that's going to be discussed better in the next talks. I'm only going to say a few basic things, is that when you have outcomes that are contagious or non-independent you really do need to involve a statistician who is well trained with expertise in this particular area of clustering. And this ability to handle clustering is not only important to

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determine the final outcome of the trial, but it's really important when you're estimating sample size and (indiscernible). Next slide.

So I'm going to give you two examples, a similar example to the one that I said before. These are two different trials. One, the CLEAR trial, was individual randomized controlled trial of 2000 MRSA carriers who were being discharged. They were discharged to either receive education and routine care or they were discharged to receive education and decolonization and that decolonization was repeated for six months and then they were followed for a whole year. So this was to prevent post discharge outcomes of infection and their associated hospitalizations.

On the flip side is the REDUCE MRSA trial. This is a cluster randomized trial of 43 hospitals and their ICU patients, so that amounted to about 75,000 patients, and this was compared in three groups: routine care, targeted, and universal decolonization in the ICU only. And those outcomes that were evaluated are things that are typically available through the electronic health record and

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normally being tracked, and that would be hospital onset MRSA culture and bloodstream infections. Next slide.

So pretty different styles for these two trials. One randomizes individuals and because of that it takes a long time to find them, to identify them, to see who's actually willing to be in a one year trial. So it had a three year intensive recruitment. The REDUCE MRSA trial randomized hospitals in a big health system. It took an eight-week period to recruit them because the system's leaders were reaching out pretty strongly and encouraging people that they knew to actually participate in the trial.

One required individual consent and compensation. The other one waiver of informed consent and no compensation being conducted usually through the -- through the usual courses and through the usual staffing related to hospital care. One required extensive chart review so that after the trial was finished there was still a two-year period where charts were being garnered, redacted, evaluated

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by more than one person, and then adjudicated to get the final answer.

The other one used data from the electronic data warehouse. That shortened the course of analytic time even though the numbers were much greater. And overall, the price per patient can be much, much lower when you're looking at something that's happening during the usual domain of care. Next slide.

So a couple more comments about a few things after the trial is done. There's just a few more concerns or considerations that are important, and one is how do you compare trials over time. And this is particularly important for infection prevention guidance. It may be important for indications, but as we all know, gold standards control stay in place for a while, but then they eventually change.

Whatever is considered gold standard today is unlikely to be the gold standard 10, 15, certainly 20 years from now. And so it raises the question about whether or not we're looking at a

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change on something that was shown to be very effective against an old control. So knowing what the controls are and having really specific guidelines for them can be really important.

A second thing that's highly relevant for infection prevention is sometimes you have three different trials and they all are targeting the same exact outcome. They use the same exact set of controls and they all find, let's say, a 20 percent reduction in the outcome of interest. And so one of the other key questions is then, do all of them need to be performed or in fact, are they additive, are they synergistic, or are they replaceable?

And so there's a lot of questions when we're talking about limited resources and also limited time to train on whether or not these things really are all -- all should be endorsed by upcoming guidelines. Next slide.

Another key thing related to this entire workshop of course is how do we think about FDA indications. Many times, these types of minimal risk trials, these types of population pragmatic trials are

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actually not being done by the companies that would or would not seek an indication. They're usually done by healthcare systems or infection prevention programs that see a need and therefore pursue this trial.

For that reason, these pragmatic trials are not structured to achieve FDA indications and in fact it's not common that a indication would actually -- a company would seek to get an indication using somebody else's trial. So it is possible theoretically, but it's not commonly done.

One thing that's thought provoking is you can imagine that sometimes we say, well it's okay, it's already out on the market. These are usually post-marketing trials, looking for additional usages that are under the domain of medical care but lack of an indication can actually hamper adoption. And why do I say that? Because let's say we just heard that there might be 50, 60 percent of hospitals that are using chlorhexidine bathing, but actually there is no manufacturer indication to do that.

So let's say another 20 percent of hospitals see the new guidelines and say, we better

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start to implement this indication which is now -- or this intervention which is now the new gold standard for the field, and now I can't find a manufacturer who will train me because this is not an indicated use.

Another thing that could actually happen is that a future trial now looks to have a control group and the control arm is going to use a product that does not carry an FDA indication for it. So there's a number of things that are going to be important when we think about what is the current gold standard, what is actually promulgated in the guidelines, and then what is actually going to be a reasonable way in which you can make comparisons or actually achieve an FDA indication. Next slide.

So in summary, there are a wide range of trial designs, trial durations that can be pursued for achieving HAI reduction and evaluating them in the course of a trial. A couple of key issues to consider is whether or not it would be advantageous to use a group level randomization versus an individual randomization, making sure of course, as always that you have sufficient sample size, but this is even more

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important if you do group randomization to make sure that you have robust ways of balancing confounders in addressing a proper control.

You do want to make sure that you count for contagious outcomes in your analysis and in the planning and it's absolutely critical to make sure that during the course of these trials that we actually disclose and assess and record competing interventions and what happens to them as well as ensure data that if a whole group drops out, how do we make sure that we retain the data ongoing so that you can complete an as-randomized analysis. Thanks very much.

DR. DAN RUBIN: Thank you very much, Dr. Huang. That was very informative. Our next speaker is Ed Bein. Dr. Bein is a senior statistician at the FDA where he has worked for five years. He has a doctorate in biostatistics from UC Berkeley. Over.

DR. ED BEIN: Okay, thank you. Okay, next slide, please.

So this presentation is devoted to a review of key statistical and design concepts for

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cluster randomized trials or CRTs, using a minimum of mathematical detail. And let me doff my cap to the two good CRT texts listed at the bottom of the slide, both of which provided much of the content in the succeeding slides. Next slide, please.

So this is a simple, somewhat idealized CRT sampling and randomization scheme. So we have a large population of clusters typically of different sizes. That is, different numbers of individuals belong to them. So for example, in the context of education research, schools might be clusters. In our present context hospitals or ICUs might be clusters. And there's an associated population of individuals which includes all individuals who belong to a cluster.

To implement the trial, we select a random sample of N clusters from the population of clusters and then each of the selected clusters is randomly assigned to treatment one or treatment zero, and then the assigned treatment is administered throughout the cluster. Then for each of the individuals from a selected cluster, we observe their

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endpoint values. And as a running example, let me use the binary endpoint of whether a nosocomial infection was acquired, yes or no. Next slide, please.

Okay. Now let's consider the N1 clusters that were randomly assigned to treatment one. Typically these clusters -- so let me know if there are a couple of typos in the slide where it states clinical success rates, that should read infection rates. So of the N1 clusters randomly assigned to treatment one, typically these clusters have variable infection rates, and I'll let pi(1)(i) denote the infection rate for the I-th cluster among the clusters that were assigned to treatment one.

This variability in cluster level infection rates is due to differences in cluster level characteristics, so in our context, important differences could include differences in funding levels, degree of understaffing, amount of staff turnover, quality of leadership, and patient characteristics. And these and other important characteristics can account for differences in cluster-specific infection rates, even among clusters

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that administered the same treatment.
Going further, we can conceptualize these cluster-specific infection rates as belonging to a population of such infection rates. That is for each cluster in the population, whether or not it participates in our trial, we can consider the infection rate it would have if it were to administer treatment one and then ditto with regard to treatment zero. Next slide.
Okay, now I'm going to talk about the intracluster correlation sometimes referred to as the intraclass correlation. So if there's positive treatment one between cluster variants, then that implies that the endpoint values from pairs of individuals belonging to the same treatment one cluster are positively correlated. This correlation is termed the intracluster correlation denoted either ICC or using the Greek letter rho.
On the other hand, endpoint values from pairs of individuals from different treatment one clusters are independent and are not correlated. So the correlation only applies to individuals from the

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same cluster and then ditto for treatment zero and its intracluster correlation. Next slide, please.
So now, let me talk about some of the downsides of employing CRTs. So let me start by noting that standard statistical methods such as t-test or chi square tests assume independent observations. However, when the intracluster correlations rho 1 and rho 0 are positive, this assumption is violated because some observations are in fact correlated.
This implies that applying standard methods to CRT individual level data will yield overly optimistic p values and overly narrow confidence intervals. Further, the effective sample size when valid nonstandard analysis methods are used is smaller than the nominal sample size. And the next slide exemplifies what I mean by effective sample size. Next slide, please.
Okay so now we're going to consider three different trials, all employing 100 subjects per arm, and you can imagine they're being run in three parallel universes. And the statistical aim of each

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is the same, to estimate the risk difference, the treatment one versus treatment zero risk difference.
And we're going to get -- let RD(hat) be the usual estimator of the risk difference; that is, we compute among all of the subjects assigned to treatment one. We compute the infection rate. Then we focus on all the subjects assigned to treatment zero. We compute the infection rate. And the difference between those two infection rates is our estimate of the true risk difference.
So in case one we're using an individual randomized trial with 100 subjects per arm. In case two, we're going to employ a CRT with 50 clusters per arm and two subjects per cluster, so again 100 subjects per arm. And let's suppose that the intracluster correlations for both arms is equal to .02.
Then this trial has the same statistical power to test the null hypothesis that the risk difference equals zero. That would be obtained from an individual randomized trial with 98 subjects per arm. That is even though the nominal number of

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subjects per arm in this trial is 100, we say that the effective sample size is 98 subjects per arm. And in the third case again it's the CRT but now employing 10 clusters per arm with 10 subjects per cluster. And we're assuming the same intracluster correlations.
Then for this trial it would have the same statistical power to test the null hypothesis that would be obtained from an individual randomized trial with 85 subjects per arm. That is, the effective sample size for case three is 85 subjects per arm.
And so the bottom line is that the statistical power for testing the null hypothesis is greatest in case one, that is the individual randomized trial, and smallest in case three, the CRT that had the fewest clusters. And so taking a step back, CRTs suffer in statistical power relative to individual randomized trials with the same number of subjects.
To what extent they suffer will depend on the number of subjects per cluster and on the magnitude of the intracluster correlation. Next

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slide, please.
Okay, but now let's talk about why we might want to employ a CRT design, and the most compelling reason is that it's the only appropriate trial design when we're seeking to evaluate treatments that are intended to be administered cluster-wide. So this is really an issue of ecological validity that to evaluate treatments that are to be administered cluster-wide, they should be administered cluster-wide in the evaluation study.
And so there's a related issue that CRTs are intended to handle within cluster contamination or interference between treatments. And this is related to the notion of indirect treatment effects that was discussed earlier today. So there's interference between treatments when patients' clinical outcomes are influenced by both the treatments they themselves receive and the treatments that others in their cluster receive.
So imagine I'm living in a household with a number of others and I'm a diabetic and there are other diabetics in my household. Then my blood

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sugar levels will be influenced by the specific treatment I'm taking for my diabetes, but my blood sugar levels will not be influenced by the treatments that may be employed by any of my diabetic housemates. So this is an example of no interference between treatments.
However, let's imagine that some hideous and highly contagious pathogen rears its ugly head and an effective vaccine has been developed for it. Then even if I'm vaccinated, my probability of becoming infected is lower if all of my housemates are also vaccinated than if none of them are vaccinated, as if all of my housemates are vaccinated, then my level of exposure within my household to this awful pathogen will probably be lower. So the treatments that are used or not used by my housemates influences my probability of becoming infected.
And so more broadly with regard to contagious diseases, my outcome when a specific treatment or prevention regime is administered throughout my cluster may differ from the outcome I would obtain if administration were not cluster-wide.

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So if a regime is intended to be administered cluster-wide, it should observe the outcomes resulting from cluster-wide administration. Next slide.
Okay, now let me talk about two different broad analysis approaches. In trials that randomized individuals, the individuals' endpoint values are the outcomes used in efficacy analyses but in CRTs, the analyst has a choice between directly using individuals' endpoint values as outcomes or alternatively using cluster level summaries as outcomes.
So an example of a cluster level summary, for each cluster in the trial, compute its infection rate and then compare the treatment one and treatment zero clusters rates using t-test. An example of a subject level endpoint analysis, analyze all of the individual binary infection outcomes using logistic regression GEE to compare treatments. This is a version of logistic regression appropriate for hierarchical data where individuals are clustered within higher level units. Next slide, please.
So you may recall that in the second

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slide, I talked about two populations of interest, the population of clusters and the population of individuals. And so treatment effects can be defined separately with regard to each of these populations. So at the cluster level, each cluster can be thought of as having its own specific risk difference. This is the infection rate the cluster would have if it were to administer treatment one minus the infection rate the cluster would have if it were instead to administer treatment zero.
And we defined the cluster level risk difference as the mean cluster specific risk difference over the population of clusters. Alternatively, imagine that all individuals in the population of individuals receive treatment one call the resulting infection rate, rate one. Ditto for treatment zero and rate zero. Then we define the individual level risk difference as the difference between rate one and rate zero. Next slide, please.
Okay, so buyer beware. In general, the individual level risk difference does not equal the cluster level risk difference. So now if we could go

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back to slide nine. So that's two slides back. Thank you. In the example of -- in the t-test example of cluster level infection rates, the null hypothesis is that the cluster level risk difference equals zero. However in the logistic regression GEE example, the null hypothesis being tested is that the individual level risk difference equals zero. So in general, these two null hypotheses differ. Okay, now if we can go forward to Slide 11.

So the bottom line is that the method of analysis should target the treatment effect at the level of clinical interest. In practice, this will typically be the individual level risk difference but this is really a substantive issue and not a statistical issue. Next slide, please.

Okay, now let me briefly talk about different kinds of CRT designs. So the design -- the simple design that I presented in my second slide was a completely randomized parallel group design. And parallel group design means that each cluster administers a single treatment over the course of the trial. But there are two other kinds of parallel

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group designs of note, one is the matched pair design and here, clusters are paired based on similarity on baseline characteristics predictive of outcome. And then one member of each pair is randomized to treatment one and the other pair goes to treatment zero.

And another type of parallel group design is a stratified design where clusters are grouped into strata defined in terms of baseline characteristics predictive of outcome, and there are at least two clusters in each stratum that are randomized to each arm.

Let me note that there are also designs that are not parallel group designs and examples would be crossover designs and step wedge design. And with these designs, each cluster administers both treatments over the course of the trial but these treatments are administered at different non-overlapping periods of time. Next slide, please.

So let me very briefly consider some considerations for choosing the type of CRT design to employ, and this is a complex topic so I'm just, you

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know, dealing with this very briefly. So a major concern is the issue of between-arm imbalance on important cluster-level baseline characteristics. And so this kind of between-arm balance matters for face validity and for statistical power.

So regarding face validity, imagine that we're running a CRT with a small number of clusters and by the bad luck of the draw all clusters from rural areas end up in one arm and all clusters from urban areas end up in the other arm. Then whatever the CRT results, readers of these results are likely to be skeptical of generalizing the results to general concerns about how the rival treatments work.

Now the concern about between-arm imbalance will be minimal if there are a very large number of clusters included in the trial, but that will be more the exception than the rule, and otherwise pair matching or stratification can improve balance as was discussed in a previous talk.

The Hayes & Moulton textbook generally recommends using stratification over pair matching, but this is an area of active research and so there's

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no final word here. And let me also note that covariate-adjusted statistical analyses can be used to adjust for some degree of between-arm imbalance and thereby increase statistical power. But particularly when the endpoint is binary endpoint, such analyses require a particular amount of care.

So that's it for the talk. Thanks very much.

DR. DAN RUBIN: Great. Thank you so much, Dr. Bein. Our next talk is Controlling Pathogens in Healthcare: A Way Forward presented by Dr. Robert Weinstein. Dr. Weinstein is C. Anderson Hedberg, MD Professor of Medicine at the Rush Medical College and chairman emeritus, Department of Medicine, Cook County Hospital, Chicago. Dr. Weinstein has been president of the Society for Healthcare Epidemiology of America. He's been chair of CDC's Healthcare Infection Control Practices Advisory Committee, an Infectious Disease Society of America board member and voting member of the President's Advisory Council on Combating Antibiotic-Resistant Bacteria. Dr. Weinstein.

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DR. ROBERT WEINSTEIN: Thank you. I'm going to be talking today about controlling pathogens in healthcare, what I see is a way forward, and disclosures are this is my personal -- these are my personal views. Next slide.

I have what I consider to be three key topics. The first is I'll start with a model of the causal pathway of spread of multidrug-resistant organisms with a focus on potential decolonization interventions. Second, I'll discuss the potential need to deconstruct infection prevention ensembles. And third, I will stress the need to understand the fecal patina, which can be defined as the coating of multidrug-resistant organisms, often on the skin of patients who are in acute and long-term care and the related microbiome interactions. Next slide.

The first topic is the causal pathway which is somewhat similar to the slides that John Jernigan showed earlier this morning, and starting in the upper left, the patient comes into a hospital with normal flora or if they're readmitted or a nursing home old patient, they may have pre-existing

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antibiotic resistance, and then some reasonable percentage of them -- I've guesstimated 10 to 40 percent -- after exposure to antibiotics or due to colonization pressure which is the patients around them who have antibiotic-resistant organisms and maybe other situational factors, will become colonized with drug-resistant bacteria or fungi.

Virtually 100 percent of these patients will have this fecal patina, that is skin colonization of these organisms, in addition to GI and respiratory carriage. And then some percentage of these patients will shed these organisms within the environment. They will contaminate healthcare worker hands. The hands will move from patient to patient and lead to patient cross colonization with multidrug-resistant bugs and then some variable percent of patients depending on their procedures, underlying risk factors, exposures, and so forth will develop clinical infections with the bacteria or fungi that are colonizing them.

Now historically -- next slide -- we started our interventions at the bottom of this list

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so we started with the device guidelines and reporting rates and cluster detection as some of our earliest interventions. Device guidelines you've heard about already today related to IV catheters, bladder catheters, endotracheal tubes, and so forth. And these are good sites for decolonization, decontamination interventions.

Reporting rates is useful for people to know what's going on -- it turns out if you know that you're worse than your neighbors, you try to do better -- and then cluster detection to try to reduce the risk of further spread of bacteria that are already causing many clusters. Next slide.

As you move up the pathway, hand hygiene is applied. Some patients are screened in some interventions. Isolation precautions are applied. And again cluster detection. Hand hygiene is a good site and patient screening are good sites obviously for decolonization interventions. Next slide.

Dealing with healthcare worker hand contamination. The obvious intervention is hand

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hygiene, and there's also potential for universal gloving which personally I think is one of the most effective interventions in this, in the interventions I'm going to show in this pathway. Next slide.

For the environment, and you've heard that the environment is particularly problematic for some bacteria like vancomycin-resistant enterococci for C. aureus, for C. difficile, also for some acinetobacter strains, for some fungi. It's a problem beyond C. aureus and improved environmental cleaning is obviously an intervention. Next slide. Next slide.

I think that the most striking intervention in this whole pathway in my view, and you've already heard about this is chlorhexidine bathing. There have been key demonstrations of the efficacy of decolonization of the skin, sometimes with even greater than expected benefits in terms of preventing bacteremias, for example in ICU patients. Next slide.

And then finally the most recent interventions have gone -- have gotten to the very

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root of the problem which includes antibiotic stewardship, microbiome restoration which you've heard about today, and other potentially situational interventions.

This leads me to topic two with all of these -- next slide -- with all of these guidelines and all of the yellow interventions that are on that -- that I put on the pathway which are largely ensembles, what does the heavy lifting? Who is important? And here I show a picture of Seinfeld. You know, is Jerry most important? George? Elaine? Kramer? Or I could have shown a picture of Big Bang Theory which actually I like better. Who does the heavy lifting? Next slide.

So I want to give you an example from a guideline. This is from 2002, so two decades ago. This is the first CDC/HICPAC IV Catheter Infection Prevention bundle and you could take all of the recommendations in this guideline and distill them, I think, down, boil them down to the first five interventions: education of personnel about taking care of catheters, checking daily.

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Is the catheter needed? Remove it if it isn't. Avoiding routine catheter replacement is an infection control strategy. Using chlorhexidine skin prep. And then subsequently after this guideline was published, it was shown that bathing patients daily in ICU with chlorhexidine is a major benefit for preventing CLABSIs and then maximum barrier precautions for those inserting lines. That is, they should be wearing masks, gowns, gloves, and so forth.

Now there are only five really key interventions in this bundle, and each of them has been shown in a randomized trial to be effective, but we don't know which of these is most important. Does it matter? You might say, so what. There are only five of them. Do them all. And that's a reasonable response. I mean you probably wouldn't want to kick Jerry or George or Elaine or Kramer out of that ensemble. So that's reasonable. So what.

But -- next slide -- if you fast forward 20 decades, you can see there is the hackneyed slippery slope and so "essential" -- in air quotes -- now is a very long list. And this is the most recent

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iteration of guidelines for preventing CLABSIs and what's considered essential.

And so you could ask again really, are these all really essential? Which are the most essential? And I think this is an important issue as you start to add decolonization to the bundles or to the ensembles and as already pointed out this morning, it's important to understand what the role of decolonization is in light of all the other interventions.

Now, how would you figure that out here? It's difficult. I suppose you could use a network meta analyses or you could do some trials and I can't really tell you how you figure it out exactly, but I can tell you it's an important issue and it will become increasingly important as decolonization strategies are added to ensembles or bundles. I want to give you one other example of an ensemble. Next slide.

And this is, you'll see on the next slide the recommendations that are being developed and this is a draft so I superimposed the lists on top of

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each other so they're not as easily read, because it is in progress but you can see for hand hygiene there are a lot of "essential" -- in air quotes again -- recommendations. Here though, I think we can be more focused. Next slide.

And I think that the guideline as written is an excellent advice for infection control of personnel for hospitals, for nursing departments that are facing a variety of administrative issues. And so we recommended -- I don't know if this is going to be accepted -- but recommended that this hygiene follow the keep it simple principle and start with this declaration.

"This is a carefully and thoroughly compiled set of recommendations for use by infection prevention groups that are responsible for developing institutional policies." But "For the individual patient provider, the single message is very simple: hand before and after every patient is essential."

So I think some bundles or ensembles can be boiled down to the simplest message, and again, I think this is going to be very important as

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decolonization strategies are added.

And this takes us to the third topic. The next slide. Microbiomes, understanding them at clinical, epidemiologic, and mechanistic levels. This is a translation of an old quote from Goethe that says, "What is the hardest of all? That which seems most simple: to see what is before your eyes." And I want to give you two examples of microbiome interactions and how important it's going to be to understand them. Next slide.

This is a picture of an axillary culture of a patient in one of Mary Hayden's long-term care studies, and you can see this is a patient receiving daily chlorhexidine bathing and before the bathing, the patient had -- this wall to wall, multidrug-resistant mucoid Klebsiella pneumoniae in the axilla. Your axilla should not have Klebsiella pneumoniae in it, and you can see afterwards, after the bathing, it's been removed.

So this is a good example of the fecal patina. You can find this bug elsewhere, on the neck, in the groin, on the back, on the chest, all over

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these patients. This is just one site that's colonized, and I think it makes the point that the fecal patina is a very interesting, important, and dynamic concept. Next slide.

You can see removing the fecal patina made the patient happy or at least in this picture made the agar plate happy. And chlorhexidine bathing has an effect on resistant gram-negatives, on resistant gram-positives like MRSA and VRE and the benefits for the patient clinically are very marked with decreased risk of infection with the bugs that are on -- the that are removed from the fecal patina, and the benefits to the hospital and the nursing home epidemiologically as John Jernigan showed this morning with a slide about VRE in an ICU that with chlorhexidine bathing daily, there's lessened likelihood of spread of MDROs.

It's important to realize that these patients may still have GI or respiratory tract colonization with this pathogen. The only thing that's been removed is the fecal patina, and yet there is a major benefit in terms of both clinical outcomes

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and epidemiologic problems. This does raise the question of the interrelations of the different microbiome compartments.

For example, using kind of an older terminology, is this klebsiella on this patient a resident flora that is it permanent flora now in the axilla and on the skin or is only transient? Well, it has to be removed every day which suggests that it may be more resident than transient.

The other implication I think is if you focus your intervention on the gut microbiome, what will happen to the skin microbiome? Because if you remove the resistant klebsiella from the gut but it remains on the skin because its resident flora, then your gut intervention may not be very effective. Next slide.

Along those lines, I wanted to show you a study that was done by Kyle Popovich looking at MRSA 300, which as you heard earlier today is the typical community-acquired methicillin-resistant staph aureus. And this is looking at genomic clusters; that is, the relatedness of MRSA among women who are detainees at

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the Cook County Jail and genomic clusters are defined genetically by looking at the number of variants between MRSA isolates.

And you can see in the top line of this table that if you have nares colonization, your chance of being in a cluster, that is having your staph aureus similar to other detainees, was much less than if -- than not being in a cluster. So women who had nasal colonization were much more likely to have unique strains of MRSA not related at all to the other strains of other individuals.

And you can see bullet one, an interpretation was nares colonization was negatively associated with being in a genomic cluster and could represent mostly endogenous colonization.

Now if you look at the bottom line of that table, this looks at those detainees who have what's called exclusive extranasal colonization. That is, they were carrying staph aureus, MRSA, methicillin-resistant staph aureus, USA-300, community acquired strains, but they had it at sites other than the nose. So their noses had no MRSA, but their

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groins or backs or axilla or other side on their body, perianal sites had MRSA. And you can see in bullet two under the interpretation that exclusive extranasal colonization was associated with being in a genomic cluster.

So those with only extranasal colonization, 80 percent of them were in a cluster, meaning their strains were similar to other patients suggesting that this colonization pattern predisposes to exogenous MRSA acquisition. And in the last bullet underlined, "the findings suggest that nasal colonization may serve a controller role in limiting exogenous acquisition."

So it's important I think to understand the interrelations of various components of the microbiome in various compartments. Next slide.

So in conclusion, a model of the causal pathway of spread of antimicrobial-resistant organisms, I believe, can help focus implementation of strategies for pathogen reduction and the role of colonization and decolonization.

Second, infection control guidelines

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and bundles are not parsimonious as currently formulated, and the relative importance of the individual components should be evaluated. And I think this is going to take on increased importance as new components may be added to target colonization.

And the third point is that studies the microbiome should assess mechanisms behind the creation of the fecal patina, how does it get there, how does it persist, and explore the interrelations of different components and compartments of the microbiome. Thank you very much.

DR. DAN RUBIN: Thank you very much, Dr. Weinstein. Our next speaker is James Kim. Dr. Kim is the vice president of Science and Regulatory Affairs and leads the scientific team at the American Cleaning Institute, the trade association for manufacturers of soaps, hand sanitizers, cleaning products, and their chemistries. Over.

DR. JAMES KIM: Afternoon. Thank you for having me today to discuss the American Cleaning Institute's ongoing research to support the safety and efficacy of over-the-counter topical antiseptics and

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also touch on an opportunity to bring innovative products to the market. Next slide, please.

As already noted, the American Cleaning Institute is a trade association for the cleaning products industry, including suppliers, formulators, and packaging companies. ACI is also the trade association representing the topical antiseptics industry and is currently supporting the safety and efficacy research for five of the six over-the-counter antiseptic active ingredients that were deferred from final regulation by FDA several years ago. Slide, please.

This is brief slide to show you who are the ACI members that are producing topical skin antiseptic ingredients and products, and these are the companies that are actively supporting the extensive FDA data requirements for generally recognized as safe and effective determination. This collaboration really has been ongoing since 1994, when FDA promulgated the tentative final monographs regulating healthcare and consumer antiseptics.

The topical antiseptics have been used

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safely for many decades in both professional and consumer settings, and as illustrated by Dr. Weinstein on the previous presentation, there is a role for effective hand hygiene practices and these antiseptic products in preventing hospital associated infections.

Just to backtrack with a little history, ethyl alcohol started being used in the 1880s in Germany for presurgical hand disinfection. And in fact, professor Philip Price from the Johns Hopkins University published a paper in the Archives of Surgery in 1939 titled "Ethyl Alcohol as a Germicide." Alcohol-based hand sanitizers have been recommended over soap and water by the CDC in their healthcare hand hygiene guidelines since 2002, and also by the World Health Organization in 2009.

And we also saw that alcohol-based hand sanitizers were a critical tool during the COVID pandemic, as evidenced by the FDA allowing emergency production of hand sanitizers. OTC topical antiseptics are regulated by FDA's OTC monographs and recently monograph reform. And while new drug approvals can be pursued for these products, this

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regulatory pathway is long, costly, and commercially risky.

It is also important to note that OTC monographs provide the criteria for antibacterial efficacy claims, but these monographs do not include antiviral or decolonization claims and this constrains development and use of products for reducing infections due to skin colonization. Slide.

Okay, this table shows the five active ingredients on the left side that ACI is supporting for safety and efficacy research, and these are cross reference with the consumer and healthcare indications promulgated by FDA in the final monographs. The healthcare indications are patient preoperative skin preparation as well as preinjection skin preparations, personal hand washes, personal hand rubs, surgical hand scrubs, and surgical hand rubs. All five ingredients that ACI is supporting are eligible for the patient preoperative and preinjection skin uses. Slide.

This table summarizes FDA's assessment of the safety data gaps for over-the-counter topical

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antiseptic ingredients. As you can see, ethyl alcohol safety is well proven and understood, but filling the remaining safety gaps for all of the active ingredients will be costly. Ethyl alcohol and povidone iodine are the two ingredients that have nearly complete safety information for a GRAS determination and also have shown no resistance potential.

ACI has also completed a literature review on resistance potential for the three other active ingredients that we are working on, including benzalkonium chloride, benzethonium chloride, and PCMX or chloroxylenol, and this literature review was submitted to FDA last year, in 2021.

This slide shows the current status of ACI research. I'm not going to go into too much detail on this slide except to say that the topical antiseptics program has been actively working on the maximum usage trials to fill the safety data gaps and is also working on several healthcare efficacy studies.

In total, we are managing over 20

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active work streams to ensure that progress towards meeting FDA's data requirements were generally recognized and safe and effective determinations continues. Programs on topical antiseptics have been searching for infection prevention study designs that are reasonable and manageable and so special thanks to Dr. Theresa Michele for providing an overview of the rule makings governing these products a few talks earlier.

For consumer antiseptics, FDA requires a clinical outcome study that demonstrates a direct clinical benefit such as reduction in infection. This is in contrast to the requirements for healthcare antiseptics that used surrogate endpoints such as bacteria log reductions to demonstrate effectiveness.

The studies that were pursuing for the consumer clinical efficacy study, FDA provided feedback to us several years ago on using an enriched population to manage confounding variables as well as to increase the power of the study. We are currently pursuing a study design using U.S. Marine Corps recruits as an enriched population with different

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barracks serving as control and treatment groups. Skin infections are always a challenge for our military, particularly in situations like basic training and in situations of close quarters like on ships, and these infections can result in significant loss of active time.

The plan is to propose to FDA to use skin colonization as one of the clinical endpoints in the study and we will have to provide evidence to FDA that correlates colonization with other outcomes including infection rates. So I am very appreciative of the earlier talks today by CBC that provided an excellent overview of these issues.

And finally, just a brief summary of some of the topics I discussed today. The current regulatory structure can be a significant barrier to the development of innovative topical skin antiseptics. While the new drug approval process for new skin antiseptics exists, it is a long, costly, and challenged with uncertainty type of process.

Monograph reform is a potential mechanism to facilitate new skin antiseptic products

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and technologies to reduce infections and pathogen transmission, but for either regulatory pathway establishment of skin decolonization and pathogen reduction as a determinant of clinical outcomes would greatly facilitate new antiseptic development.

So we look forward to working with FDA to clarify these requirements for new products and continue to enable innovation to benefit public health.

So finally, I'd like to thank you for your time and turn it over to my colleague Nicholas Georges who will talk about surface disinfectants in healthcare settings.

DR. JOHN JERNIGAN: Thank you, Dr. Kim. Let me -- this is Dr. Jernigan. Let me introduce Dr. Georges who will talk about Development of Efficacious Cleaning and Disinfecting Products in Healthcare Settings. Mr. Georges is the senior vice president, Scientific and International Affairs for the Household and Commercial Products Association. HCPA represents member companies that manufacture and sell products used for cleaning, protecting, maintaining, and

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disinfecting homes, commercial, and institutional environments. Mr. Georges.

NICHOLAS GEORGES: Thank you. My name is Nicholas Georges and I'm the -- with the Household and Commercial Products Association, a trade association representing the interests of member companies which are involved in the manufacturing, supply, and marketing of trusted and familiar products used for cleaning, protecting, maintaining, and disinfecting home and commercial environments including healthcare settings, as just was said.

HCPA is comprised of seven products divisions including a dedicated product division for antimicrobial products such as disinfectants and sanitizers and a product division dedicated to cleaning products which we'll be getting into here shortly.

Before working for HCPA, I came from industry where I held roles in which I was responsible for formulating these types of products as well as ensuring their compliance with applicable laws and regulations, so I have hands on experience when it

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comes to these products.

All right. Products used to kill viruses and bacteria on surfaces are registered as antimicrobial pesticides. I'll be discussing sterilants, disinfectants, and sanitizers today and I should note that when I say sanitizer, I'm referring to products used on inanimate objects and not on the human body. I will not be talking about antiseptic rubs, which James Kim just covered.

For the most part, the products that I will be talking about are regulated by the Environment Protection Agency under the Federal Insecticide, Fungicide, and Rodenticide Act, also known as FIFRA. FIFRA is the federal law that sets up the basic U.S. system of pesticide regulation to protect humans and the environment. To kick things off, I'm going to first be discussing disinfectant sanitizers. Disinfectants are subject to more rigorous EPA testing requirements and need to meet a higher bar for FDA than sanitizers.

For both product types, either the product meets the efficacy requirements or they do

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not. Once they meet the efficacy requirements, industry is not allowed to compare them against another. For instance, for products that meet the efficacy requirements, I cannot say an aerosol products is a better delivery form than a trigger spray or compare those to a wipe product. This is a requirement under FIFRA and EPA takes it very seriously.

Sterilants get a bit more complicated, as they are regulated by FDA when they're used on medical devices. Whereas they're regulated by EPA for all of their applications. Registrants are not allowed to have products, you know, mix their claims, that is both have medical device and other applications, and as such because companies cannot have one product that is one label for multiple applications that cover both, it makes it easier to distinguish who has authority over regulating the product. This approach stems from the 1993 memorandum of understanding between FDA and EPA.

Then cleaning products don't undergo the same rigor that disinfectants and sanitizers do as

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they do not make any biocide claims to control microbial pests. Cleaning products are either regulated by the Consumer Product Safety Commission or the Occupational Safety and Health Administration, depending on where the product is being used.

If a cleaning product were to make a biocidal claim, the product would need to be registered with the EPA as a disinfectant (indiscernible) sanitizer, otherwise the company may -- would be making a claim in violation of FIFRA. Next slide, please.

EPA, through the Office of Prevention, Pesticides, and Toxic Substances has developed a series of test guidelines for the use and the testing of pesticides, including disinfectants, sanitizers, and sterilants. Group B within Series 810 offers antimicrobial efficacy test guidelines which are intended to meet testing requirements under FIFRA.

The term product performance refers to all aspects of a product's effectiveness and usefulness conducted in light of expressed and implied labeling claims or recommendations concerning pests,

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sites, methods of application, application equipment, dosage rates, timing and number of applications, new situations, nature and level of pest control, duration of pest control, compatibility with other chemicals, benefits and or adverse effects of product use, compatibility of common practices associated with the sites, active ingredient status of chemicals and formulation and equipment.

FDA as part of their guidance for industry and FDA reviewers also has guidance as part of the premarket notification submission of sterilants. This guidance facilitates the assembly of the necessary data to support the introduction of a sterilant for medical devices into the market. Cleaning products don't have this level of detail in terms of guidance from federal agencies. However, there are industry standards that help companies determine the effectiveness of their products and those standards can be referenced by government programs.

For instance, EPA's Safer Choice program, a government program which helps consumers

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and businesses identify effective green cleaning products utilizes both ASTM and our HCPA performance test methods and guidelines for their certification. Next slide, please.

So how should healthcare institutions go about selecting the right product? There are a few things to ask oneself before selecting your product. What is it that you are looking the product to do? Are you looking to clean a surface or disinfect and sanitize it? If clean, what type of surface or surfaces and is the chemistry of the cleaning product compatible?

If you're looking to disinfect or sanitize, are you looking for a general disinfectant or sanitizer or is there a specific bacteria or virus you are concerned with? If it is the latter, ensure the organism is listed on the label. And in all cases, it is critical to read and understand the label. Next slide, please.

So in closing, choosing the correct product for the specific task can help reduce the chance of infection. So with that I would like to

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thank you for your time today.

DR. DAN RUBIN: Thank you very much for that presentation. Our next speaker is Erin Duffy. Dr. Duffy is the chief of research and development at CARB-X. CARB-X is a global biopharmaceutical accelerator for the discovery and early development of products to prevent, diagnose, and treat bacterial infections. Most of her professional growth was with Melinta Therapeutics founded as Rib-X Pharmaceuticals where over 17 years she became executive vice president, chief scientific officer, R&D site head. Over.

DR. ERIN DUFFY: Thanks very much, Dan and the organizers for the invitation to participate in this workshop. It's been terrific so far. I hope I don't mess that up. Next slide, please.

So for those of you who aren't familiar with CARB-X, as you just heard, we are a biopharmaceutical accelerator funded by three international governments and two foundations for the purpose of supporting the discovery and early clinical development of products to diagnose, treat, and

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prevent bacterial infections.
You can see the numbers here. We have about now $800 to $900 million to deploy in these endeavors. Some stats in the bottom here. We've funded just about 10 percent of all of the applications that we've received since 2016, and I should say these are all through active funding calls.
Today, there are 45 active projects and we've had a lot of maturation in the program in terms of movement into clinical stage programs and into advanced clinical development. And this is going to frame a lot of what I'm going to talk to you about, especially where our non-traditional portfolio is concerned. Next slide, please.
So just to give you a sense of the types of products that we invest in the non-traditional space, I should say our heritage certainly was direct acting small molecule therapeutics but we recognize, like many have said today, the need for many different ways to target antimicrobial resistance. And so on the left, you see the distribution of the types of modalities that we

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support, non-traditional modalities for treatment that includes programs in anti-virulent antibody-based programs, immune-directing programs, and bacteriophage programs and other modalities as you can see.
On the right is a representation of our prevention portfolio, and certainly while half of that is vaccine directed, we do embrace other modalities as well. The two that I'm calling out here are our live biotherapeutic portfolio and our engineered bacteriophage portfolio, and these are programs that are focused on decolonization in different -- of different pathogens in different populations.
So I should say these programs are maturing towards a clinical stage and one of the things that we want to do, even though it is true we only fund to the end of first in human, we feel it's important to prepare these programs for success so that there is a next best advanced development partner and so that the work and the money that we've spent to bring these programs forward doesn't die on the vine but rather delivers a meaningful product for patients. Next slide, please.

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And so to that end, we are commencing a series of discussions on decolonization, both to educate ourselves and then hopefully to give some quality advice to our product developers. And so this is a workshop that we convened in early July. It followed on a series of discussions that we had at ECCMID this year in a small session with surgeons titled, "How do I treat my transplantation patients?"
And so this is the group that we assembled. The first, his name is Maxime Mallet. He is a surgeon, a French surgeon who's focused on liver transplantation. Eugene Katchman from Israel is a transplant ID consult. Miriam Furst-Wilmes is part of our accelerator network at (indiscernible) and so she participated to give the view of (indiscernible) on decolonization.
Many of you will know Mark Goldberger, former medical director of Emerging and Pandemic Threat Preparedness, and also director of Office of Antimicrobial Products. And then finally, David Cook, who is an advisor of our, formerly the chief scientist of Seres and now with Forma Therapeutics. Next slide,

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please.
So we raised a number of questions or poised a number of questions to the participants, and I'm not going to read all of these for you, but it was really to set the stage for the discussion. And I want to highlight two key questions where we spent most of the discussion, and the first is -- we've heard a lot about this today -- what patient populations or populations are best suited to obtain early proof of concept, and then what endpoints in a clinical setting do you feel are meaningful to show a benefit for decolonization product. And relatedly, what is the time frame where you would consider a patient sufficiently de-risked from an infection perspective. Next slide, please.
So here are some key themes that emerged from the discussion. In terms of our surgeon and surgeon consult, decolonization was not routinely employed in their practices, but they feel that they need something beyond antibiotics. They're not using antibiotic prophylaxis now because of the extreme prevalence of colonization with ESBL, CRE, and

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fluoroquinolone-resistant organisms, in some cases greater than 80 percent.

And so the discussion sort of ended saying, well, what if we worked back from a label that might begin with, "For the reduction of colonization in a closed population..." And so the closed population is meant to say that there was a lot of feeling that we really needed a homogeneous group or as homogeneous as you can get in order to reduce the signal to noise and perhaps have meaningful outcomes.

So in terms of proof of concept, we agreed that a quantitative microbiology endpoint is good but what is a sufficient measure of success? So for instance, what if, you know, there's 10 to the 11th colony forming units at the outset and you reduce that to 10 to the 8th; is that meaningful? You're still leaving a lot of bacteria on the table.

So how do we think about this and what are the bounds that we should put on that? The second point of course is that for pivotal studies the quantitative microbiological endpoint will not be enough. There needs to be a link to clinical benefit.

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And of course this might vary with the closed population, so can we in fact translate results to other populations.

We certainly discussed biomarker strategies and felt that while they're interesting, the question is what is relevant and what is the signal to noise where we can harvest interesting and usable information, again a big question about translatability from one population to the other, and then finally a need to understand the effects of decolonization, how they manifest over time, and what external variables might influence them. Next slide, please.

So I'm going to give you four examples of populations that we felt were perhaps reasonable to consider in the conduct of clinical trials, and the first was patients awaiting liver transplantation and here are the reasons. They often present with recurrent ascites. Greater than 30 percent are carriers of CRE, ESBL, and fluoroquinolone-resistant organisms, and again, this varies by country and by hospital. They're at risk for developing infection

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post transplantation and indeed they are most fragile in days following surgery. And it's important to note that it was not felt that infection would be gained in the ICU.

So thoughts about a study could involve decolonization at some time point prior to transplantation and then with early and late readouts. Now of course, we would need an understanding of the time course with respect to transplant for the development of infection. It's likely that this would be placebo controlled unless, of course, standard care requires preventative antibiotic therapy where it would be on top of. And then we would need an understanding of how this impacts those on the transplant list. Next slide, please.

The second population that we discussed was cirrhosis patients who are hospitalized with ascites and this is because they are reported to have about a 10 to 30 percent likelihood of developing a spontaneous bacterial peritonitis. And indeed in a study in 2016 published in the World Journal of Hepatology, it appears that There's a 40 percent

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chance after six months and a 70 percent chance after 12 months of recurrence following antibiotic use.

And so a thought was that the study could be a small pilot to understand durability of the antibiotic effect, treat at some point after discontinuation of the antibiotic, and then follow up. Of course some patients are eligible for preventative use of antibiotics. Do we add decolonization on top? Do we compare decolonization to the use of antibiotics? Do we consider studying lower risk patients versus placebo?

Third population -- next slide -- that we discussed with patients awaiting induction chemotherapy? The reasons is that there are many of them. They're often less complicated and fragile. Many are neutropenic and need antibiotic therapy. And so a thought here was that a study would be on top of standard of care antibiotic versus antibiotic alone, and likely we would need to demonstrate a benefit in mortality.

And then finally, a population on the next slide that we discussed was something that's been

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discussed here today, which is decolonization of residents in nursing homes. Certainly as we learned here today, high rate of multidrug-resistant organism colonization and the worries about that with potential transfer to the hospital for higher level care.

Now thoughts where we could randomize by facility but we had some questions. Need to have similar demographics across those facilities. We would need decontamination of significant reservoirs. There's the issue of testing of staff as well as all new residents that come in. Decolonization product would need to be broad spectrum unless you want to start slicing and dicing within that community. And that this is, in our estimation, best considered after proof of concept has been shown in one of the other populations that I just shared.

So in summary, on the final slide I just want to emphasize that we are committed to bringing solutions from nontraditional approaches forward because we feel they're going to be important in the overall approach to antimicrobial resistance. We see both several challenges and opportunities in

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decolonization strategies, but we emphasize that a closed population is critical and the need for both microbiological and clinical endpoints is clear.

And then finally, and I think the purpose of a meeting like this is to emphasize that a coordinated approach among many of the stakeholders will be beneficial to the ecosystem. Thank you very much.

DR. JOHN JERNIGAN: Thanks very much, Dr. Duffy. It's great to hear that CARB-X has been thinking about this and has been having discussions to advance this field along.

Our next talk is entitled Challenges and Lessons Learned Developing DAV132, a Novel Therapy Protecting the Gut Microbiota from Antibiotic-Induced Dysbiosis. It will be given by Ms. Florence Sejourne. Ms. Sejourne is the CEO of Da Volterra, a biotech company that develops innovative products such as antibiotics targeting medical needs, including prevention of infections. She's also the founding board member of the BEAM Alliance, which represents European biotech companies involved in developing

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innovative products to tackle antimicrobial resistance. Ms. Sejourne.

FLORENCE SEJOURNE: Thank you very much, FDA and CDC, to have invited me as the representative of De Volterra as well as the BEAM A Alliance. I'm glad to present to the virtual audience today the status of development of a novel microbiota protective therapy named DAV132 and highlight challenges faced and lessons learned. Next side.

Everyone in the audience is very familiar now after a few hours of workshop with the well-described impact of antibiotics on the intestinal microbiota which leads to a decreased diversity called dysbiosis triggering a series of deleterious consequences as human. This has actually been very well covered earlier today by the colleagues from CDC. Next slide.

Da Volterra has been actually developing for the last 15 years gut microbiota protective therapies to be co-administered with any antibiotic in order to prevent such deleterious consequences and maintain the function of a healthy

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and diverse microbiota. Several benefits are expected for such novel drug: prevention of C. difficile infections, reduction of colonization by resistant strains, and more recently maintenance of the immune system enabling, for example, immune oncology drugs like ENTPD1 to remain efficient in cancer patients who have infections and need to be treated by antibiotics. Next slide.

DAV132 is the most advanced product developed by Da Volterra. It is composed of a powerful absorbent and selected coating that capture and inactivate antibiotics only in the colon. The full and only delivery of the absorbent in the colon enables the antibiotic block peaking levels to remain intact while protecting the microbiota. Next slide.

So a lot of data has been generated on DAV132 those last years, most of which being published. I have a list of publication here at the end of the slide set. We have first validated DAV132's capacity to prevent CDI in a series of preclinical experiments with multiple antibiotics using the hamster reference model. More recently, we

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have demonstrated in a proof of concept study in mice the capacity of DAV132 to actually maintain the ENTPD1 one efficacy which was impaired by only five days of antibiotic exposure using fecal samples or clinical studies, and that will be presented very shortly at SMO in Paris.

I will comment in the next four slides some of the clinical and microbiological data obtained in a series of seven clinical studies where DAV132 was shown to have an efficient and reproducible mode of action in humans with a good safety profile enabling us to move to Phase 3, and the CMC package of the product was validated for Phase 3 as well. Next slide.

So first set of data there. You can see DAV132 can, on the left, inactivate most antibiotics in vitro and ex vivo. Then we moved to clinics and we've shown that DAV132 was efficiently capturing antibiotics in the colon, both fluoroquinolones as well as beta-lactams, whatever oral and IV, without impacting the plasma concentration that is here presented on the right.

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Next slide.

Such decrease of antibiotic exposure in the colon has led to a nice protection of the microbiome diversity, once again both demonstrated with fluoroquinolones and beta-lactams. This was evaluated both from diversity indexes as well as microbiome composition heat map as you see here with 16S and shotgun technologies. Next slide.

So in order to associate such biological demonstration of microbiome protection to actual biological functions, we have conducted additional analysis. The first analysis was done here was done in ex-vivo study conducted with fecal samples from our clinical trials showing that in patients receiving our product DAV132 together with either fluoroquinolones or beta-lactam, fecal samples when exposed to C. difficile spores were protected from proliferation. This really meant to us that DAV132 maintained the gut barrier effect and allows the resistance to colonization function by C. diff to be protected.

In addition to this -- next slide -- we

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looked as well at VRE counts within our clinical Phase 2 trial and here you see that at the end of the antibiotic treatment DAV132 group had a significantly reduced VRE count. So overall, all we manage in those series of clinical studies to have a solid Phase 1, Phase 2 clinical package in order to move forward to Phase 3 study which was designed to demonstrate the prevention of C. difficile infections in patients at risks. Next slide.

So we decided to select the AML patient population as an enriched patient population at risk of CDI, as they were described actually to have more than 12 percent risk of C. diff infection four months after the start of their induction chemo. Furthermore, in those patients protection of the microbiota from antibiotic dysbiosis is expected to lead to additional clinical benefits such as reduction of resistance colonization, infections, and even prevention of GvHD for those who have to undergo (indiscernible).

The protocol was designed as a multicenter randomized placebo controlled parallel arm

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clinical trial and the study was designed and launched in a public private partnership with European academics via the COMBACTE-NET consortium, co-funded by IHI in 2021 and 2022. Next slide.

An interesting point I wanted to highlight today was the discussion we've had with the FDA division on the primary analysis in such severe at-risk patient population. We actually selected CDI occurrence as an event of interest and death as a competing risk with cause specific hazard ratio as a statistical outcome.

It's -- we don't really have time to go through in details through that today, but this analysis proposed was really innovative and was actually worked out through collaboration with experts from STAT-NET Group in Europe, now part of the e-cred network.

So we managed to launch that clinical trial in 13 countries in Europe, but unfortunately we had to stop it this summer for operational futility because of too low recruitment rates in the hemato-oncology settings to conduct the study in reasonable

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timelines. So unfortunately at this stage, DAV132 development towards prevention of CDI is unfortunately in standby status even though it has shown as a very solid safety and biological efficacy profile in 500 individuals. And of course this raises a few questions for the development of such protective therapy. Next slide.

So there has been quite a lot of data presented earlier today, so I'm going to go really fast through those slides, especially by the CDC team. But here are a few examples of papers in the literature showing for example here the association correlation between low diversity microbiota and occurrence of CDI clinically and in -- pre-clinically. Next slide.

Those, you know, references been have been as well pointed out early on. It shows the association between low diversity gut microbiota and antibiotic use to colonization by MDROs, which is well described in literature.

And finally, next slide, we have a list of papers correlating colonization bacteria -- by

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resistant bacteria such as ESBL and VRE to increase risk of HAI, especially in severe patients with cancer in ICU or in dialysis. So I've seen a few of those earlier today, so the data behind dysbiosis induced by antibiotics and the cause of those secondary infections is quite there in the literature and recognized with CDC. Next slide.

So I would like to end this intervention by sharing a few thoughts after having faced the challenges around DAV132 development path in the prevention of infection, especially putting a few questions on the table for regulators to consider new endpoints. So I'm taking kind of my two hats here, Da Volterra and the BEAM Alliance.

Obviously, with DAV132, clearly co-admins prevention approaches reducing dysbiosis and colonization by bacteria and yeast caused by antibiotics make clear medical sense and today's session is extremely clear indeed about that. So the question is how could we envision to facilitate their access to market considering rather microbiological markers as surrogate endpoints to combat those urgent

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threat infections and AMR dissemination.

Similarly, some colleagues of the BEAM Alliance developed pathogen-specific antibacterials that have microbiota sparing properties expected to lead to reduced risk of selection of resistance and minimizing the overall burden of resistance. So we all realize that it represents an important competitive advantage in Phase 3 efficacy study to show such an asset as well as in a higher economic valuation.

The question is, you know, how could we imagine including new achievable biomarkers such as colonization with bacterial species in the gut associated with mortality and morbidity risk which could then be described and included in the clinical section of a label for a such an antibiotic.

And we talked right before with Erin about decolonization strategy and the need for new endpoints as well to be considered there. Otherwise, it's true that those studies are really big. So the next and final take home message that are on my final slide here.

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You know, there has been brainstorm together with Da Volterra scientific founder Antione Andremont, microbiologists in Paris, who dreamt of protecting the microbiome while giving antibiotics and obviously today after many, many years and efforts behind, sparing the microbiota from antibiotic dysbiosis and colonization is technically possible.

We've done it. We have very solid and nice data but however it's really not yet operationally financially feasible because we are asked to show reduction of secondary infections which necessitates really too large and expensive studies, especially as you know, most of the research is done by SMEs in that field and definitely our belief is that new regulation which could -- which would accept an accelerated path prevention of colonization as endpoints for clinical development would be a really, nearly a necessity to be able to develop that strategy later on for the benefits of individual patients as well as the global control of AMR.

So I thank you very much for your attention and happy to exchange later on and these are

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the publications for interest.
DR. DAN RUBIN: Thank you very much for that presentation. Our next speaker is Vince Wacher. Dr. Wacher is currently the head of corporate and product development at Synthetic Biologics. He has nearly 30 years of experience leading corporate strategy, partnering research, clinical development and intellectual property programs for startups, small companies, and new business units within large companies. Over.
DR. VINCE WACHER: Thank you very much. The -- today I'm going to talk about our product SYN-004 as a potential point of care preventative for healthcare-acquired Clostridioides difficile infection. Today I want to concentrate on the lessons we learned. All of our information is being published and I refer everybody to the publications, but you will hear a little bit of reiteration of the previous talk and some of the challenges that we meet as we try to develop these products. Next slide, please.
Synthetic Biologics is a publicly traded company, so our aspirations and our

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expectations are all subject to SEC disclosure requirements and our forward-looking statement description is on -- in our presentation, but also in all of our literature that we filed and made public. Next slide, please.
So SYN-004 itself is a pretty simple concept. The microbiome is complex. We know that for sure. We also know that the microbiome protects us from different kinds of diseases, and when we damage the microbiome we are subject to all kinds of potential different diseases and one of the worst offenders in this particular instance is beta-lactam antibiotics.
So we are looking to prevent the effects of beta-lactam antibiotics on the microbiome and by doing that let the microbiome do the heavy healthcare lifting. Let the microbiome protect us and prevent the diseases. We have in fact advanced, you know, forward to the end of a Phase 2b study looking at Clostridioides difficile infection but also looking at vancomycin-resistant enterococci decolonization and now we're in a Phase 1b2a study looking at acute graft

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versus host disease with this product. Next slide, please.
The concept for SYN-004 is very simple. Once the person is admitted to hospital, they get an IV beta-lactam antibiotic. Some of that is excreted into the bile. That moves down and damages the microbiome. SYN-004 is an orally administered beta-lactamase enzyme that is given that is enteric protected. The patient takes that during the time that they're being given this antibiotic. The product passes through the stomach and releases the enzyme into the upper GI tract and it's there waiting to degrade the excess antibiotic that gets into the colon -- sorry, into the GI tract and then breaks it down before it gets the colon.
And that way we preserve this microbiome. Again this is a preventative. We want to make sure that the microbiome is preserved to prevent these diseases. And as you can see, this is something that's done at the time of the antibiotic administration, so a point of care preventative is the way we view this product. We go on to the next slide,

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please.
So in looking at the life cycle and where we intervene with this product, this is a very simplified model but I hope it helps people understand the kinds of things that enter into the thought process around the development of these point of care preventative. So a patient comes into the hospital with what's called their index infection, their index admission, the reason they come there, and in our Phase 2 study, it was lower respiratory tract infections.
They are treated with an antibiotic. In this case, it was intravenous ceftriaxone. The antibiotic, as we saw, can be excreted into the GI tract and cause dysbiosis and then that can cause damage to the microbiome that ends up leading to Clostridioides difficile infection.
And there's a lot on this slide, but I want to point out that red arrow, that red there where it says C. difficile colonization bloom and toxigenesis. This is a challenge. Twenty percent of us are sitting around here today and we have

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asymptomatic Clostridioides difficile infection -- colonization in our gut. Most of us will never end up getting an infection, and that is true, too, for the hospital population.

In our study, when we treated the patients with IV ceftriaxone, about 3.4 percent of the patients got CDI. None of them were pre-colonized. Anybody that was colonized when they walked in the door of the hospital, they did not get CDI. Everybody picked up new colonization. About half of them got CDI in hospital and half of them when they left the hospital. So that's a challenge. Just having that that bacteria in my gut doesn't predispose me necessarily to getting the disease.

Once the person gets CDI, obviously there's treatment and management involved and there's different medicines for that, different processes, and then the number one challenge or significant challenges is this recurrence. Once you've had CDI, you're -- you have a dramatic increase in your chances of getting it again. And in fact, getting recurrent CDI, the number one risk factor for getting CDI is

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having previously had CDI. That doesn't really help us when we were trying to prevent primary CDI.

So there's two things that we should be thinking about now before we get onto even the bigger challenges. One is having the bug doesn't equal getting the disease. And second of all, the risk factors involved require that you either were previously in hospital or previously have had disease.

Underneath, some numbers. And this is just an example because one of our challenges here is how do we define the value of this intervention? Medically unquestioned. Patients don't want to get it. Doctors don't want patients to get CDI. There's about 46,000 deaths a year from CDI. Clearly, preventing CDI is a medical imperative but there is a challenge. And the challenge is these clinical trials don't happen for free.

So let's have a quick look underneath there at the way this potentially works, a very simplified model. So the absolute numbers are not important. But for say 1,000 patients come to the hospital and they're treated with the antibiotic.

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That's paid for by insurers by what's called the diagnosis-related group, a lump sum payment that covers that payment.

As we go through, if the patients get CDI, there's obviously an added cost and the added cost can be significant and so here we're saying about $500,000 additional per 1,000 patients. And then there's recurrence and the cost of that is even higher, so another $300,000 on top of that. And this is before we consider mortality, before we consider the patient burden, before we consider potential penalties. Just as a as a simple baseline, let's look at the $810,000 worth of increased cost per 1,000 patients.

If we go to the next slide, point of care prevention has the opportunity to really knock that down. That's a 70 percent decrease in the total cost, just in this very simple model. That doesn't, again, include the death. It doesn't include the patient burden. It doesn't include the liabilities.

But the challenge here is how much is this intervention worth? Is it something that you

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have to break even or is it something that has a more expansive value because once we start including the mortality, the patient burden, and all these other issues.

So that's been one of the underlying challenges of development in this space is defining the value, and I don't mean the therapeutic value. I mean for someone who's going to pay to develop this product, what is the value that enables them to come forward and actually to develop this program? Next slide, please.

So I want to give you three of our four key lessons on this slide and the first, based on our experience with Clostridioides difficile infection, is that the trials are large and costly. And part of the reason is that you have to treat everybody that comes in, because as I said before, just having that CDI -- the Clostridioides difficile in your gut really doesn't help you pick the patient population because it doesn't necessarily mean that patient is going to get the infection, which is the actual disease, the actual disease outcome.

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The other, as we know these are patients in hospital. So there are adverse events and there are deaths and balancing out the incidence of the disease with the incidence of the adverse events and deaths again requires a large number of patients to try and tease those apart so you can get a proper therapeutic outcome from your clinical trial. And so when we looked at this for our Phase 3 study, that's about 4,000 patients and then we're up to about $100 million. That is a very, very large amount of clinical trial funding required and gets back to this concept of how do we convince people to -- this is something that should be paid for?

The second lesson in all of this was really that clinical trial recruitment is difficult. As you can see, if our incidence is about 3 percent in our population, there is no immediate benefit to 97 percent of the patients that come in. None. Ninety-seven percent of the patients won't get anything from this. So that's a philosophical challenge to get patients into the study.

The other is, and we found this out

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very quickly, is when you start talking about CDI, doors start closing because hospitals and healthcare facilities are working extremely hard to not have CDI or any other of the potential hospital-acquired infectious organisms in their institutions. So it's quite difficult to actually get these trials up and running.

And then the third thing we learned in in the market outreach study was that hospitals are the primary customer, and I mean this from a from a financial point of view, not necessarily from a therapeutic point of view. Hospitals are the ones that bear the burden because the insurers, they look at it and go well if this person has had an adverse outcome, a hospital-acquired infection from your index admission, you should just pay for it out of what we gave you for the original infection. So the payers aren't really thinking about it that way. So that means there's a shortfall in the overall payment to the Hospital.

There are also healthcare acquired condition reduction programs from Medicare, and if

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you're not familiar with this, if you're in the lowest 25 percent of hospitals that are -- based on your healthcare-acquired infectious scores, you're penalized 1 percent of all of your Medicare reimbursements per year, and then your name -- naughty list. There's a public list of hospitals that are in that lower 25 percent, so nobody wants that.

So on top of that, there's a potential liability from patients and patient advocates and the lost revenue to the hospital of having to deal with this. So the hospitals are extremely keen to use the product, but they don't pay for the development of the product. And then the next slide please.

The lesson that that absolutely stopped us in our tracks when we first heard it -- I mean, it hasn't stopped us moving the product forward but this was an absolute jaw dropper. We were looking around for partners for this program and got this specific feedback and -- to our face. Incidence is low. Drugs are cheap. Just treat the CDI.

That's a problem. That's a value perception problem because if I have to find 4,000

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patients and $80 to $100 million, I need people to understand the value. So this is a significant challenge in the development of preventatives for these kinds of infections, because again we know medically, we know therapeutically it's valuable. How do you make this value proposition to people that will pay for the drug development. So if we go to the next slide, please.

So some of the things, and I'm just going to reiterate, echo what I think we've heard a lot today. We need to find some risk factors and some biomarkers that help us with patient pre-selection and things that we can follow in a meaningful timeframe and an affordable timeframe to actually be able to say this product is something we can develop. We can take it to the market and patients will use it to protect patients from these kinds of diseases.

The other thing that -- this is something that we're pursuing now and as was said in the previous talk, can we conduct trials in patient populations with higher incidences of the endpoint and bone marrow transplant patients is one and we're

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moving forward with a study in the bone marrow transplant patient population. And just one more slide.

Because I've talked a lot about money, but let's face it at the end of the day this is feedback from a chief medical officer of a hospital that's very encouraging. We want to heal people. We want to do it the right way. I think that within these hospitals if the products are available, they will be willing to pay for it for therapeutic reasons, but also for the to protect themselves.

So I think the value is there. The opportunity is that if we can overcome that energy of activation, that financial challenge and be able to do trials that get us to the market. And with that, thanks very much for listening and thank you for the invitation.

DR. JOHN JERNIGAN: Thank you very much, Dr. Wacher. Our next talk is Defined Bacterial Consortia, a Novel Approach to Tackle Healthcare-Associated Infections given by Dr. Silvia Caballero. Dr. Caballero is director of infectious diseases at

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Vedanta Biosciences in Cambridge, Massachusetts. She is also the head of Vedanta's multidrug resistance program aimed at reducing risk of MDRO infections by promoting reduction of intestinal carriage with defined bacterial consortia. Dr. Caballero.

DR. SILVIA CABALLERO: Thanks, John, for the introduction and thanks to the organizers for the invitation.

Today, I'm going to be sharing with you some of our learnings from recent clinical as well as pre-clinical studies using microbiome therapeutics based on bacterial consortia specifically in the context of CDI and MDR decolonization. Next slide.

As we've heard from multiple speakers today, one of the major risk factors for C. difficile infection and expansion of MRDOs is treatment with broad spectrum antibiotics. This causes a disruption of the microbial ecosystem in the intestine and reduces the pool of beneficial metabolites such as secondary bile acids and short-chain fatty acids which have been shown to be important for preventing CDI.

And with this in mind, we at Vedanta

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developed our lead drug product, VE303 to reestablish organization resistance against C. difficile and restore a protective gut environment. Next slide.

VE303 is a defined bacterial consortium consisting of eight well characterized strains isolated from healthy human donors, which makes VE303 a safter alternative to FMT, given that there is no donor material and therefore the likelihood of pathogen transfer distinction is essentially zero.

We selected this consortium based on its ability to prevent C. difficile infection and restore beneficial metabolites in preclinical models. Each strain is grown from clonal cell banks under GMP conditions, enabling a pure and consistent drug product with the same quality attributes from batch to batch.

Also, the manufactured drug is stable, which enables flexible storage conditions and dosing, and in the next few slides, I'm going to show you that VE303 is able to colonize human subjects and prevent C. diff (indiscernible). Next slide.

VE303 was given to healthy volunteers

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in a Phase 1 study where the goal was to evaluate safety and tolerability of the drug adding from the dose for our Phase 2 study in (indiscernible) patients. We had multiple culprits that were given differing doses of VE303 on a single day or multiple days after every course of vancomycin.

Pharmacokinetics for us in the microbiome field refers to detection of the drug components in the host, which is what this one is showing. So on the Y axis, there is a number of VE303 strains detected in these patient cohort and on the X axis is time from the start of dosing out to one year.

And what we observed was that the multiday culprits that received the highest VE303 dose showed the most robust and persistent colonization where we were able to detect 100 percent of the VE303 strains. Another takeaway from the study was that in the absence of vancomycin, our strains (indiscernible) on the scan, and that's the panel that I'm showing on the right.

Pretreatment with an antibiotic, as we know, reduces microbial density which in our case

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helps create a niche for our strains so that they can colonize. So this is an important consideration for microbiome-based therapeutics to ensure that the drug product is able to get in. And in the case of CDI patients, they are already getting antibiotics as part of their standard of care, so no additional antibiotics are necessary.

Lastly, I'm not showing this data, but we also saw recovery of the indigenous microbiota and beneficial metabolites which refers to the pharmacodynamics of the drug. And as far as safety is concerned, there were no severe adverse events associated with VE303. Next slide.

So that was our Phase 1 study. Then we moved to a Phase 2 studying in CDI patients to assess efficacy of VE303. So here I'm going to show you some of our key findings. This plot, and I apologize it's so small, shows the probability of being recurrent free. So the larger the number, the better. Once again, we found that dose levels do matter. We had two groups of patients, one that received a low dose of VE303 which is shown in red and a second one that

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received a high dose, which is indicated by the blue line, and this is the dose that we selected based on the Phase 1 data.

As you can see, there was no difference in outcomes between the low dose and placebo, which is shown in gray, and only the high dose met our primary efficacy endpoint where we saw an 85 percent sustained cure rate, which is comparable to what has been seen with FMT.

Interestingly, most of the action seems to happen -- seems to be happening within these 14-day window which is the area highlighted in blue where we observed the most recurrences in all groups, but once the treatment course was completed, difference in efficacy became very clear. Next slide.

And what we know is that around this timeframe, the prevalence of VE303 strains is much higher in the high dose group shown in red compared to the low dose group, and that's the panel that I'm showing in the upper right corner. And if we stratify these patients based on clinical response -- that's the panel below -- you can see that the patients that

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didn't refer had a higher level of colonization of the majority of VE303 strains, so that's the blue line, again suggesting that colonization of our drug is a strong predictor of cure. Next slide.

And last but not least, microbiota recovery is also important for clinical success. We saw that responders, here shown in blue, had a more diverse microbiome than non-responders, and this increase in diversity was much more pronounced in the high dose group. Next slide.

So switching gears a bit, we also have a program where the focus is on gram-negative bacilli. This is our VE707 program, currently in a preclinical stage where the goal is to educe defined bacterial consortia to prevent infection in the hospital setting by reducing carriage of these organisms in intestine. And we're specifically looking carbapenem-resistant Enterobacteriaceae producing E. coli and Klebsiella pneumoniae.

As others have mentioned, the clinical evidence that decolonization translates to less infections is very strong. This has been demonstrated

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with selective digestive decontamination and fecal microbiota transplantation, but there are caveats associated with these modalities, as we know.

I the case of SDD, antibiotics can foster the development of resistance and also the ecological dysbiosis which is the main culprit for colonization and infection is not addressed, which is why recurrence rates tend to be a bit high with SDD. And for FMT, as we know, the main issue is donor and batch-to-batch variability which we know can impact the efficacy of the FMT material. Next slide.

There are several patient populations where the risk of MDRO infection goes up significantly, if they happen to be colonized and one of them is the bone marrow transplant population. This is just an example of the microbiota changes that these patients go through during the course of the transplant. They start out with a very diverse microbiota. These are indicated by the brown and gray colors. And once antibiotics are administered, pathogens like E. coli, shown in red, emerge and increase in abundance days before it is detected in

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the bloodstream, in the case of this one patient.
This particular infection was readily treated with antibiotics and you can see E. coli going away, but we then see a massive expansion of another pathogen, vancomycin-resistant enterococcus, which now puts the patient at risk for VRE infection.
So having a surveillance system in place where patients are routinely monitored for colonization can be extremely helpful to identify a timeframe where we can intervene and minimize the risk of conversion from colonization to infection. Next slide.
And something that's important that we need to remember is that complete MRDO elimination is not required for infection prevention. FMT studies like the one that I'm referencing here have shown that the risk of MDRO infection can be significantly reduced despite modest decolonization. And that's because in addition to reducing carriage to low enough levels which is important, there the other functions that microbiota exert on the host, like the production metabolized that produce -- that promote health and

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reestablishment of the gut epithelial barrier which together limits the ability of these pathogens to become invasive. Next slide.
So going back to VE707, we tested around 60 defined bacterial consortia in mouse models of colonization and VE707 was the most potent (indiscernible) where we saw at least 1,000-fold reduction in klebsiella and E. coli carriage over time.
Now, we think this degree of decolonization could be clinically meaningful based on evidence from (indiscernible) and others where it is more common to see high infection rates in patients who are dominated or have high titers of an MDRO. Next slide.
Okay, so in closing, we understand that there are many challenges but we believe that we can make a difference in the lives of these patients, especially those that are high risk, by modulating the microbiome. In the case of CDI, we have shown that it is possible to do this and the same idea applies for decolonization and an MDRO infection prevention where

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by doing so we also hope to be able to reduce antibiotic use in the clinic. Thanks very much.
DR. DAN RUBIN: Thank you very much, Dr. Caballero. Our final speaker of this session is Matt Henn. Dr. Henn is executive vice president and chief scientific officer at Seres Therapeutics. He has been involved in the discovery and development of multiple microbiome therapeutics across infectious, inflammatory, and oncology indications. Over.
DR. MATTHEW HENN: Good afternoon. Let me start by thanking the organizers of this timely and important workshop for the opportunity to speak today about Seres microbiome therapeutic technologies and our progress on deploying our novel drug technologies to combat bacterial infections and AMR. Next slide, please.
In the next ten minutes, I'll provide a quick snapshot on how we are advancing novel microbiome therapeutics that are consortia of multiple species of bacteria. Briefly, our drugs are designed to have the bacteria engraft into the gut, meaning they germinate and vegetatively grow in patients' GI.

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Engraftment is a measure of the drug's pharmacogenetics.
Next, the engraftment of bacteria from our investigational drugs leads to broader restructuring of the microbiome and modulation of the metabolic landscape of the gut. These are measures of the drug candidate's pharmacodynamics. These are -- importantly with our technology we're engrafting several species at the same time with a single investigational drug. This allows us to attempt to modulate multiple disease relevant pathways at the same time with one treatment. Next slide, please.
As heard throughout today, the increasing emergence of AMR is a significant public health threat. It is a slow pandemic. Recently in a review of the global impact of AMR in The Lancet, bloodstream infections tied to AMR were identified as a major cause of death. As those involved in this workshop know well, there has been limited innovation in new antimicrobials despite the growing impact of AMR and as we've heard multiple times today, beneficial microbes in our gut are an important piece

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of the puzzle in combating infection and AMR.

Microbiome therapeutics provide a novel approach to manage AMR and their mechanisms of action are potentially less susceptible to the emergence of resistance. Moving a slide forward, please.

Data from our ECOSPOR III study of SER-109 shows that this novel therapeutic modality can work successfully in the clinic. As published earlier this year in The New England Journal of Medicine, SER-109 achieved superiority compared to placebo at eight weeks of follow up. Only 12.4 percent of subjects in the SER-109 arm recurred in the C. difficile patients, whereas 39.8 percent of subjects in the placebo arm recurred.

This translates to a sustained clinical response of 88 percent. The relative risk at eight weeks, which was the primary endpoint, was highly significant at 0.32 but the upper bound of the 95 percent confidence interval is well below the threshold predefined for the trial to be a single pivotal trial.

While not shown here, results from our

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ECOSPOR IV open label safety study were confirmatory of these results and demonstrated comparable sustained clinical response rates in both multiple and first recurrent patients. In both ECOSPOR III and IV, SER-109 was well tolerated with most adverse events being GI related. As stated publicly previously, we are in the final stages of a BLA submission for SER-109. Next slide, please.

SER-109 was designed to restructure the gastrointestinal microbiome and modulate the metabolic landscape in the GI to establish colonization resistance to C. difficile. Pathogenesis of C. difficile infection is a two-hit process. The first hit is the use of broad spectrum antibiotics that lead to loss of beneficial bacteria and their associated functions which play a dominant role in host defense, leaving the patient with a disrupted microbiome that is vulnerable to potential pathogens.

The second hit is patient exposure to C. difficile spores. These pathogenic spores germinate into the toxin producing bacteria that lead to diarrhea and colitis. Next slide, please.

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I'm showing data here that supports some of the mechanisms of action of SER-109 in establishing colonization resistance to C. difficile. As shown in the left panel, we observed significant engraftment of bacteria in our drug as compared to placebo patients. Here we are reporting the total number of drug species observed. Engraftment is rapid and durable with significant signatures observed rapidly and as early as one week, which is important in the context of treating an infectious disease.

Engraftment leads to restructuring of the disrupted disease state microbiome and modulation of the metabolic landscape in the gastrointestinal tract. As example shown on the right in the log scale plot, this includes a significant increase as compared to placebo patients in secondary bile acids that inhibit C. difficile vegetative growth and not shown on the graph a reciprocal depletion of primary bile acids that stimulate C. difficile spore germination. Next slide, please.

I'll now switch gears to focus on observations that SER-109 can reduce additional

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pathogens that harbor antimicrobial resistance. Treatment with SER-109 rapidly and significantly reduced the abundance of proteobacteria in patients' guts. These are the bacteria that harbor antibiotic resistance genes. As shown in the plot on the left, the proteobacteria in the Enterobacterales and Enterobacteriaceae that were most significantly reduced are also those significantly associated with more frequent carriage of genes that confer antimicrobial resistance.

The Y axis shows statistical significance in terms of negative log P values. As has shown on the right side, SER-109 treatment leads to significant reduction in the total abundance of antimicrobial resistant genes in the gastrointestinal tract of patients as compared to placebo. Our SER-109 program provides strong in-human proof of concept that a microbiome therapeutic has the potential to be a novel technology to address AMR and decolonize potential pathogens. Next slide, please.

Seres microbiome therapeutics provide a novel potentially transformative technology for the

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protection from the treatment of infections, AMR, and bacteremia. As noted earlier, a disrupted gastrointestinal microbiome can lead to domination in the gut by undesirable microbes and we've heard about that multiple times today. It can also lead to the breakdown of the mucosa and epithelium that can lead to bloodstream infections resulting from bacterial translocation.

Seres consortia are designed to restore colonization resistance to pathogens, bacteria, and our drugs can out compete pathogens and inhibit their growth through nutrient competition and other mechanisms. This can decrease pathogen abundance in the gut which both potentially reduces the likelihood of patient-to-patient transmission and of bacterial translocation to the bloodstream.

Our drug candidates are specifically designed to also reduce translocation through enhancing epithelial barrier integrity. And lastly, our drug candidates are designed to modulate immune responses. Next slide, please.

I will now transition to our SER-109 --

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sorry, SER-155 program specifically. Building on the data and the mechanisms I just spoke about, we have designed SER-155 using our reverse translational MVTX discovery platform. Briefly, SER-155 is an investigational consortium of a unique human commensal bacterial strains that are cultivated from master cell banks and encapsulated for oral delivery. SER-155 is currently in a Phase 1b study that targets assessment of drug safety and drug pharmacology in hematic stem cell transplant patients that are highly immunocompromised and susceptible to VRE and CRE colonization and bloodstream infections. Next slide, please.

In the case of SER-155, we optimized the consortia to have a powerful effect in directly decolonizing CRE and VRE. These bacterial species are frequent pathogens in people receiving stem cell transplants as well as in a broad spectrum of antimicrobial resistant infections in various hospital settings that we heard about a couple of times today.

As shown here in mouse models of VRE and CRE colonization shown on the left and right

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respectively where mice are first infected and heavily colonized with VRE or CRE, the red lines, subsequent therapeutic oral administration of SER-155, the blue lines, led to significant 2 to 3 log reductions in VRE and CRE titers in the gut compared to untreated mice.

Notably, these reductions in VRE and CRE occur rapidly after SER-155 dosing. SER-155 also includes bacteria that produce metabolites that have the potential to prevent bacterial translocation and reduce graft versus host disease. Next slide, please.

As I noted earlier, SER-155 is specifically designed to also improve epithelial barrier integrity and is effective in doing so in our in vitro primary colonic membrane assay. In this screening model, an intact epithelial barrier is established and as shown in the left panel treatment with interferon gamma alone will lead to epithelial damage and permeability.

In this model, we include consortia that are designed to not produce the metabolites that we have optimized SER-155 to produce. As you can see, these negative consortia are not protective of the

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epithelium. In contrast, SER-155 is protective and achieved significant greater barrier protection than both experimental controls.

This pharmacological property of SER-155 enhances its potential ability to protect patients from infections, not only by targeting the pathogens directly to decolonize them, but also by reducing the ability of the pathogens to translocate from the GI tract to the bloodstream.

As shown on the right, SER-155 also is designed to modulate immune responses that are of relevance to graft versus host disease. Unfortunately, I don't have time to cover that data today, but those can review the slides after which are publicly available. Next slide, please.

So Seres is committed to advancing microbiome therapeutics as a novel technology to combat infections and AMR. In addition to SER-109 and SER-155, we have active programs in multiple high risk populations including cancer, neutropenia, cirrhosis, and several others of the populations discussed earlier today.

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Our preclinical and clinical data support that our investigational products can directly decolonize various GI pathogens and that they have the potential to prevent infections, translocation, and bacteremia. I've touched today on some of the novel mechanisms of Seres' drug technologies and I'll close by providing a few considerations based on our experience over the past ten-plus years in developing these drugs that are important as we broaden the arsenal of microbiome therapeutics.

These include continuing to improve the translatability of our preclinical screens and models for lead optimization; continue to enhance methods to evaluate drug PK, PD, and dosing strategies; refining our understanding of patient subpopulations on disease pathogenesis and drug pharmacology; developing drug formulation strategies that optimize patient access and can capture the broad breath of microbial biology we have accessible to us; and lastly scaling GMP manufacturing capabilities to be able to leverage those and manufacture those.

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So I'll go to the last slide, please and just like to close by thanking really many folks who helped make this work possible and our collaborators to advance and most importantly, I'd really like to take a minute to specifically acknowledge the patients and the clinical investigators that participate in our trials and really make the ability to advance these programs possible. Thank you.

DR. JOHN JERNIGAN: All right. Thank you, Dr. Henn, for a fascinating presentation and thanks to all the speakers for what really I think was a great stimulating and encouraging and hopeful session. So thank you all for the work you put into those.

We'll take a brief break now and reconvene at 3:50. So that brings us to an end of this section. Again, we'll see you again at 50 -- that's five, oh -- minutes after the hour, 3:50 eastern time. Thank you. Bye bye.

(Break)

MICHAEL CRAIG: Welcome back,

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everybody. This is Michael Craig, the director of Antimicrobial Resistance at CDC and I'm joined by my colleague Peter Kim. Peter, do you want to introduce yourself?

DR. PETER KIM: Yes. Thank you, Michael. My name is Peter Kim. I'm the director of the Division of Anti-Infective in the Office of Infectious Diseases in the Center for Drugs at FDA. Thank you for joining us today.

MICHAEL CRAIG: And Peter --

DR. PETER KIM: -- back over to you, Michael.

MICHAEL CRAIG: Thank, Peter. Peter and I are going to be moderating the last session here for today's meeting, and I wanted to note to everybody that what we're going to be doing here is actually having a Q&A session, a question and answer session with the panelists that you heard throughout the day today. So as you can see on the screen there, there's a list of panelists from FDA, CDC, as well as the external panelists that we had, and there are three questions that Peter and I are going to be asking the

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panelists and we're going to be having time allotted for each of these.

So we have roughly half an hour allotted for each of the three questions and we're going to have the panelists -- we're going to start with specific panelists and then have the panelists raise their hand in the Zoom function and then we're going to call on them and hear from them about their thoughts on each of these questions.

So it's sort of an open conversation and I think a great opportunity for us to hear more about some of the specific issues that we've heard today and areas that we think are maybe greatest need or areas of potential challenge that that we'd all like to overcome. So with that, why don't we get started. And as you can see there, question one is please discuss the greatest needs for drug product development for the prevention of healthcare associated infections. And I think we were -- we've been talking about including it within that antimicrobial resistant bacteria. And you heard a lot from that in the morning session.

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So we're actually going to kick this off with Dr. Bob Weinstein and hear from him on his thoughts on question one. Dr. Weinstein, why don't you turn on your camera and unmute yourself.

DR. ROBERT WEINSTEIN: I'm unmuted. When I go to turn on my camera, it says, you cannot start your video because the host has stopped it.

MICHAEL CRAIG: Okay.

DR. ROBERT WEINSTEIN: So host, unstop it. So while we're waiting for that I'll go ahead. I think as demonstrated by today's great symposium, the great need is brainstorming. And although I commented that infection control bundles might be parsimonious, I think research has to be broad based. So I want to comment on four general areas of need for product development, some of which have already been highlighted today by outstanding talks, and I will try to highlight what I see is one of them which I see as the greatest need.

So the first of the four is the role of topical agents, antimicrobials and antiseptics considered broadly to include topical decolonization

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of the fecal patina which has been a highly successful approach and patients need to be bathed anyway, so in my view, I see this as the potential for the greatest need which could include bringing this approach to additional venues, assess additional agents besides chlorhexidine in the event that resistance develops or more because of some agents like clostridium difficile may have very high MICs for chlorhexidine, and so assess topicals that might get into deeper layers of the dermis.

We saw in one of the slides this morning about hair follicles having MDROs in them and there may be some agents that may get better into hair follicles.

I think also as systemic antibiotics are developed they could be assessed for the possibility of excreting antibiotic into the sweat perspiration so that axillary glands might have antibiotics in them which might control or prevent development of MDRO fecal patina. All of these have pros and cons as everything does today.

In the category of topicals, you know,

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and anti-infective coated devices which really didn't discuss much today, seems like a good idea but has never yet made a major splash and maybe that could be reconsidered.

A second area is product development for GI tracts which has been discussed extensively today and I'm not going to go over any more of that.

A third area is for treatment of infections and I want to add to today's discussion two things that I didn't hear and that's development of antibiotics that delay or defeat or resist bacterial resistance, especially for those pathogens such as Pseudomonas aeruginosa that can spin off resistant progeny with great proficiency. Something like 15 percent of Pseudomonas aeruginosa become resistant during the course of therapy, so we need antibiotics that can overcome that.

And also we should consider whether advanced molecular diagnostics can be used to alert prescribers to the presence of even low levels of pre-existing resistant elements, for example in the patient's stool (indiscernible) mucosa that might help

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when the prescriber has to choose between different classes of antibiotics. So that might be directed in part by knowing what resistance pre-exists there.

And the final, the fourth areas to develop products that attack bacterial mechanisms facilitate infection. I didn't hear a discussion today -- I may have missed it -- about products to block quorum sensing so that bacteria cannot communicate with each other. There's no communication, no infection, there'll be no resistance. We've already heard about compounds that destroy or inhibit biofilms. We talked about monoclonal antibodies and there's a lot of the literature about compounds that attack virulence, that is, make MRSA less virulent.

But of all these again for product development, as I said at the outset, my personal view is the approach to control the fecal patina which I believe plays a pivotal role in the epidemiology of many MDROs and control of the fecal patina has had an impressive impact on the risk of spread and infection with a variety of resistant strains, bacteria and

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potentially fungi. And I think we should capitalize and improve on these successes. That's my view.

MICHAEL CRAIG: Thank you, Dr. Weinstein. Other speakers, other panelists, who would like to share their thoughts on this question? What are some of the areas of greatest need from your perspective and point of view, and please use the raise hand features so that we can get -- identify folks and get them in order. The raise hand feature is at the bottom of the screen. Lilian Abbo.

DR. LILIAN ABBO: Hi. I agree with everything Dr. Weinstein mentioned. I think another area where we have great need is more effective antimicrobials to decolonize against Candida auris and more effective therapies. We have a very limited armamentarium and so far nothing has worked for decolonization other than repopulating the gut, and as we saw many of these, you know, gut microbiota products that are being developed are targeting bacterial pathogens, but we also need to think of fungal pathogens that are emerging with increased resistance and very rapid horizontal transmission.

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And then if there is any topical antimicrobial that can substitute and improve hand hygiene and make it even easier than alcohol and water and soap, I think that would be a Nobel prize winner because we would stop a lot of the problems as well. Thank you.

MICHAEL CRAIG: Thank you, Dr. Abbo. And Matthew Henn.

DR. MATTHEW HENN: Sure. Thanks, Michael. You know, I think the thing I'll emphasize as well, we heard about it quite a few times today throughout multiple different talks, is really thinking about what the proximal cause of disease is in some of these settings, and so there I really think about that need to really think about the gastrointestinal microbiome and the important role that it plays in the pathogenesis of multiple of these different diseases that we talked about and how we think about restructuring that microbiome, protecting that microbiome, because I think we know that that has pretty substantial implications both in terms of the ability to establish colonization resistance but as

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well as general health of patients as well, and so I think as we think about that as a target that's important for us to keep that in mind.

MICHAEL CRAIG: Thank you. Other panelists. I am not going to be shy about calling on folks if you don't raise your hand. There was great conversation today and many engaging talks. There's Dr. McDonald. Cliff.

DR. CLIFFORD MCDONALD: Yeah, thank you, Michael. I would maybe add and maybe this is for FDA to comment on, is what would be the studies that could be done that would perhaps lift the entire field around establishing surrogates and what do they see maybe as most important? Maybe it is -- could be a couple of these larger studies. I think we've heard several in industry talking about the prohibitive size of studies and what would those need to be to help establish surrogates that then could smooth a pathway, building the better mousetrap to achieve reaching surrogates.

MICHAEL CRAIG: Thank you, Cliff. And I think some of that response, I think touched on some

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of our questions two and three that we're going to get to momentarily, but thanks for teeing those up for us. Want to still focus on, you know, what are the areas of greatest need. I'm going to take the moderator's prerogative here and actually call on Susan Huang. She's worked in this field very extensively and had a great presentation earlier today. Dr. Huang, what do you see as some of the areas of greatest need for product development?

DR. SUSAN HUANG: I think that there's a lot of good questions out there. I think we're going to need to move faster and be able to do pragmatic trials. I think one way in order to do that is to actually continue to enable the trials that are done while you're in a learning health system to actually matter for FDA indications. So I think there's a real use case to talk about, what does it take to do that when they're created to be real pragmatic trials and influence what happens today.

So that's one of the things that I think there's great questions, but we need more trials and they can't cost the amount that they're costing

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now, and so availing ourselves of a lot of people who are interested in the operational need can be one great way to be able to move something forward.

I want to just echo the other thing that was stated earlier, I think by Dr. Weinstein, about deconvoluting some of the bundles that are out there. I think that that's true in two different ways. One, when you have completely disparate things that go into the bundle, sometimes it's a device plus an antiseptic plus something else, those types of head of bed, you know, all those things are kind of pretty different, but I actually want to talk about also the fact that when you do something like decolonization, you can attack different body sites.

So what is that relative proportion of value and can we actually measure that, so that we understand when you have to have the budget in a certain amount, you're going to always go after the most effective things first. So I thought that was a really thoughtful approach as well.

MICHAEL CRAIG: Great. Thank you, Dr. Huang. And it looks like we have Theresa Michele from

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FDA. Theresa.

DR. THERESA MICHELE: Thank you. So one thing that I just wanted to note as we're considering these things, another point to consider is that we also have to think about the safety of the regimens that we're prescribing and that we are, you know, considering which was part of the point of the limitations in the data that we have for some of these agents. And certainly as we develop new agents you have to think about that as well.

Some of the basic science behind it, the toxicology studies, making sure that these things aren't carcinogenic if you're using them over and over and over again or you're exposing, you know, large body surfaces. And I thought Dr. Wacher really presented this very beautifully when he talked about the number needed to treat that you are potentially exposing 100 patients to an intervention to prevent three infections with C. diff.

So we have to remember that when we are thinking about these preventative therapies safety is very paramount because a lot of patients who receive

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them won't receive benefit.

MICHAEL CRAIG: Thank you. Very good point and I think that's a strong consideration for how do we address these preventative agents where we're talking about benefit to both the individual and the group and the application of those. Dr. Jernigan.

DR. JOHN JERNIGAN: Thanks. And I agree with Dr. Michele totally that the safety issues are first and foremost. First do no harm. I did want to comment on your very last thing about the number needed to treat, and again bringing this argument of the indirect benefit.

When you consider the indirect benefit of infections -- colonizations and subsequently infections prevented through transmission, the number needed to treat comes way, way down and one of the problems with the number needed to treat for diseases like this is it doesn't consider the indirect benefit. I think, tried to show some of the modeling data -- again, they're only models -- but they're parameterized based on real world good observational data -- suggest the number needed to treat for, for

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example, CRE decolonization to prevent infection, when you consider the indirect benefit is really much, much lower than that.

So I just wanted to make that point to not forget about indirect benefit when we think about these things. I acknowledge that there -- it's challenging to measure and quantify indirect benefit. But I think that's one of the things we need to grapple with because I think the promise of these agents is going to be most of the harm that's going to be prevented I believe will be through indirect benefit more than the direct benefit. Over.

MICHAEL CRAIG: Thank you, Dr. Jernigan. I'm going to call on a couple other folks here because I think they had some very interesting and engaging talks that I think this question is particularly important for hearing from them. Dr. Brown with the CF Foundation, what do you think are some of the areas of greatest prioritization and -- in terms of product development here?

DR. A. WHITNEY BROWN: Thank you. For our patient population, I think I highlighted that the

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multidrug resistance, the inherent nature through a lifetime of infections and healthcare exposures, so really I think the development of new novel antibiotics to address MDR and how to entice companies when the financial benefit may, you know, may not be there because we're not talking about volumes and volumes of patients, but to keep our armamentarium growing and to do that in a responsible way.

Of course, we want to reduce our antibiotic use as well and I think we've been very lucky in our population that that has happened over the last couple of years for a confluence of reasons, as I said, but being good antibiotic stewards but also having the right powerful, appropriate antibiotics available for the most vulnerable MDR infections and to include looking at bacteriophage therapy as an option as well.

MICHAEL CRAIG: Thank you. And Jim Kim, you had a very interesting talk and wanted to see what your thoughts are on potential product development.

DR. JAMES KIM: Yeah, thank you. So

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from my vantage point, you know, one of the things that we're working on, a lot of the healthcare efficacy studies for the products that we're working on our ASTM methods, so they're validated methods using those surrogate endpoints. What I talked about today were some of the challenges facing our consumer antiseptics and I thought it was just an opportune time to review a surrogate endpoint, like decolonization.

This is something that I think will take some data to convince FDA that this could be a useful end point for the development of products, but certainly I think I was very excited to see this workshop. I thought that a lot of our work pertains to what's going on in this field, and so for me it was a great learning experience to see the other talks today.

But I think that's sort of one of the areas and I think OTC reform gives us, I think, an avenue to talk about what FDA's data requirements are, so sort of what I'm looking forward to.

MICHAEL CRAIG: Thank you. It looks

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like we have a hand. Dr. Walker.

DR. VINCE WACHER: Thanks very much. I just wanted to maybe follow up on the indirect benefit question or comment, because it's terrific that if we can measure the indirect benefit, the number of patients in my study goes down. But even if I have to cut that number to 2,000 or 1,000, I still have to follow them into the community and maybe for a year or maybe even two years and then I have to follow who they're connected to and who they're connected to until I can determine, have I spread antimicrobial resistance? Have I spread CDI?

So it doesn't necessarily change the challenge of my study even if the number of people are smaller. But I mean clearly the indirect benefit getting out in the community, spreading it around, going back into hospitals. We had a group from Mexico that had to close an entire wing of a hospital forever because they could not get it under control, the CDI.

So you know, the indirect benefit is a tremendous potential outcome therapeutically for the community. But again, just incorporating that into my

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study design gives me another one or two years to follow patients in pretty difficult circumstances.

MICHAEL CRAIG: Thank you. And I think Dr. Jernigan is back to discuss the same topic.

DR. JOHN JERNIGAN: Well, I just want to agree with you that one of the challenges we have here is that the adverse effect of acquiring colonization is sometimes very, very far removed in time from the actual acquisition, as you point out, maybe years later. So how do we study that? That's tough.

One sort of plug, and this may get into study designs and study populations which I know is the second topic, Michael, but I want to point out, you know, healthcare settings where the lengths of stays are very long and where prevalence and transmission of some of these pathogens is very high. This may not help C. diff much, but I'm thinking of CRE, Dr. Henn, et cetera. I mean, you may have considered LTACH populations or other long-term care populations, again, that have pretty high prevalence, pretty high incidence of transmission, pretty high

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incidence of infection, long length of stay where you might be able to enrich capture of those indirect benefits. Something to consider. Over.

MICHAEL CRAIG: Thank you, Dr. Jernigan. And Matthew Henn.

DR. MATTHEW HENN: Yeah, so I'll just quickly respond there. I mean, I think it's an important point. I think we'll probably get into this a little bit in the next question, but it really does also important to aging populations and (indiscernible) targeting and where you can see the outcomes, you need to see (indiscernible) most rapidly.

So you know, at Seres, we focused our infection portfolio on immunocompromised patient populations and that's where we are focused. That's very intentional because we feel we can design trials in that setting and get to meaningful potential readouts rapidly.

At the same time, I think there needs to, as was brought up earlier today by multiple of our CDC colleagues, to really think about other readouts

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that can be more rapid such as decolonization readouts or things of that nature because I think those are certainly needed.

And I think we need -- I can tell you as a drug developer we need increased guidance and would benefit from increased guidance from the agency on how to best think about a decolonization surrogate endpoint, particularly for Phase 1 or Phase 2 trials.

MICHAEL CRAIG: Thank you, Matthew. Well, I think we can close out question one but I just want to see if there's any other hands and panelists who want to talk about our greatest need for product development. Bob Weinstein.

DR. ROBERT WEINSTEIN: Yeah, I think we haven't really discussed the community very much, so Latania Logan at Rush Children's, when she looked at kids coming in the hospital, in a bunch of hospitals in Chicago, I think every children's hospital in Chicago with resistant organisms, resistant Enterobacteriaceae, those were kids from the community. They had not been in the hospital ever before. So somewhere in the community they acquired

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this.

I think there was a Dutch study showing that your risk of having fluoroquinolone resistance in your gut was greatest if you lived in a community where there's a lot of fluoroquinolone use, not you necessarily but other people in the community.

So I think we have to look in the community and when we looked at MRSA in some of the zip codes in Chicago, we've seen that having been in the jail was a risk factor for MRSA in the community. So I think we have to look at the extension of some of these interventions into communities very specifically and focus on the epidemiology in the community to understand the spread there. It's not always the hospital or the nursing homes.

MICHAEL CRAIG: Yeah, a very good point that when we're talking about transmission here, the transmission is certainly not limited to the healthcare setting and can go beyond that. Silvia.

DR. SILVIA CABALLERO: Yeah, something that I would add is that having a good understanding of the mechanism of action is something that I think

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we should also think about. So regardless of the product in question, right, whether it is antibiotics or (indiscernible), I think that knowing how the products work will help rationalize failures and successes in the clinic, and we need human data for that. Preclinical models, mouse models, in vitro models, they're great, but we need human data.

And the other thing that I would add is that something else that that would help with is the identification biomarkers that will help us select patients that would benefit the most (indiscernible) products and I don't know if this was mentioned already, but also thinking about the microbes that we're targeting.

Some of these organisms may be very difficult to decolonize. Even strains within the same species, you know, can be difficult to target, so you know, spending, you know, more time sort of looking into how active these products are preclinically can also help us to, you know, develop better products in the future.

MICHAEL CRAIG: And Dr. Elkins from

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CDC.
DR. CHRISTOPHER ELKINS: Well, thanks, Michael. One thing I wanted to bring up and it does develop off of what Silvia's last comment was, but something that Dr. Weinstein brought up which was quorum sensing and I think it's an interesting piece with mechanism of action. So how do we look at it from the microbes perspective?
And I think it hearkens back to a lecture that I attended with Dr. Stuart Levy at one point and you know it straddles both antimicrobial drug development but also how you can apply it in a decolonization sense, so targeting the organism in a much more subtle way. So it does get to the mechanism piece and I think taking that into account with product development is very, very important.
In other words you're not really killing the microbe, you're just inhibiting or, you know, at least with quorum sensing you are able to in effect reduce its ability to colonize and to communicate properly without killing it. So you do have some aspects there on the downstream as far as

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developing resistance, but I think those are keys I think in in developing that and appreciate his comments along those lines as Silvia's as well.
MICHAEL CRAIG: Thank you, Chris. More hands up is great. Erin Duffy, CARB-X.
DR. ERIN DUFFY: Yeah, thanks. I just wanted to build on also something Silvia said which is we didn't emphasize much the things that remain not understood in the translation from preclinical to clinical work and this is particularly when a lot of these products are going on top of standard of care.
There's a lot of shenanigans. I don't mean that in a negative sense. I think that's a negative word, but there's a lot of stuff that's done to demonstrate, you know, efficacy preclinically including like fractions of a dose of the antibiotic to try to demonstrate an effect that we really have no sense of how that translates clinically.
And so I think some dedicated work to understand what's enough to feel confidently moving into patients is really important.
MICHAEL CRAIG: Thank you. And Dr.

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Abbo.
DR. LILIAN ABBO: Hi again. One of the other areas I think it's important to consider in addition to the community is also the global impact of all of this. We're in Miami and we don't live in an isolated bubble in the United States, and we saw that in COVID, we're seeing it with monkeypox. So I think as we're trying to develop cost effective solutions they need to be scalable to the rest of the world and having effective therapeutics and effective point of care diagnostics would be very helpful.
For example, we saw the difference that maybe not 100 percent of the antigen testings work, but if we could have a point of care flow, you know, analytics like a pregnancy test to determine colonization with MDROs, it might be very helpful upon admission because the cost of all of this is adding to our (indiscernible). It's not just the cost of preventing and the cost of treating this multidrug-resistant infections, adds to everything. So anything we can do to prevent and early detection will stop the chain of transmission.

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Other things that I think are important for -- especially with cystic fibrosis and other multidrug-resistant gram-negatives is really looking at more effective ways of combining therapeutics, right, whether it's synergy testing through TREK panels and deciding, hey, combination therapy in this situation short course may be more effective than -- rather than you know burning each one antibiotic individually.
We need more studies looking at that. What are the effective combinations and what's the right duration when we use combination therapy especially for these extreme drug-resistant organisms that are very challenging and in particularly immunocompromised populations which we deal with transplant and oncology in which sometimes it's very hard to restore the immune system and eradicate the colonization or the infection. So that's an area where we need more therapeutics.
MICHAEL CRAIG: Absolutely. Thank you. And I think that is actually the time we have allotted for question one, so I'm going to turn it back over to

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Peter Kim of FDA who's going to take questions two.
DR. PETER KIM: Thanks, Michael, and thanks everyone on the panel for the excellent responses.
Okay, so question two, please discuss ideas for study designs that could provide evidence of the contribution of a new therapeutic for prevention of healthcare-associated infection on the background of existing infection prevention measures including but not limited to the pros and cons of cluster randomized study designs as well as enrichment strategies for populations at greatest risk.
And we would like to call on Dr. Susan Huang to kick off the response to this question.
DR. SUSAN HUANG: Thank you, Peter. So, I'm going to answer in a way that actually I think bridges questions one and two a little bit more in a provocative way. I'll just generally say that there are a large number of options for study designs that could really complement standard randomized controlled trials and I'm just going to name three specific ones that can be really, really helpful when you're trying

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to account for contagious outcomes.
So the group designs, which are less commonly discussed, would be the standard cluster randomized design that I talked about, but also to just remember that there are other ways that you can do randomized crossover design. You don't have as many hospitals. As I mentioned, even 20 is a really large trial. You could assign someone to be both a control and a participant in the intervention. They just can't choose when. So that's a randomized process.
There's also randomized stepped wedge design. That is, it's really hard to roll out something in a hospital, it takes a lot of phase-in time and so maybe you can only roll it out to ten, which is a lot at one moment, so you have a 40, you know, trial, 40 group trial and so you're going to roll ten at a time, but they can't when.
So there's So there's many different ways that you can try to use group designs that can be really, really powerful and still allow for the proper roll-out of these types of designs.

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I'm going to now switch my comment to hopefully something that's a little more provocative. I'm really interested in how people will respond, but when we think about these designs, I think of two different things about the products we've been talking about. There's the post market indications that don't exist and there's the premarket approvals or indications.
And one of the things that's really interesting about, for example, each of us, FDA, CDC, the manufacturers, and then those of us in academia or those of us who actually, you know, run hospitals and hospital infection programs, is we all have really, really important but critically different vantage points.
And I will just highlight what Teresa Michele said about, you know, safety. So is there a way to actually, as the next step, take a case example, really do a case study and I'll throw out the example of using chlorhexidine in ICUs for routine bathing. There is no indication for that. There have been many trials on children and adults. It's been

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used daily. It is now guidance.
So yes, we have no safety that's been submitted to the FDA that's really specific to this, but it's been done in millions of patients every couple of months, millions. And so can we sit down and have the right people at the table to talk about these really complex vantage points because if you're an agency and you're authorizing a safety, you're -- you've got a lot of responsibility, you know, compared to a doctor that's saying, you know what, I'm going to try this off label.
So I don't want to dismiss anybody's valued perspective, but getting us all at the table to talk about one explicit example can really, really help, and dig into the trials that have been done in hundreds of thousands of patients might be really illustrative and open up the mind of someone like myself when we do the trials about what else can we collect, because that would be really meaningful, but maybe also open up the idea that there are ways in which we can think about stuff that's already happening and try to garner that so we don't have to

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start from square one.
And similarly for premarket approval, I was just thinking about the same thing. There's lots of things that are not here in the United States. For example, there are antiseptics that have been commonly used in other European countries for years. So do we have to start the safety discussion at zero?
Is there a way to create some two-tiered structure that would be understandable and amenable for everybody to say, you know what, small consent studies for safety and then large waived consent studies for population outcome or some small studies really hard to do that show the connection between carriage and infection, and then once that's been shown in a way that's definitive enough, now we can use a surrogate endpoint.
And I think we've got to really put -- we've got to get down to real details to talk about what it really would take to get us to that point. So more questions than I think an answer.
DR. PETER KIM: Thank you, Dr. Huang. I thought I saw a hand up for a moment. Perhaps, Dr.

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Duffy?
DR. ERIN DUFFY: That was a mistake.
DR. PETER KIM:. Okay. Dr. Wacher.
DR. VINCE WACHER: So -- yeah, Wacher. Perfect, thank you. So the trial design -- and thanks, Dr. Huang, for bringing up sort of premarket and post-market and things like that and to go completely out there, completely out there right now, how would we be able to get our point of care preventative evaluated effectively. And that is if we could be approved to put it on formularies based on safety, and then let the hospitals evaluate this and collect the data over time.
So maybe the product is safe enough to be on the formulary. I know that the infection control people will prescribe it. I know physicians will prescribe it if they think it will benefit the patient, but rather than having dedicated efficacy data, maybe we have some signal that encourages efficacy but definitive safety and then we can put it in multiple hospitals and that way get a massive trial that funds itself, even if we were to charge this at

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cost.
And I know I'm sounding very mercenary, but honestly this is what's stopping things going forward right now. We've got to find ways that this can be done because otherwise it's not going to get done and it's very sad to hear about Phase 3 trials, Phase 2 trials that cannot go ahead because of the cost.
DR. PETER KIM: Thank you, Dr. Wacher. Dr. Weinstein.
DR. ROBERT WEINSTEIN: Yes. To expand on one of Susan Huang's points, I think that the COVID pandemic really made it clear that we need to have a mechanism for using global data. So studies done in other countries of products that we might use here, how do we use that without having to have the full registration data, in a pandemic at least.
The other aspect I think is that if we're going to understand, we're going to develop interventions for communities, we have to understand the epidemiology communities which we don't yet and I think this requires citizen science and enrolling, for

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example, parents to see where their kids may be picking up resist and bugs. You know, are they picking up on the playgrounds, where are they getting it.
And so I think we need to think of ways that we can enroll community members to study problems in the community more efficiently than we're doing now. Otherwise we'll never be able to craft community interventions.
DR. PETER KIM: Very innovative thoughts. I see a hand up and I'm sorry, I'm going to mispronounce --
FLORENCE SEJOURNE: Florence --
DR. PETER KIM: -- your last name.
FLORENCE SEJOURNE: Florence, it's okay.
DR. PETER KIM: Florence, please.
FLORENCE SEJOURNE: You can say my first name. Yes, I mean I'm coming back to, you know, following the two last comment, three last comment from Robert and Vince. I'm coming back to Cliff McDonald's question because at the end, I think this

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is it. I mean, what would -- I mean based on today's workshop where we have heard for the morning sessions CDC showing us how much colonization makes sense and is associated to risk of infections, and as companies developing products where we have trouble showing directly the prevention of infection but we could definitely show prevention of some biological markers and I've shown a few that we have developed at Da Volterra.

So what would be required today to move to the next steps in terms of endpoint demonstration in association, of course, with safety database.

DR. PETER KIM: Yeah. I mean, this is truly the question of the hour and that's part of -- I'm sorry go ahead. Go ahead, John.

DR. JOHN JERNIGAN: So Dan, did you want to start or do you want me to make some comments, or Peter?

DR. PETER KIM: I think so --

DR. JOHN JERNIGAN: I wasn't sure if you were going to talk about this one. Okay. So here's what I learned today, and I've learned a lot

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actually from this process because I feel like I've been living in COVID-land for two-and-a-half years, as do most of you probably.

So I think that the population and the pathogen is important and each situation is going to be different in terms of whether use of a surrogate in a clinical trial is scientifically supported or actually makes sense to a sponsor, you know, in terms of feasibility.

So I think that first of all, you don't need necessarily clinical trial data to support the clinical benefit of a surrogate, but you do need high quality prospective observational data and preferably more than one source for folks to talk about, and there are a number of processes to come in and begin to have those discussions.

We can do that more globally with Cliff's team at CDC. We are happy to do that with sponsors under a pre-IND focused on a particular product, a particular population, a particular pathogen, and talk about, you know, how strong is the data.

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I can tell you that most of the experience of using either new endpoints or new justifications for noninferiority margins largely gets driven by development programs and that tends to be more efficient than a global qualification process.

But the first thing to do is be -- is someone being willing to put the data together and actually have that discussion. That's step one.

I think there are a fair number of pros and cons of considering that as a trial endpoint, and I think a lot of that came up in the CARB-X focus group that that Erin talked about that, that you could see. And none of them actually -- we ended up in the scenarios they were discussing talking about other than a clinical endpoint. There is the need, unless it's a very robust surrogate that can be kind of defined as a validated surrogate, going to be the need to confirm the clinical benefit, you know, perhaps by continuing the trial.

And I think there's another stakeholder at the table these days, which is very important, which is payers in terms of what you've demonstrated

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in your trial and whether or not that product's going to be supported either by a formulary committee or by payers at that level. So those are just some general observations and I would invite others to add.

DR. PETER KIM: And just to add on to what John was saying, we are open to ideas and considerations. That's part of why we partnered with CDC on this workshop and this is probably the first of several conversations. But once again, as John had noted, we need someone to come in with a consolidation of the evidence for us to evaluate.

I'll let Dan speak. He has his hand up.

DR. DAN RUBIN: Sure. I had actually raised my hand before the surrogate question came up, so I don't want to derail us, but just to add a few points to this. I mean, I agree with John that whether a surrogate is reasonably likely to predict clinical benefit can certainly depend on the pathogen, the disease, and the intervention. And there are definitely hierarchies to the levels of evidence that at one level you would need a strong mechanistic

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rationale.
Then I guess the next level of endpoint would be a correlate where you've shown that the surrogate you're trying to reduce is correlated at the individual level with the clinical outcome and then really the highest form of evidence would be kind of large outcome trials showing that your treatment effect on the surrogate at the trial level was associated with the treatment effect on the clinical benefit, but how those different forms of evidence are weighed in different settings is obviously complex and it may be hard to get to today.
So I guess the more minor point I wanted to raise was just listening to Dr. Huang's presentation one idea I had when she was talking about kind of the competing interventions in the background of that trial, that some of the settings we've talked about today could be good settings potentially for platform trial. I think they've shown their worth in in COVID-19.
These are trials where different sponsors work together and interventions can come, you

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know, into the trial in different arms as the study's ongoing or if there aren't competing mechanisms, potentially certain types of sectorial randomization can be used, but just kind of thinking about the different interventions and the bundles. This could be a potential setting for platform trials. Thank you.
DR. PETER KIM: Thanks, Dan. Susan, I see your hand up.
DR. SUSAN HUANG: Yes. I wanted to just ask, there was a -- someone had mentioned that sometimes the sponsor to FDA of raising to get an indication is not the manufacturer, and I wanted to better understand.
Let's say that there was a value for infection prevention. Can an infection prevention society or can CDC come and raise the ability to have something be accepted as an appropriate indication and barring the fact that that might take billions of dollars -- I actually have no idea what that cost is - - but someone raised the fact that it's not always the manufacturer. So who else would be a sponsor and put

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up that kind of dollars to actually get that read by FDA?
DR. JOHN JERNIGAN: I can make some comments if you want me to start. So I think we do have examples where noncommercial sponsors, you know, have actually taken drugs through the process. The TV consortium is one example.
One of the important points about the United States is that we the government can't take the intellectual property of another. And so whoever is sponsoring needs a right of reference to the data that might be important. And that may be the product quality data, the nonclinical data for the particular molecule in question. And that sometimes is an issue. Just something to keep in mind, but there's nothing barring a consortium from taking, for example, something that's well off patent in for a regulatory action, Susan, and we'd absolutely be delighted to work with you, of course.
DR. PETER KIM: And I would --
DR. SUSAN HUANG: Likewise.
DR. PETER KIM: I'm sorry go ahead.

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DR. SUSAN HUANG: No just saying likewise.
DR. PETER KIM: I would just add the -- that probably the best mechanism to facilitate the beginning of the discussion would be a pre-investigational new drug application, a pre-IND. That way, we can begin the conversation. We can look at submitted data and whatnot and provide some consultative advice.
DR. JOHN JERNIGAN: And for those of you unfamiliar, a pre-IND is our way of making sure we don't -- we have access and file the stuff properly that you've submitted and we actually have a process for offering you a meeting. There is no cost for receiving advice through that that program, but then you have a dossier that we're keeping through the development program and eventually if you're ready to move to human trial and need an IND, we can then rely upon that file and it simply becomes an IND file.
DR. PETER KIM: Absolutely. I see Dr. Sharon Wright has her hand up.
DR. SHARON WRIGHT: Thank you. I just

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wanted to pivot us back just for a minute to the question that came up about population, particularly what Drs. Huang and Weinstein were mentioning. You know, I think the distinction between community and the healthcare setting is becoming increasingly blurred.

And this may be that my newer view looking from the health system but as we start moving things, particularly complex surgeries into the ambulatory setting and then patients going directly home afterwards, of things that, you know, some patients might have even wound up in a community ICU afterwards to recover, and as we look into medical home and giving full medical care in patients homes, I think thinking about how we design these studies and for maybe larger systems that have combined electronic health records may be a way to look at that data and follow patients through all settings, including things we often don't think about like freestanding psychiatric facilities where things pass very quickly, like summer camp when they are all sharing kitchen space and activities together or, you know,

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immunocompromised units.

So just taking those things in mind when we think about some of the study design and the populations that are at risk who bring those things then back into our tertiary and quaternary care setting.

DR. PETER KIM: Thank you, Dr. Wright. I see Dr. Dmitri Iarikov. Would you like to comment?

Dr. DMITRI IARIKOV: I thank everyone. A great discussion. Just a few points to add to what John and Peter was saying to Dr. Huang's point.

Please keep in mind that approval of the IND, it's not the end of the process. There should be an entity responsible for maintaining the product, right, so there should be someone to keep manufacturing in order, providing stability data, providing reports, paying fees.

So it's not just that -- not, it's just. It's not only a collection of the data and submitting it to the agency. It's just the beginning of the process. Over.

DR. PETER KIM: Very good point,

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Dmitri. Dr. Kim, would you like to comment?

DR. JAMES KIM: Yeah, thank you. I guess to build off of Dr. Huang's statements about looking at things from all the different vantage points, I think that discussion here on new drug applications is very interesting and timely subject.

I also want to sort of, you know, think about the way that Dr. Weinstein spoke about the different places where you can have interventions. And you know, thinking about hand hygiene and the importance of hand hygiene, I think Dr. Weinstein specified several places where I think proper hand hygiene could have a real positive impact on decreasing transmission of hospital-associated infections.

So just want to sort of put that on the table that, you know, we do have a toolkit here. The OTC active ingredients that we use in antiseptics that I think could be, you know, expanded in the way that they're used or used more effectively. And I think that, you know, is something that we should have some discussion about also with FDA, thinking about the

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ultimate goal of improving.

DR. PETER KIM: Thank you. Thank you, Jim, for your comment. I'll just ask if Dr. Michele would like to comment.

DR. THERESA MICHELE: Nothing further. Thanks.

DR. PETER KIM: Thank you. Any other thoughts or questions before we move on to the next question? I think we are close to time. Dr. Jjingo, would you like to go? Would you like to speak?

DR. CAROLINE JJINGO: Yes. I just wanted to say in terms of Dr. Wacher's presentation, I think you brought up a lot of important at least I think logistical and operational issues which at least from the regulatory standpoint, I think it's good for us to consider, like -- and also many of speakers in terms of the expense of these trials and really I think there needs to be probably and I don't know how to think of this, but in terms of like funding frameworks.

I don't know -- I mean, I know Dr. Farley talked about some consortiums but I don't know

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if maybe down the line we might need to think of, I don't know, government strategies to try and fund what might ultimately be really expensive studies, you know, to get the information that we need, especially because I think culturally when we look at how our healthcare systems, it's usually less proactive in terms -- and more reactive. So in terms of when we're thinking about things in terms of like prevention, where do we get the buy-in to even fund what will ultimately seem like it's going to be expensive studies?

And on top of that, the point that you said in terms of like with stakeholder buy-ins, if we think about hospitals and how I guess several of them I guess, you know, based on, you know, being dinged for, like, healthcare acquired infections, so how, if we're going to think about cluster randomized trials, do we get those -- where we're looking at health care institutions, be they hospitals or long-term care facilities in order to even try and volunteer yourself to be a part of a study?

I mean, somehow it seems like there

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might be some tension between the fact that you don't want to actually have -- you don't want to have healthcare-acquired infections, but yet we would need their buy-in in order to conduct these studies. So I think there are several conundrums, be they funding mechanisms and also getting necessary stakeholders to even be able to conduct the science that we need to answer then these regulatory questions and to fulfill the public health and at the individual level patient level need that we need to even do this.

So it's not necessarily the science but I think it's the operational logistics that are important. So I thank you guys for bringing those up, but -- and I don't know the answer.

DR. PETER KIM: Thank you, Caroline. Florence, would you like --

FLORENCE SEJOURNE: Yes.

DR. PETER KIM: -- to go?

FLORENCE SEJOURNE: Yes, I wanted to just rapidly reply to Caroline. We had the chance in our program to have a co-funding from Europe, from the European Commission through IHI. So this issue of

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logistic was actually not a problem really of money. At the end we -- it was a problem of, you know, we managed to get regulatory authorization. We managed to get some level of funding.

The thing is the study would last nine years. We don't have that time. So why? Because we have selected the right patient population which is an enrich patient population. I think that's part of the question of the designs. However, those are hemato-oncology patients and hemato-oncology patient, as we well know they take a lot of antibiotics and therefore have a very high risk of secondary infection, C. diff as well as resistant bacteria and sepsis.

But guys, when they do clinical studies, what they're concentrated in in getting treated, their cancer. So the competition in those patient population, enrich patient population of infectious disease are very difficult to recruit for very good reasons which is their own -- their physician own priority to get treated, to treat their cancer.

And even though we understand

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microbiome protection is not only about infection but as well as immune system towards GvHD, et cetera, et cetera. This is still a little bit science fiction for physicians so that it's difficult to recruit big population in those severe oncology patients because we just have as well competition with cures for cancer.

DR. PETER KIM: Thank you, Florence. Okay, we'll take Vince as our last comment for this question.

DR. VINCE WACHER: Thanks very much. And so first of all, everything Florence said, absolutely agree. It took us a year to just get to our patients. So it is a tough even in an enriched population with a high incidence endpoint like the bone marrow transplant population. But I did have an idea about how we can force this along. Maybe we could talk to CMS and talk to -- about the HSCRP program, and you have a choice.

We will take 1 percent of all your Medicare reimbursement or you will have let us do clinical trials in your institutions. And that way

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they have a way out of their thing and we have an opportunity to get to some patients.

DR. PETER KIM: Thank you, Vince. And thank you all for this -- for the responses to the question. It's been really helpful to hear your thoughts.

Okay, now the third question. Please discuss clinical endpoints effects on how a patient feels, functions, survives that would be most relevant for evaluating the efficacy of a new therapeutic for the prevention of healthcare-associated infections including but not limited to possible differences and endpoints used in trials randomized at the unit level versus the patient level, defining endpoints for pathogen specific versus broader spectrum therapeutics and handling of dust during the study in endpoint analysis.

And we'd like to ask Dr. Vance Fowler to start off with a response to this question. Vance.

DR. VANCE FOWLER: Sure. Thanks Peter. I appreciate the opportunity to participate and learned a great deal from the previous speakers. So

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yeah, it's a tricky issue, this endpoint thing, because in many ways it's governed in part by the audience to whom you're ultimately designing your trial.

And I mean, two sort of broad buckets are strategy trials and registrational trials and unavoidably, because they have fundamentally different goals that are both critical, the audiences of these trials are different. You know, strategy trials are fundamentally about how do we best use the product that we have in our hands. Registration trial is about getting that product into the hands of clinicians at the end of the day.

I'm going to focus my comments on registrational trials because that's ultimately why we're all here. Four sort of thoughts on endpoints that can hopefully get things going. You know, the interesting thing about these prevention trials is that the end point in this situation is the event that you don't see and that really permeates the way the trial is interpreted, the way it's designed, and you know, because ultimately you've got a study in which

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you've got at-risk patients who are not infected at the time of enrollment and you want to see which arm of your trial is best able to keep them that way.

This fundamentally differs from your traditional anti-infective trials in which all of the patients at the beginning have got an infection and the goal is simply to compare the efficacy of two different comparator anti-infective agents and that's going to drive how these trials are designed. It's going to drive how they're interpreted.

So given that, the second thing, I think the primary endpoint in these prevention trials needs to -- wherever possible, needs to be a micro biologically confirmed and blindly adjudicated event. So you know, interventions that target specific pathogens -- and I'm going to largely focus my comments on staph aureus just because it's far and away the most interesting pathogen -- is you know, really should be assessed on its ability to reduce infections that are caused by the pathogen of interest.

I think that in terms of how resistance

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infuses into that scenario, you know, really in the absence of biological basis, microbiological endpoints should be calculated by including both antibiotic susceptible and antibiotic resistant bacteria. In other words, in this sense, the example, methicillin-susceptible and methicillin-resistant staph aureus, again, unless there's some sort of biological or mechanistic reason to the contrary.

Interventions that don't target specific organisms should also be evaluated by micro biologically confirmed events whenever you can. But the problem is in some clinical syndromes, in fact, some big clinical syndromes we have to deal with like hospital-acquired pneumonia, you're almost never going to get a microbiological endpoint, just because of the nature of the disease and I think in that instance, the least bad scenario that we can come up with is going to be a blinded clinical adjudication committee using pre-established guidelines.

So that's probably how I would think about tackling that in the particular settings where you're targeting specific pathogen, you're targeting a

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syndrome, and you're targeting a syndrome without any organism.

Quality of life and economic impact, I think, should be captured both as secondary endpoints but for different reasons. Quality of life, I think, should -- would fundamentally fit into the overarching mission of you know, evaluating how patients feel, function, and survive for obvious reasons. It's tricky because you're almost certainly going to need a validated syndrome specific quality of life instrument.

I mean, if you look at the OVIVA trial published in 2019 in New England Journal, looked at oral antibiotics for osteomyelitis, when they looked at oral versus IV antibiotics and asked the question, does oral antibiotics improve the quality of life of patients as compared to IV antibiotics, the answer was no. And if you -- you know, I think all of us would fundamentally say that's probably not right. And a lot of it has to do with the tool instrument in which they use to try to answer the question. So you're going to have to get specific. They use a thing

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called the EuroQol-5, which was not really a specific to that syndrome.

Economics are obviously critical, less so from the perspective of regulatory but absolutely vital for the purposes of, you know, of dealing with the third party payers as our other speakers have raised.

And the final point I guess I'd make would be, you know, endpoints for interventions that reduce rates of infection by reducing bacterial colonization, that's tough. We've already heard several examples here on this call. You know, I think that they're almost certainly going to require hard endpoints such as infection until we've got a validated surrogate endpoint.

And we've heard several examples of why that's the case, the struggles with it. You know, there's staph aureus carriage versus post-operative infection. There's the C. difficile scenario. I don't see that as being a realistic expectation from industry, personally, because I think the cost and the time are far beyond the scope of sponsor driven

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research.

I see that as something that's ultimately going to fall on the shoulders of government, of federal funding, and I think that we can try to stimulate appropriate trials looking at surrogates through RFAs, targeted RFAs.

You know, you think about Mike Saag's science paper that demonstrated the, you know, the role of HIV quantitative viral load as a valid surrogate for the use of HIV -- in HIV clinical trials and, you know, how do you translate that to the scenario of C. diff where, you know, you can colonize and not only could you colonize, but then you have to express the toxin for it to go -- you know, so it's going to be tricky.

How do you do it? Well, I think that for example, you could start, do your RFAs with targeting the top five to ten top syndromes that a group of experts like Susan Huang and, you know, a bunch of others on this call could come up with. Say these are the ones we really need to crack. We need some sort of system by which to establish, you know,

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what if, what would -- you know, how are we going to trust a surrogate.

And then, you know, in terms of funding, some of the options include, well you know, the ORISE fellowship. I can tell you, you know, we're doing that right now with some of the members of this call using a collaboration between ARLG and the FDA to focus on the possible exploration of door endpoints for the four most common anti-infective indications, and it's just been fabulous. So you know, there's precedent in which some of these scenarios such as an ORISE fellowship for one, the CTTI, Clinical Trials Transformation Initiative that, you know, Dr. Farley and I had the opportunity to work on years ago with hospital acquired pneumonia is another, and things of that nature.

So maybe I'll stop there and appreciate the opportunity. Thank you.

DR. PETER KIM: Thanks, Vance. Thank you for your thoughts. Very provoking. I'm looking for hands. Any takers before I start asking -- we have about roughly ten minutes. Dr. Huang, could you

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like to comment on any aspect of this question?
DR. SUSAN HUANG: You know, I think that my first thought when I see this question is just the plethora of studies that you could do because each of those things are incredibly important. Of course, patient reported outcomes are important. The things that drive hospital systems to want to adopt something and quality improvement is incredibly important. The ability to hone in the microbiome as we understand it and influence it to prevent disease is critically important.
So I really I think that the answer all of us, our first reaction is going to be yes all of that matters deeply and how can we -- however how can we translate something like a patient reported outcome much like the ecological outcomes of an ICU into something that can move into an FDA indication.
And I do think that there is a divide, maybe it's a chasm but it was there for a good reason, you know, safety really, you know, really defined endpoints. There's a reason why the system exists the way that we have it. But given the gray spaces that

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exist with the microbiome and a lot more attention on patient desires and interests, this idea of population health, which you know, how do you get an indication for a population, right, and who governs that population and who owns consent for that population?
Is it public health? Is it the health system? Is it -- who is it? I think that if we can all agree that there is a new world of conversations that needs to be furthered and how we get there and how it might change what we have held fast to as the dogma of how we conduct studies or approved products or, you know, I think that what we're saying through all of this is that these things need to shift in some way, none of us are certain exactly how, but we need to come closer together because there's a lot of people who need us and they need these products and they need them in a way that can't be decades in the making and we don't -- we can't afford it because the resistance is growing because of the way we Americans use antibiotics.
And you know, these are, you know, first world problems, but they're very, very germane

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to public health here. So I think it's a great conversation. I hope it's the first of many more.
DR. PETER KIM: Thank you. Thank you, Dr. Huang. Anyone else? Dr. Jjingo, I see your hand is up.
DR. CAROLINE JJINGO: Yeah, hi. I just wanted to ask Dr. Fowler or any of our panelists, but since Dr. Fowler mentioned about quality of life measures or -- like, how would you approach? I mean, how would you approach that? Would it be like, I mean, what kind of, like, instrument would you -- or are there any existing ones or how would you go about that and at what point it seems like it might be -- have to address something that's longitudinal or some sustained or early on or -- yeah, I just wanted to hear your thoughts or anyone's thoughts about how it would capture quality of life measures from a patient perspective,
DR. VANCE FOWLER: Would someone else like to respond first? Okay, I can comment then. So, you know, as you will -- you doubtless know, they're sort of quality of light -- quality of life that these

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instruments that haven't been fully validated by the FDA takes years and years and it's onerous.
In no way am I proposing them. There is sort of a middle ground which is being developed and in fact there's a Duke faculty person working, I think the majority of his time at the FDA on quality of life instruments that can be developed in that regard.
ARLG is also working on quality of life instruments amongst the, you know, the four anti -- primary indications for anti-infectives. And that can be, you know, it's sort of essentially internally validated, largely using -- I know I'm going to get the wording wrong because I -- usually we have to have a responsible adult with these quality of life guys which -- when we start these trials, but they have essentially validated pods or sections of previous quality of life studies that they can then build in and integrate into a syndrome specific indication.
For example, we're doing it with complicated urinary tract infection. As a matter of fact, we're also as a second trial with the ARLG,

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we're asking kind of interesting response to that and that is, evaluating how well physicians estimate the quality of life of their patients. So you're asking the quality of life of the patient and then simultaneously of those same providers that are providing care to them asking the same -- asking their expectation and their interpretation of it.

I can't wait to see what that one is going to be, because my guess is we probably don't get it quite as well as we think we do. But I think it's going to have to as the OVIVA example sort of illustrates, I think it's going to have to have some specificity of a particular syndrome in place and, you know, that can be done with a reasonable price, you know, and a reasonable timeline using some of these sort of pre-existing validated components. I'll stop there.

DR. PETER KIM: Thanks, Vance. Any last minute thoughts? Florence, would you like to take the floor?

FLORENCE SEJOURNE: Sorry --

DR. PETER KIM: Florence, you're on

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mute.

FLORENCE SEJOURNE: -- muting. Yeah. I'm sorry to give a very brief private company reaction to the discussions. It's very good that CDC, FDA gathered together to put this on the table and that we share the info. It's going to be too late for some of us, maybe not all, but to bring those products to market now. The example of DAV132 is $18 million for 15 years already spent. Five hundred, you know, volunteer patients treated with safety, good safety database. This takes time. This takes a lot of money.

As you well know, pharma is not really interested in that and biotech have trouble fundraising. So there is some kind of emergency if we want actually the products already kind of available and developed today to go to market -- similarly to new antibiotics where we know this is an issue and CARB-X knows that more than anyone else. Sorry for the negative comment in terms of timelines, but that's the reality we're into.

DR. PETER KIM: Thank you, Florence.

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Dr. Weinstein.

DR. ROBERT WEINSTEIN: Yeah, I think the issue of patient reported outcomes is fascinating and comparing it to what we think and what the patient thinks. I think the other aspect is the nursing staff. I don't think we get enough input from the nursing staff for interventions and what they think of them. And if you've had patients in the -- relatives in the hospital recently, you value the nurses more than the doctors. No question about it in my mind.

You certainly see them a lot more. And I think understanding what they think of some of the interventions and how they affect their day-to-day work, I think would be very useful to incorporate into some of the studies we do.

DR. PETER KIM: Thank you, Dr. Weinstein. So, we're at time for this panel discussion. What we'll now do is Michael and I will split the summary of today's session. So, Michael, I turn the floor over to you.

MICHAEL CRAIG: Thank you, Peter. And I want to thank all of our panelists and everyone for

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today. And I think for all of our participants, we had, I think at times over 1,000 folks participating in the day, so really appreciate everyone's engagement and interest in the topic.

I just want to note from the CDC perspective, as I noted at the outset, we're incredibly grateful to our colleagues at FDA, John Farley and his team for bringing this meeting together with us. This is an area of intense interest from CDC, as you heard this morning from my presentation as well as that of my colleagues, and I think what we wanted to highlight was just the challenge that we see in public health that I think is growing. And it's one that we really do think that there are enormous opportunities here for collaboration and I think it's collaboration between the public health side, the FDA regulatory side, as well as the private sector.

And I think what you heard this morning is, you know, the challenge that we see is the transmission of these dangerous pathogens, many of them antimicrobial resistant is growing. And how do we address that? And the issues of resistance are

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only increasing.

You heard from Dr. Jernigan talking about that the power of the indirect effect on prevention and what that could potentially hold and some of the modeling that we have seen and that we think is important. You heard from Dr. McDonald talking about agents that are currently available that are being used for some of these purposes already and the positive benefit that we're seeing from many of those and the potential that there could be more, especially as we, you know, potentially could have pathways for some of these products being brought to market.

And then you heard from a series of CDC experts, fantastic presentations that delve deeply into the specific pathogen areas. And I'm not going to go over all of them, but I just want to commend all of them for very fantastic, in-depth perspectives that really show the expertise and the data that we have in many of those areas and the potential for what prevention could mean for all of the people who are affected, both in terms of colonization and infection

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of those pathogens as well as those who are potentially at risk of those pathogens.

And then I would also just really like to highlight and thank our panelists who followed the CDC presenters, both our public commenters as well as those who from -- that shared the patient perspective. I think, you know, we had tremendous presentations about cystic fibrosis and the impacts of a MRSA infection on patients and the ongoing challenges that patients face because of those infections. And I think that they highlighted really, what we all need to remember is what is the patient experience, how can we bring prevention to bear on patients and how can we protect patients ultimately from risk of infection and the risk of transmission.

So that's I think where I would note it and I again want to thank everybody for their participation and Peter, I'll turn it back over to you.

DR. PETER KIM: Thanks, Michael, and I would also like to thank everyone involved, all the stakeholders, and thank you for this great working

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relationship with you, CDC, Michael, and also with academia and we will continue to work with industry as well.

All right, so I'm going to go through a whirlwind of session two. All right. So Heidi Smith discussed Regulatory Considerations for the Registration of Products for the Prevention or Reduction in the Incidence of Healthcare-Associated Infections. She discussed FDA's standards for approval of new products, the characteristics of adequate and well-controlled trials. She provided illustrative examples of possible development programs such as drugs for the prevention of surgical site infections, and also drugs to reduce the incidence of catheter-related bloodstream infections and she discussed safety database considerations.

Next, Dr. Theresa Michele's talk was Regulation of Healthcare Antiseptics, and Dr. Michele discussed the categories of over-the-counter antiseptics such as healthcare antiseptics including but not limited to patient preoperative skin preparation. She compared and contrasted pathways for

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marketing nonprescription drugs, namely the new drug applications, abbreviated NDA, versus the drug review process through the OTC monograph.

She provided an example of the indication and labeling for a patient preoperative skin preparation and described the in vivo and clinical simulation testing for efficacy for a drug product, for patient preoperative skin preparation.

Next, Dr. Paul Carlson's talk, Regulatory Considerations for Microbiome Based Therapeutics. Dr. Carlson touched on the investigational new drug application regulations and the additional chemistry, manufacturing, and control considerations for INDs for fecal microbiota transplantation as well as live biotherapeutic products and then discussed some of the challenges and the regulations of FMT such as how to ensure safety and how to characterize the product for consistency of an effectiveness and also discussed and noted that live biotherapeutic products should contain sufficient information to assure the proper identification, quality, purity, and strength of the investigational

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drug.

Next Dr. Susan Huang. Her talk was clinical considerations and operational challenges for healthcare-associated infection prevention trials. Dr. Huang touched on common features of healthcare-associated infection prevention trials such as the desire to evaluate a quality improvement strategy, determining the group of focus whether it be units or hospitals, et cetera, targeting a contagious outcome. The trials are spurred by urgent common need and that there is limited funds in this space.

She then discussed common features of classical versus pragmatic trials, the differences between efficacy and effectiveness trials. She then characterized infection prevention populations of interest, the importance of defining the question under study such as temporary prevention versus long-lasting prevention.

She also discussed the importance of partnership within healthcare system and also had considerations for minimal risk trials and waiver of consent, the importance of choosing appropriate

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controls, discussed analysis approaches such as difference-in-differences approach, the need for accounting for contagious outcomes.

She discussed the differences between the conduct of the CLEAR trial and the REDUCE MRSA trial and some lessons learned and she delineated special considerations for what may be considered minimal risk indication.

In conclusion, she noted that a wide variety of trials with varying durations may be pursued and once you consider the value of group versus individual randomization, ensure sufficient sample size for balancing confounders and assessing outcomes, ensure obtaining the best possible controls for gold standard comparison, and ensure data for as-randomized analysis when groups drop out.

Next, we had Dr. Ed Bein, statistical considerations related to cluster randomized trials. Dr. Bein noted that the use of a cluster randomized trial is appropriate when evaluating treatments and intended to be administered cluster-wide and that CRTs are intended to handle within cluster contamination

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interference between treatment and that there is contamination interference between treatments when patients' outcomes are influenced by both the treatments they themselves receive and the treatments others received.

Let's see. Dr. Weinstein's talk was Controlling Pathogens in Health Care, A Way Forward. He noted the model of the causal pathway of spread of antimicrobial resistant organisms can help to focus implementation strategies for pathogen reduction and healthcare epidemiology. He noted the relative importance of the individual components of infection control guidelines and bundles should be evaluated and the studies of microbiome should assess mechanisms behind the creation of the fecal patina and explore the interrelations of different microbiome components.

Dr. James Kim, his talk was OTC topical antiseptics, an opportunity to bring innovative decolonization products to market. He provided background information on the American Cleaning Institute, discussed topical skin antiseptics and the regulation of these products, noting that current

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regulatory frameworks may pose a barrier to the development of innovative topical skin antiseptics and noted that the establishment of skin decolonization and pathogen reduction as a determinant of clinical outcomes would facilitate new skin antiseptic development.

Nicholas Georges' talk was Development of Efficacious Cleaning and Disinfecting Products in Healthcare Settings. He discussed the differences between disinfectants, sanitizers, sterilants, and cleaning products. He noted that testing is dependent on the claims and the surface types to be treated which results in determining which agency regulates the product in question. And he touched on how one might select the product for a particular use.

Dr. Erin Duffy's talk was Considerations in the Development of Nontraditional Therapeutics, a CARB-X Perspective. She provided an overview of the CARB-X program as well as their portfolio of treatment and prevention products. Dr. Duffy discussed takeaways from her recent decolonization workshop including but not limited to

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thoughts on potential patient populations for studying decolonization strategies.

She also noted that there are several challenges and opportunities for decolonization strategies and a coordinated approach would be beneficial.

Florence Sejourne. Her talk was Challenges and Lessons Learned Developing DAV132, a Novel Therapy Protecting Gut Microbiota from Antibiotic-Induced Dysbiosis. She discussed how antibiotics provoke intestinal microbiota dysbiosis and how dysbiosis may result in additional downstream consequences. She discussed the DAV132 development program and lessons learned. She noted the association between low diversity microbiota and the risk of CDI as well as the risk of colonization with multidrug-resistant organism.

She noted that current regulations do not allow for feasible clinical development because of the demonstration of reduction in colonization followed by reduction secondary infections and dissemination necessitates large, expensive trial.

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Next, Dr. Vince Wacher. His talk was Lessons Learned in Developing SYN-004, a Potential Point of Care Preventative for HA-CDI. He discussed the development program for SYN-004 for the proposed indication of prevention of CDI. He also proposed ways to help facilitate CDI prophylactic drug development.

Dr. Silvia Caballero. Her talk was Defined Bacterial Consortia, a Novel Approach to Tackle Healthcare-Associated Infections. She noted that microbiota and metabolic alterations characterized colonization and infection with C. difficile and MDRO. She discussed development programs for VE303 and VE707 bacterial consortia for either decolonization or preventing CDI and MDR Enterobacteriaceae.

And finally, Matthew Henn. His talk was Microbiome Therapeutics to Potentially Transform the Management of Antimicrobial-Resistant Infection. He noted that encapsulated consortia of commensal bacteria may be designed to establish colonization resistance and target inflammatory and immune pathways

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and discussed development programs for SER-109 in patients with recurrent CDI.

And then we also heard from our panelists on three questions and we had a rather provocative conversations and a lot of take home from the discussion.

So once again, thank you very much for everyone's participation, everyone who made this workshop possible. We hope this is the first of several discussions. I would like to thank our partners CDC as well as academia and industry and the patient groups as well who provided valuable information related to their experiences.

Michael, I think you want to -- why don't you go ahead.

MICHAEL CRAIG: Yeah, Peter. I just wanted to close by noting, folks, that we have been recording today and it is going to be posted on the registration page for folks to see and it's also going to be on CDC's YouTube page and those will be available and thanks for pulling up the post-webinar information.

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If you have questions you can email us at ARX@CDC.gov and we'll get back to you with that. And I also want to close by thanking the planning and logistics teams, Katie, Sunita, Amy, all the other folks who have been behind the scenes who have pulled this together and we've been working on this for about a year, so really appreciate everyone's great work on it. There's a lot of work that happened behind the scenes that folks didn't see. So thank you all and I think with that we can close for today. Thanks, all. Bye bye.

DR. PETER KIM: Thank you, everyone.

(Whereupon, at 5:22 p.m., the proceeding was concluded.)

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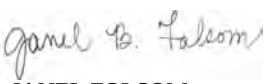

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