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Drug Development Considerations for the Prevention of
Healthcare-Associated Infections

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<p style="text-align: right;">Page 2</p> <p>1 A P P E A R A N C E S</p> <p>2 Meeting Moderators:</p> <p>3 John Farley, FDA</p> <p>4 Michael Craig, CDC</p> <p>5 Heidi Smith, FDA</p> <p>6 Timothy Bensman</p> <p>7 Dan Rubin, FDA</p> <p>8 John Jernigan, CDC</p> <p>9 Peter Kim, FDA</p> <p>10</p> <p>11 FDA:</p> <p>12 Edward Bein</p> <p>13 Timothy Bensma</p> <p>14 Paul Carlson</p> <p>15 Dmitri Iarikov</p> <p>16 Caroline Jjingo</p> <p>17 Peter Kim</p> <p>18 Theresa Michele</p> <p>19 Dan Rubin</p> <p>20 Heidi Smith</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 4</p> <p>1 P R O C E E D I N G S</p> <p>2 DR. JOHN FARLEY: Good morning,</p> <p>3 everyone and welcome to this virtual public workshop,</p> <p>4 Drug Development Considerations for the Prevention of</p> <p>5 Healthcare Associated Infections. My name is John</p> <p>6 Farley and I am the director of the Office of</p> <p>7 Infectious Diseases in the Center for Drugs at FDA.</p> <p>8 So innovation in drug development to</p> <p>9 prevent healthcare-associated infections will be</p> <p>10 critical to reduce morbidity and mortality and address</p> <p>11 antimicrobial resistance. Our colleagues at CDC and</p> <p>12 the team at FDA have partnered to host this workshop.</p> <p>13 This is one -- this is what we hope will be the first</p> <p>14 of a number of public dialogues to address drug</p> <p>15 developmental -- development challenges in this space.</p> <p>16 And special thanks to our CDC colleagues, the national</p> <p>17 thought leaders, and industry development leaders that</p> <p>18 are able to join us today and are here. Next.</p> <p>19 So just an overview of today's program.</p> <p>20 Session one will focus on background and epidemiology.</p> <p>21 The team has put together a state of the art review of</p> <p>22 prevention science and the major healthcare-associated</p>
<p style="text-align: right;">Page 3</p> <p>1 CDC:</p> <p>2 Michael Craig</p> <p>3 Christopher Elkins</p> <p>4 Alice Guh</p> <p>5 Cal Ham</p> <p>6 John Jernigan</p> <p>7 Lawrence Mcdonald</p> <p>8 Joe Sexton</p> <p>9 Maroya Walters</p> <p>10</p> <p>11 External:</p> <p>12 Lilian Abbo (University of Miami)</p> <p>13 A. Whitney Brown (Cystic Fibrosis Foundation)</p> <p>14 Silvia Caballero (Vedanta)</p> <p>15 Erin Duffy (CARB-X)</p> <p>16 Vance Fowler (Duke University)</p> <p>17 Nicholas Georges (Household and Commercial Products</p> <p>18 Association)</p> <p>19 Matt Henn (Seres Therapeutics)</p> <p>20</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 5</p> <p>1 infections, and I think we're all going to learn a lot</p> <p>2 from that this morning. We have patients to provide</p> <p>3 their perspective and impact statements and we have an</p> <p>4 opportunity for formal public comments.</p> <p>5 We'll then turn our attention to the</p> <p>6 regulatory perspective and trial design challenges and</p> <p>7 considerations and there are a number of regulatory</p> <p>8 considerations, first of which is that there really</p> <p>9 are a number of different products that are under</p> <p>10 discussion. So there are drugs, there are drugs that</p> <p>11 are regulated as antiseptics, and there are</p> <p>12 microbiome-based therapeutics which are often</p> <p>13 biologics, and each of those has unique considerations</p> <p>14 and we do have some speakers today to provide a good</p> <p>15 overview of those issues.</p> <p>16 There are a lot of clinical,</p> <p>17 statistical, and operational considerations to talk</p> <p>18 about and we'll conclude the day with a moderated</p> <p>19 panel discussion focusing on some important questions</p> <p>20 as well as discussing next steps and a way forward.</p> <p>21 So there are a number of crosscutting</p> <p>22 regulatory considerations that I just wanted to</p>

<p style="text-align: right;">Page 6</p> <p>1 introduce early as we begin to think about the data. 2 I think it's important that we also keep those in 3 mind. So the first has to do with endpoints and 4 endpoints form the basis of labeling claims. And 5 there are clinical endpoints, endpoints that describe 6 or reflect how an individual feels, functions, or 7 survives, a concept developed early on by the 8 Institute of Medicine and ultimately formally codified 9 by the FDA and its accelerated approval regulations. 10 Clinical endpoints are not the same as 11 surrogate endpoints. Surrogate endpoints are used as 12 a substitute for a direct measure of how a patient 13 feels, functions, or survives and are thought to 14 predict such effects. Now in terms of approval 15 pathway, there is -- pathways, there is accelerated 16 approval which can be supported by trials establishing 17 an effect on a surrogate endpoint reasonably likely to 18 predict clinical benefit. 19 There's also traditional approval 20 usually supported by trials establishing an effect on 21 a clinical endpoint, but can also be supported by 22 trials establishing effect on a validated surrogate</p>	<p style="text-align: right;">Page 8</p> <p>1 continue that. Next slide, please. 2 So we're going to be talking a lot 3 about use of decolonization this morning and use of 4 decolonization as a surrogate endpoint in clinical 5 trials would have pros and cons. So in addition to 6 other endpoint regulatory requirements, sponsors would 7 need to discuss the data with the agency that supports 8 that the endpoint is reasonably likely to predict 9 clinical benefit for this particular pathogen and 10 clinical situation. 11 And if there's accelerated approval, 12 sponsors would need to discuss with the agency the 13 plan to verify the clinical benefit. So I just wanted 14 to highlight that this morning. Heidi Smith this 15 afternoon will be going into the regulatory 16 considerations in more detail. Next slide, please. 17 I also think it's important that we 18 consider bundles in this space or prevention 19 strategies that usually involve these bundles or 20 evidence-based practices that are implemented 21 collectively. So for a new product that's part of a 22 bundle, data will be needed to understand the</p>
<p style="text-align: right;">Page 7</p> <p>1 endpoint. Now a validated surrogate endpoint has very 2 persuasive data demonstrating its ability to predict 3 clinical benefit. That takes a fair amount of work 4 and data synthesis and a good example of that is HIV-1 5 plasma viral load which is a validated surrogate 6 endpoint. Next slide. 7 Now in terms of accelerated approval 8 which would be based on a surrogate endpoint, I just 9 wanted to highlight one part of the regulations for 10 you, that approval under this section will be subject 11 to the requirement that the applicant study the drug 12 further to verify and describe its clinical benefit 13 where there is uncertainty as to the relation of the 14 surrogate endpoint to clinical benefit or of the 15 observed clinical benefit to ultimate outcome. 16 So what this translates into is that 17 for Subpart H approval or approval based on a 18 surrogate endpoint, there is a requirement to continue 19 to study the drug further to demonstrate an effect on 20 a clinical endpoint. Usually sponsors do this by 21 simply continuing the clinical trial that initially 22 was evaluated based on the surrogate endpoint and they</p>	<p style="text-align: right;">Page 9</p> <p>1 contribution of the new product to the benefit 2 demonstrated in the trial. And as others will point 3 out today, a consideration in this scenario is that 4 standardization between study sites needs to be 5 addressed in terms of these other evidence based 6 practices. Next slide, please. 7 And then lastly, there are some other 8 design considerations. Ed Bein this afternoon is 9 going to talk us through some of the unique 10 statistical issues for cluster-randomized trials. And 11 it's important that these be discussed with the agency 12 as a trial is being designed because there's actually 13 quite a bit to wrap your head around and I think this 14 will be the beginning of a dialogue around some of 15 these issues. 16 For example, the cluster level risk 17 difference may not be equivalent to the individual 18 level risk difference and that individual patient 19 benefit is of course going to be a review 20 consideration. So lots to think about and we're 21 probably just going to start that process today. So I 22 want to thank everyone for joining us today and for</p>

<p style="text-align: right;">Page 10</p> <p>1 your commitment to prevention of healthcare-associated 2 infections.</p> <p>3 I think we'll now have some 4 introductory words from our colleagues at CDC.</p> <p>5 MICHAEL CRAIG: Thanks so much, John. 6 I'm Michael Craig. I'm director of Antimicrobial 7 Resistance at the Centers for Disease Control and 8 Prevention. We are very excited to be with you today 9 and really want to appreciate John and the rest of the 10 FDA team for co-sponsoring this meeting with us today.</p> <p>11 This is something that is very 12 important to us at CDC and something that we think 13 really holds a lot of potential in terms of saving 14 lives and importantly addressing the challenges of 15 antimicrobial resistance that we face, not only in the 16 United States but around the world.</p> <p>17 And so from our perspective, and I 18 think the bottom line for us, is that we -- this day 19 to us is focusing on drugs that could potentially 20 prevent transmission of deadly pathogens, especially 21 those that are antimicrobial resistance. These 22 pathogens are often found in healthcare settings like</p>	<p style="text-align: right;">Page 12</p> <p>1 crosscutting antibiotic resistance portfolio. He is 2 the CDC's representative on the President's Advisory 3 Committee for Combating Antibiotic Resistant Bacteria, 4 align public health activities and related antibiotic 5 resistance across multiple federal agencies. Michael, 6 look forward to your talk.</p> <p>7 MICHAEL CRAIG: Thanks so much, Heidi. 8 And as I noted at the outset, this is very important 9 for us today, and one theme that you're going to hear 10 throughout the day is really prevention and the 11 challenge of stopping or limiting, reducing the 12 transmission of some very deadly pathogens. So why 13 don't we get started. Next slide.</p> <p>14 I have nothing to disclose. And the 15 problem. So this is the big picture that, you know, 16 I'm not going to go into all the data on this. I 17 think a lot of you are familiar with it, but when we 18 talk about some of these deadly pathogens we're 19 talking about antimicrobial resistance pathogens which 20 have a high burden in the United States. When you 21 include the burden of C. diff, that's even higher. 22 We're talking about healthcare-</p>
<p style="text-align: right;">Page 11</p> <p>1 hospitals and nursing homes, and I think the challenge 2 that we see is that increasingly transmission is 3 driving the movement of infections and the movement of 4 these pathogens around the world.</p> <p>5 So that's -- wanted to give that sort 6 of big picture context and then I'll pause here for 7 our moderators to introduce ourselves and then I'll 8 dive into my talk.</p> <p>9 DR. HEIDI SMITH: Hi, good morning. 10 This is Heidi Smith from FDA. I'll be moderating 11 session one along with Timothy Benson from FDA. I'll 12 be introducing the speakers for the first half of the 13 session, while Tim will be handling the second half of 14 the session. He'll introduce himself at that time. 15 In the interest of time, we'll get going with our 16 first speaker who is Michael Craig who now is going to 17 be talking about Prioritizing Prevention and 18 Diversifying our Patient Safety Toolbox: 19 Decolonization is a Missing Tool We Need.</p> <p>20 Michael Craig is director of CDC's 21 Antibiotic Resistance Coordination and Strategy Unit 22 and leads coordination of CDC's \$180 million</p>	<p style="text-align: right;">Page 13</p> <p>1 associated infections. We're talking about sepsis. 2 And all of these things were problems even before the 3 pandemic, but the pandemic has increased and made all 4 of these issues worse. So we've seen an increase of 5 15 percent of the number of antimicrobial resistant 6 infections and deaths in hospitals because of the 7 pandemic. And so these are challenges where we feel 8 like we need new prevention tools to better address 9 them. Next slide.</p> <p>10 And the challenge that we face is 11 really only getting worse, and what this slide really 12 represents is the fact that antimicrobial resistance 13 is really accelerating and that we have more difficult 14 to treat pathogens every day and fewer effective 15 treatments. And we have some challenges with the drug 16 pipeline that we need to overcome, and I want to 17 highlight we're very supportive of new antibiotics to 18 treat some of these infections, but we also want the 19 conversation to be talking about what we can do to 20 prevent them as well. Next slide.</p> <p>21 And the thing that we want to underline 22 is that it's not about just preventing an infection,</p>

<p style="text-align: right;">Page 14</p> <p>1 but it's really that we've come to rely upon effective 2 antibiotic treatment for a variety of things. Modern 3 medicine and our healthcare system is really 4 predicated on it. And we've made incredible 5 advancements in all of the areas that you see on this 6 slide, including many others, but those advancements 7 and that longer lifespan that we have because of those 8 advancements is really predicated on the efficacy of 9 antibiotic therapy. 10 And as that declines and as we see more 11 prevention of very deadly pathogens, so too we're 12 going to lose the innovation and the and the extra 13 years saved by many of these innovations in our 14 country. Next slide. 15 And so where are we today? Next slide. 16 So, one thing I want to underline is 17 that we're, you know, still dealing with COVID and 18 there are some prevention lessons that I think that 19 are important to bear for this conversation. One is 20 that importantly, we cannot treat our way out of a 21 pandemic, an epidemic, or an outbreak. We need to 22 have treatment options, but we also need to have</p>	<p style="text-align: right;">Page 16</p> <p>1 challenge that we face. So Boxes 1 and 2 really 2 underline how we address these issues today, and Box 3 3 sort of underlines what's missing. So we have the 4 ability to detect when someone is colonized with one 5 of these deadly pathogens. So that means that the 6 pathogen is living in them, on them. It's not 7 necessarily causing infection but it increases their 8 risk of infection, and we have ways to reduce the 9 potential transmission and the potential risk to that 10 patient. 11 A lot of these are very familiar. They 12 are infection prevention and control, they are hand 13 washing. They're the bread and butter that you see 14 and that we stress so many times by the CDC in terms 15 of prevention of infections. They are good, but they 16 are not perfect and they cannot eliminate the risk to 17 the individual and they cannot eliminate the risk of 18 transmission. 19 And so what we would like is we would 20 like to add additional modalities, additional 21 potential drugs, or other things that could be brought 22 to bear so that we could further reduce and maybe even</p>
<p style="text-align: right;">Page 15</p> <p>1 prevention therapies or prevention modalities that can 2 really stop the spread of infectious diseases and 3 deadly pathogens. 4 The other thing that I want to 5 underline is that we get what we pay for. I think 6 this is very much evidence by the pandemic when there 7 was a lot of advancement and a lot of investment that 8 went into the development of the vaccines that we then 9 later accelerated for development for the pandemic. 10 And because of that previous 11 investment, we had those ready to go and I think 12 that's the thing that we want to underline here is 13 that, as John said, we want to start this conversation 14 and we want to bring attention and resources and time 15 to bear on these problems so that when we need these, 16 which I would say we arguably already need them, but 17 when these problems get even worse, we have some of 18 these potentially ready to go and that we can use and 19 deliver to fight these problems, especially if we're 20 in the situation where we're fighting those pathogens 21 again in the middle of another pandemic. Next slide. 22 This is to illustrate really the</p>	<p style="text-align: right;">Page 17</p> <p>1 eliminate the risk of that colonization becoming an 2 infection in an individual or that colonization 3 spreading to others and being transmitted in sites 4 like nursing homes or ICUs. Next slide. 5 And I think the thing that we want to 6 note is a prevention approach we know works. So this 7 slide already notes to you that when we've used some 8 of these steps before, even without drugs, we have 9 been able to show that a prevention approach can have 10 success against these bad bugs. The one thing that we 11 would also like to underline is that from the patient 12 perspective, the best infection is really the one that 13 never happens, and that's what we want to go for. 14 Prevention ultimately saves lives, 15 reduces -- and infections, and I think the thing to 16 also note that is very important for some of these 17 conversations especially when we're talking about 18 antimicrobial resistance, is that prevention reduces 19 our need for antibiotics and antifungals to treat 20 these. So if you prevent the infection, you don't 21 have to worry about whether the antibiotic or the 22 antifungal that you have is going to work or not. So</p>

<p style="text-align: right;">Page 18</p> <p>1 it reduces a lot of that pressure.</p> <p>2 The other thing to note that I think</p> <p>3 often goes overlooked is that even if someone survives</p> <p>4 an infection, they can sometimes have lasting and long</p> <p>5 term consequences and these could be related to the</p> <p>6 antibiotic use, the antifungal use, or they could</p> <p>7 potentially be related to sepsis or whatever happened</p> <p>8 during the course of that infection. Next slide.</p> <p>9 So from the CDC perspective, the thing</p> <p>10 that we want to really highlight is that we want to</p> <p>11 have a prevention mindset related to some of our drug</p> <p>12 development and what can happen. So we want to focus</p> <p>13 on treatment, but we also want to focus on prevention</p> <p>14 and how do we use potentially these drugs to reduce</p> <p>15 that pressure of transmission and to reduce some of</p> <p>16 what we're seeing in terms of antimicrobial resistance</p> <p>17 spreading in some of these settings.</p> <p>18 So we need evidence, as John noted, and</p> <p>19 I think he very articulately noted many of the</p> <p>20 challenges that you're going to hear more today in</p> <p>21 some of the discussions, and we need to figure out how</p> <p>22 we can do this also without accelerating antimicrobial</p>	<p style="text-align: right;">Page 20</p> <p>1 to ten times those that are affected. If you look at</p> <p>2 specific cohorts at risk, as you can see here, we have</p> <p>3 five million patients admitted to U.S. ICUs. We have</p> <p>4 1.3 million people in nursing homes. These are</p> <p>5 cohorts of people where we know they are potentially</p> <p>6 at risk because of colonization and transmission and</p> <p>7 where we have a lot of engagement.</p> <p>8 And lastly, I would just note, is that</p> <p>9 we know the resistance problem goes well beyond the</p> <p>10 United States and that the burden of this is</p> <p>11 increasing globally with an enormous burden around the</p> <p>12 world. Next slide.</p> <p>13 This is just a note to you that this is</p> <p>14 again not a flash in the pan consideration for us.</p> <p>15 This is something that is important for CDC and</p> <p>16 important for FDA and something that we want to make</p> <p>17 sure that is a part of our national action plan and</p> <p>18 would note that this is in fact something that we put</p> <p>19 in our national action plan in 2020, and as John said,</p> <p>20 this is really what we see as a kicking off a</p> <p>21 conversation with you all about how we can best do</p> <p>22 this to protect patients and individuals from</p>
<p style="text-align: right;">Page 19</p> <p>1 resistance. And I think that's an important point</p> <p>2 that we want to make is that we don't want to use any</p> <p>3 drug to treat transmission, but we don't want that</p> <p>4 drug to exacerbate the problem in another way.</p> <p>5 So these are going to potentially be</p> <p>6 unique products that have unique qualifications and</p> <p>7 you're going to hear some of those considerations</p> <p>8 later, but we think it is important to focus on</p> <p>9 whether we can bring these to market and whether we</p> <p>10 can use them in our patient populations.</p> <p>11 The other thing that I would note is</p> <p>12 that there's a lot of challenges that we see in the</p> <p>13 drug pipeline and some of the issues are whether</p> <p>14 there's a market for new antibiotics. The thing that</p> <p>15 I think we see as a potential positive benefit and a</p> <p>16 consideration is that if we talk -- start looking at</p> <p>17 the number of people who are colonized, it's</p> <p>18 potentially a much greater market and potentially a</p> <p>19 much greater engagement with the private sector to</p> <p>20 bring something to market.</p> <p>21 So the number of people who are</p> <p>22 colonized versus infected with some of these is five</p>	<p style="text-align: right;">Page 21</p> <p>1 transmission of these pathogens. Next slide.</p> <p>2 So I'm going to highlight briefly what</p> <p>3 we need, but you're going to hear from some fantastic</p> <p>4 CDC colleagues later about -- that go into more</p> <p>5 specific pathogen areas, but the things I want to note</p> <p>6 for you is that we really want to prevent recurrence</p> <p>7 and do more than decontaminate. So we want to protect</p> <p>8 and potentially restore the microbiome because we</p> <p>9 think that this will have long lasting positive</p> <p>10 benefits both to the individual as well as to cohorts</p> <p>11 in reduction of transmission.</p> <p>12 We want to reduce pathogen burden</p> <p>13 and/or eliminate pathogens completely. And it's even</p> <p>14 better if that has a targeted application body site.</p> <p>15 And you're going to hear later from some patient</p> <p>16 advocates, and there are communities out there,</p> <p>17 specifically the cystic fibrosis community where, you</p> <p>18 know, decontaminating the lungs and reducing the</p> <p>19 burden on that community from these resistant</p> <p>20 pathogens would be a major game changer and a major</p> <p>21 benefit in terms of giving them more quality of life</p> <p>22 and longer life. And those are some areas that we'd</p>

<p style="text-align: right;">Page 22</p> <p>1 like to see if they have potential for targeting.</p> <p>2 The other thing that we want to note is</p> <p>3 that sub-bullet there, is that we do not want these</p> <p>4 products to drive or increase antimicrobial resistance</p> <p>5 and we want to make sure that we're using them in a</p> <p>6 way that is effective at reducing transmission and</p> <p>7 reducing the problem and not adding to the problem.</p> <p>8 Finally, as John noted, we want to</p> <p>9 consider both benefit for the individuals as well as</p> <p>10 populations that they may be a part of. We</p> <p>11 appreciate, as you can see on the right side of this</p> <p>12 slide, that there are some challenges with this and</p> <p>13 that's why we want to enter this dialogue with you and</p> <p>14 see what we can do to overcome these challenges.</p> <p>15 These are things that, you know, we</p> <p>16 don't take for granted and we appreciate that this is</p> <p>17 some out-of-the box thinking, but we also think that</p> <p>18 it's critically important for the way we address</p> <p>19 antimicrobial resistance and healthcare-associated</p> <p>20 infections moving forward, and if we can come up with</p> <p>21 development pathways and prove this and overcome some</p> <p>22 of these challenges, we think that this could be a</p>	<p style="text-align: right;">Page 24</p> <p>1 So our next speaker will be John Jernigan who will be</p> <p>2 talking about Rationale for Decolonization as a</p> <p>3 Strategy for Preventing Antimicrobial-Resistant</p> <p>4 Infections. Dr. Jernigan serves as the chief of</p> <p>5 Epidemiologic Research and Innovation Branch in the</p> <p>6 Division of Healthcare Quality and Promotion at CDC.</p> <p>7 He has 30 years of experience in clinical infectious</p> <p>8 diseases and healthcare epidemiologic research. Thank</p> <p>9 you, John.</p> <p>10 DR. JOHN JERNIGAN: Thank you very</p> <p>11 much. Next slide.</p> <p>12 In this presentation, after reviewing</p> <p>13 some definitions, I'll cover some important</p> <p>14 observations about the epidemiology of healthcare-</p> <p>15 associated infections or HAIs. I'll discuss the role</p> <p>16 of colonization in the pathogenesis of HAIs, the role</p> <p>17 of transmission in driving antimicrobial resistance,</p> <p>18 and finally the potential role of decolonization as a</p> <p>19 prevention strategy. Next slide.</p> <p>20 First, a few definitions that will be</p> <p>21 helpful for our discussions today. Colonization</p> <p>22 simply refers to the presence of a microorganism</p>
<p style="text-align: right;">Page 23</p> <p>1 major game changer in our ability to address these</p> <p>2 threats in the United States and beyond. Next slide.</p> <p>3 And so we just want to note to you our</p> <p>4 objectives today and I think these are in some of the</p> <p>5 materials that you've seen and I think John gave a</p> <p>6 great overview of this to begin with, so I won't</p> <p>7 belabor it. It's really to talk about where we are</p> <p>8 and where we could go and again start that dialogue</p> <p>9 with you and start the conversation, talk about some</p> <p>10 of these challenges, and see what we could potentially</p> <p>11 do to address them.</p> <p>12 For discussion, these three questions</p> <p>13 are going to be part of a moderated panel with all of</p> <p>14 our speakers at the end of the day that myself and</p> <p>15 Peter Kim will be moderating and we really look</p> <p>16 forward to active engagement and dialogue with</p> <p>17 everybody. Next slide.</p> <p>18 And with that, I will close and turn</p> <p>19 over to the moderator for additional presentations for</p> <p>20 today. And I again want to thank you on behalf of the</p> <p>21 Centers for Disease Control and Prevention.</p> <p>22 DR. HEIDI SMITH: Thank you, Michael.</p>	<p style="text-align: right;">Page 25</p> <p>1 living on or in a host, but not causing disease or</p> <p>2 symptoms. But there are some nuances that are</p> <p>3 relevant for today's discussions. The duration of</p> <p>4 colonization is often prolonged and colonized body</p> <p>5 sites such as mucosal surfaces can serve as a source</p> <p>6 of transient contamination of another body site such</p> <p>7 as the skin.</p> <p>8 In addition, the burden or microbial</p> <p>9 load of colonization can be dynamic over time. For</p> <p>10 example, the microbial load of a resistant organism</p> <p>11 might increase with antibiotic exposure. Finally,</p> <p>12 colonization can and does transition to infection</p> <p>13 through various routes or mechanisms. Next slide.</p> <p>14 Decolonization, by its strict</p> <p>15 definition, refers to complete elimination of the</p> <p>16 colonizing microorganism, but for the purpose of our</p> <p>17 conversations today, I invite you to think about</p> <p>18 decolonization in a slightly broader context to</p> <p>19 include pathogen burden reduction or reduction in</p> <p>20 microbial load of the colonizing pathogen.</p> <p>21 And even further, I invite you to think</p> <p>22 about how even transient reduction in microbial load</p>

<p style="text-align: right;">Page 26</p> <p>1 might be beneficial, especially if it is strategically 2 designed to correspond to a relatively short period of 3 increased infection rates, such as during a period of 4 high risk healthcare. You will hear Dr. McDonald's 5 presentation, how this principle is already being used 6 to some extent in some antibiotic prophylaxis 7 applications. Next slide.</p> <p>8 Now to the epidemiologic principles 9 that underpin the rationale for decolonization.</p> <p>10 First, we know that colonization is important in the 11 pathogenesis of HAIs. Patients in healthcare are 12 often subjected to interventions that provide 13 opportunities for colonizing pathogens to invade 14 sterile body sites. Examples include surgical 15 incisions and use of various indwelling catheters. In 16 addition, a disrupted microbiota such as that of the 17 large intestine can create a niche where pathogens can 18 proliferate and find their way into sterile body sites 19 either through contamination of invasive devices and 20 incisions or through translocation directly from the 21 gut. Next slide.</p> <p>22 So let's review some evidence that</p>	<p style="text-align: right;">Page 28</p> <p>1 And on the right, in a study of 2 patients undergoing colorectal surgery, colonization 3 by ESBL-producing organisms was independently 4 associated with a twofold increased risk of surgical 5 site infections and infections caused by ESBL 6 producers was four times more likely in carriers than 7 in noncarriers. And although the references aren't 8 shown here, colonization with ESBL producers has also 9 been found to increase the risk of infection following 10 transrectal prostate biopsy and also liver 11 transplantation. Next slide.</p> <p>12 There's also clear risk with staph 13 aureus colonization where preoperative carriage risk 14 increases risk of postcardiac surgical wound infection 15 by a factor of ten. And importantly, there's also 16 evidence that the risk of infection varies with the 17 microbial load of colonization. In a prospective 18 study of residents of long-term acute care hospitals, 19 the relative abundance of carbapenemase-producing 20 <i>Klebsiella pneumoniae</i> colonization was predictive of 21 subsequent bacteremia caused by this organism.</p> <p>22 Similarly, in stem cell transplantation</p>
<p style="text-align: right;">Page 27</p> <p>1 colonization plays a role in pathogenesis. First, we 2 know that HAIs are usually caused by pathogens that 3 colonize the patient prior to the infection onset.</p> <p>4 This slide provides a sampling of evidence. For the 5 sake of time, I won't go through all of these but will 6 highlight that greater than 80 percent of staph aureus 7 bacteremia and surgical site infections are caused by 8 pre-infection colonizing strains and similar 9 observations are described for a wide variety of 10 pathogens in a variety of healthcare settings. Next 11 slide.</p> <p>12 Although studies -- these studies 13 demonstrate an association between colonizing and 14 infecting pathogens, does colonization by a pathogen 15 actually increase the risk of a subsequent infection? 16 There's growing evidence that it does. In the Swedish 17 cohort study results shown on the left, individuals 18 colonized with extended-spectrum beta-lactamase 19 producing Enterobacteriales had a 32-fold increased 20 risk compared to the general population of incident 21 bloodstream infections caused by the same organism 22 over the six-year observation period.</p>	<p style="text-align: right;">Page 29</p> <p>1 patients, intestinal domination by enterococcus 2 defined as greater than 30 percent of sequences in the 3 microbiota was associated with a ninefold increased 4 risk of VRE bloodstream infection. Next slide.</p> <p>5 Another epidemiologic underpinning for 6 decolonization as a resistance prevention strategy is 7 that transmission is an important driver of resistance 8 burden. In other words, transmission between 9 individuals either directly or indirectly increases 10 the number of people who become colonized and infected 11 with resistant organisms. To help make this point, 12 let's review how antibiotic resistance usually emerges 13 in bacteria. Next slide.</p> <p>14 Oftentimes when an individual is 15 exposed to an antibiotic, they're already carrying 16 bacterial strains having resistant strains, but those 17 strains may be present in small clinically or 18 epidemiologically insignificant numbers. How did 19 those strains get there in the first place? By one of 20 three mechanisms: one, random genetic mutation; two, 21 through acquisition of resistance genes from other 22 bacteria; or three, through transmission from other</p>

<p style="text-align: right;">Page 30</p> <p>1 people or the environment.</p> <p>2 The first mechanism, random genetic</p> <p>3 mutation, is often a very rare event for some of our</p> <p>4 most prevalent resistance problems and so transmission</p> <p>5 plays a critical role in determining the ultimate</p> <p>6 burden of resistance.</p> <p>7 Once a resistant strain is present in</p> <p>8 or on an individual, exposure to antibiotics confers a</p> <p>9 selective advantage, increasing the proportion and</p> <p>10 total burden of resistant organisms which increases</p> <p>11 risk of onward transmission of resistant strains to</p> <p>12 others and may also increase the risk of horizontal</p> <p>13 transmission of resistance genes to other bacteria,</p> <p>14 some of which may already possess characteristics</p> <p>15 making them quite adept at transmission and causing</p> <p>16 infection.</p> <p>17 An acquisition of resistance genes by</p> <p>18 such bacteria may result in creation of a new and more</p> <p>19 dangerous resistant pathogen, one that is highly fit</p> <p>20 for spread. Next slide.</p> <p>21 It is the case that some of our most</p> <p>22 serious resistance problems have been driven largely</p>	<p style="text-align: right;">Page 32</p> <p>1 colonized patients who can serve as a reservoir of</p> <p>2 transmission to the healthcare workers who care for</p> <p>3 them and who in turn can transmit to other patients in</p> <p>4 their care. The patient can also contaminate the</p> <p>5 environment, which can also serve as a reservoir of</p> <p>6 transmission. The thickness of the transmission lines</p> <p>7 in this graphic denotes the magnitude of transmission</p> <p>8 risk. Next slide.</p> <p>9 Under conditions where the patient's</p> <p>10 microbial load of colonization is high, there's more</p> <p>11 shedding and increased risk of downstream</p> <p>12 transmission. Next slide.</p> <p>13 Infection control practices such as</p> <p>14 hand hygiene, use of gowns and gloves, and</p> <p>15 environmental cleaning create barriers that reduce the</p> <p>16 risk of onward transmission, but their effectiveness</p> <p>17 is not 100 percent. Under conditions of high</p> <p>18 microbial load colonization and high shedding, there</p> <p>19 may be substantial residual transmission despite</p> <p>20 infection control barriers. Next slide.</p> <p>21 Under conditions where the microbial</p> <p>22 load of colonization is low, the same proportional</p>
<p style="text-align: right;">Page 31</p> <p>1 by transmission of highly fit clonal strains. Some</p> <p>2 examples of this include MRSA colonial groups USA100</p> <p>3 and 300, which account for the lion's share of</p> <p>4 healthcare- and community-associated MRSA</p> <p>5 respectively; group ST258 carbapenemase-producing</p> <p>6 <i>Klebsiella pneumoniae</i>, helping to drive international</p> <p>7 spread of carbapenem resistance; rapid growth of</p> <p>8 ESSBL-producing <i>E. coli</i> associated with clonal group</p> <p>9 ST131; and rapid emergence of ribotype 027 <i>C. difficile</i>.</p> <p>10 <i>difficile</i>. Next slide.</p> <p>11 Transmission of highly fit strains may</p> <p>12 have been a particularly important driver of</p> <p>13 antimicrobial resistance in healthcare settings, where</p> <p>14 there exists a confluence of factors that favor</p> <p>15 transmission of resistant organisms such as high risk</p> <p>16 patient populations, intense antibiotic use and dense</p> <p>17 contact networks involving close interaction among</p> <p>18 patients, healthcare workers, and the environment.</p> <p>19 Next slide.</p> <p>20 This graphic depicts a simple</p> <p>21 illustration of how burden of colonization in patients</p> <p>22 may drive transmission. In the pink box, you see a</p>	<p style="text-align: right;">Page 33</p> <p>1 decrease in risk attributable to infection control</p> <p>2 will likely translate into a substantially lower</p> <p>3 absolute residual risk in comparison to their use of</p> <p>4 conditions of high colonization burden.</p> <p>5 Theoretically, therefore, reducing microbial load of</p> <p>6 colonization may work synergistically with traditional</p> <p>7 infection control precautions to prevent transmission</p> <p>8 in healthcare. Now, is there any real world evidence</p> <p>9 that reducing colonization burden translates into less</p> <p>10 transmission? Next slide.</p> <p>11 In this study, Dr. Weinstein and</p> <p>12 colleagues examined the effect of daily chlorhexidine</p> <p>13 bathing of ICU patients on burden to VRE transmission</p> <p>14 and colonization. After implementing chlorhexidine</p> <p>15 bathing, they demonstrated reduction of VRE on</p> <p>16 patients' skin, decreased VRE contamination on</p> <p>17 environmental surfaces and on the hands of healthcare</p> <p>18 workers, and most importantly, decreased acquisition</p> <p>19 of VRE colonization by patients.</p> <p>20 You'll see similar data showing the</p> <p>21 relationship between colonization burden and</p> <p>22 transmission for other resistant pathogens in</p>

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<p>1 subsequent talks by Dr. Walters and Dr. Sexton. Next 2 slide.</p> <p>3 Prevention of colonization is important 4 intermediate outcome, but is there evidence that 5 decreasing colonization translates into decreased 6 infections? The answer is yes, and quite a bit of it. 7 Here, for example, are six randomized trials all 8 showing significant reductions in infection 9 attributable to decolonization strategies in various 10 patient populations. I'm not going to review these in 11 detail. You'll hear more about some of these in Dr. 12 Ham's talk a little later. Next slide.</p> <p>13 It's important to examine more closely 14 the mechanisms of action by which decolonizing agents 15 can provide benefit. First, they can reduce risk of 16 transitioning from colonization to infection in 17 colonized individuals who were treated. We refer to 18 this as direct benefit. Second, they can reduce risk 19 in uncolonized individuals and the surrounding 20 population, even if they are untreated, through 21 decreasing shedding and transmission from the treated 22 colonized individual. We refer to this as indirect</p>	<p>1 And each of these colonized patients 2 transmitted to two additional patients. Next slide.</p> <p>3 And these in turn also transmitted to 4 others. Next slide.</p> <p>5 And so on, so that the index patient 6 was the original source of transmission to 30 7 additional patients. Next slide.</p> <p>8 And let's assume that of these 30 9 additional colonized patients, nine of them progressed 10 to infection, resulting in a total of ten infections, 11 including the index patient. Next slide.</p> <p>12 Again, for the purposes of 13 illustration, let's assume the mortality of infection 14 given the decreased effectiveness of existing 15 infection treatment drugs due to resistance is high at 16 40 percent. Therefore, four of the ten infected 17 patients including our index patient die. How might 18 new treatments have impacted the outcomes here? If 19 the pharmaceutical industry were to produce a novel 20 treatment drug that reduces mortality of infection by 21 half in comparison to existing therapy this would, by 22 current standards, represent a significant advance in</p>
<p>1 benefit.</p> <p>2 A third mechanism occurs in settings 3 where decolonizing agents are used in all members of a 4 population, regardless of known colonization status, 5 for example, daily chlorhexidine bathing in ICU 6 patients. In this case, the intervention might 7 further reduce risk of acquiring colonization in 8 uncolonized individuals who are treated. Let me give 9 a simple illustration of the concept of indirect 10 benefit of decolonization. Next slide.</p> <p>11 Imagine a patient gets admitted to a 12 healthcare facility and is colonized with a resistant 13 pathogen, colonization depicted here by the yellow 14 color. Next slide.</p> <p>15 And let's assume colonization 16 progresses to infection in this patient, depicted by 17 the change to red. Next slide.</p> <p>18 And that the infection results in death 19 depicted by the X. Next slide.</p> <p>20 Let's also assume that before death, 21 the patient served as the reservoir of transmission to 22 two additional patients. Next slide.</p>	<p>1 therapeutic options. In our scenario, using the novel 2 treatment agent -- next slide -- would bring the 3 mortality down to 20 percent, meaning we would have 4 seen only two deaths rather than four.</p> <p>5 In other words, two lives were saved by 6 the novel treatment. Note that no infections were 7 prevented. Next slide.</p> <p>8 On the other hand -- next slide.</p> <p>9 On the other hand, what if the 10 pharmaceutical industry provided a novel and 11 effectively colonizing agent? If such an agent had 12 been used by the index patient at the time of 13 admission -- next slide -- it would have had the 14 direct effect of preventing the index patient from not 15 only becoming infected but also subsequently dying. 16 Next slide.</p> <p>17 But in addition, it would have also 18 prevented the index patient from becoming a source of 19 transmission, thereby preventing 30 colonizations, 20 nine infections, and the two deaths that occurred 21 despite use of the new and improved treatment agent. 22 This additional benefit resulting from prevention of</p>
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<p style="text-align: right;">Page 38</p> <p>1 transmission is again referred to as indirect benefit. 2 Next slide. 3 These simple graphs summarize and 4 compare the benefit of the two novel agents. Direct 5 benefit is depicted in blue and indirect benefit is 6 depicted in yellow. In the graph on the left, you can 7 see that the decolonizing agent prevented twice as 8 many deaths as the infection treatment agent, and most 9 of that benefit was indirect. From the right, you can 10 see that the novel infection treatment drug prevented 11 no infections while the decolonization agent prevented 12 10 infections, again mostly attributable to indirect 13 benefit. 14 Now obviously this is an oversimplified 15 demonstration designed to emphasize the theoretical 16 importance of indirect benefit. Well, what would such 17 benefit look like in real world use? To gain some 18 insight, let me present some evidence from 19 mathematical modeling. Next slide. 20 These are results from a mathematical 21 transmission model developed by Damon Toth and 22 colleagues at the University of Utah designed to</p>	<p style="text-align: right;">Page 40</p> <p>1 prevented increases by an order of magnitude when the 2 indirect effect is considered. Or another way to look 3 at it, studying the benefit of decolonizing agents are 4 likely to be dramatically underestimated if only 5 direct benefit is measured. Next slide. 6 This graph represents work by Dr. 7 Prabasaj Paul and Hannah Woolford at CDC who modified 8 and extended Dr. Toth's model to include not just 9 LTACHs, but U.S. acute care inpatient facilities and 10 skilled nursing facilities or SNFs. Their model also 11 accounted for interfacility CRE transmission by 12 patient transfer and examined three different 13 decolonization strategies. 14 Green portions of the bars represent 15 CRE BSIs in LTACHs and ventilator-capable SNFs, while 16 blue represents infections in acute care facilities 17 and non-ventilator capable SNFs. Each bar represents 18 annual national incidents under a specific 19 decolonization strategy. From left, the first bar 20 estimates annual incidents of CRE BSIs if no 21 decolonization therapy is used. The next bar 22 represents incidents of decolonization if it's used --</p>
<p style="text-align: right;">Page 39</p> <p>1 quantify the effect of a hypothetical decolonizing 2 agent targeting carriers of carbapenem-resistant 3 Enterobacteriales or CRE and long-term acute care 4 hospital in-patients or LTACHs. The model was 5 parameterized using a study of Chicago area 6 LTACHs which provided real-world observational data on 7 rates of CRE transmission prevalence, clinical 8 detection, and bloodstream infection rates. 9 Using this model, they estimated the 10 number of CRE bloodstream infections that would be 11 prevented if an effective decolonizing agent was used 12 for all known CRE carriers as detected through routine 13 clinical culturing. And then they extrapolated to 14 national estimates based on the number of LTACH beds 15 and annual discharges nationally. These findings were 16 based on it a presumed admission prevalence of 1 17 percent. 18 The green bar depicts the number of CRE 19 bloodstream infections prevented by direct effect, 20 while the blue bar depicts CRE bloodstream infections 21 prevented when considering both indirect and -- 22 indirect benefit. You can see that the number of BSIs</p>	<p style="text-align: right;">Page 41</p> <p>1 in all incidents of CRE BSIs if decolonization is used 2 for all CRE-colonized patients, again as detected 3 through routine clinical cultures in both LTACHs and 4 ventilator SNFs. 5 The third bar represents incidents when 6 decolonization is used for CRE-colonized patients in 7 all facility types. And the fourth bar represents a 8 strategy similar to the third bar, the exception being 9 that for LTACHs and ventilator SNFs, all residents 10 were screened for CRE colonization, rather than 11 relying on routine clinical cultures to detect 12 carriers, and therefore all CRE-colonized patients 13 were treated in these facilities. 14 According to the model, this approach 15 would result in prevention of greater than 9,000 CRE 16 bloodstream infections annually in the U.S. compared 17 to baseline, a 64 percent reduction. Note that the 18 model suggests that at steady state a reproductive 19 number or R0 would be reduced to less than one, 20 meaning that CRE transmission and the risk of CRE BSIs 21 would be essentially eliminated. Next slide. 22 Dr. Paul also calculated the number</p>

<p style="text-align: right;">Page 42</p> <p>1 needed to treat with decolonization therapy to prevent 2 a single CRE infection. You can see that the values 3 for the number needed to treat are around one 4 representing substantial public health benefit and 5 return on investment. Next slide.</p> <p>6 To summarize, I tried to demonstrate 7 that colonization by antibiotic resistant pathogens 8 increases risk of infection as -- and is an important 9 driver of antibiotic resistance, particularly in 10 healthcare. Therefore, reducing colonization may be a 11 potent antibiotic resistance prevention strategy. 12 Furthermore, because of their potential for indirect 13 benefit, efforts to produce and improve and approve 14 novel safe and effective decolonizing agents are 15 likely to prevent substantially more harm from 16 antibiotic resistance than can be prevented if we 17 focus drug development solely on drugs that treat 18 infections. Next slide.</p> <p>19 We're hoping that today's discussion 20 can encourage more research and development for agents 21 designed to reduce or eliminate colonization by 22 pathogens and also spark conversation about a roadmap</p>	<p style="text-align: right;">Page 44</p> <p>1 and do not necessarily represent the official position 2 of the CDC. Also I will be speaking today of some 3 non-FDA approved drugs that are currently under 4 development as well as off-label use of FDA approved 5 drugs. My take home messages are that decolonization 6 and pathogen reduction are already widely used for 7 prevention in some forms of antimicrobial prophylaxis.</p> <p>8 Second, we can learn from unfolding 9 failings of antimicrobial prophylaxis. From what we 10 learn, we can propose certain attributes that future 11 decolonization strategies should ideally possess. 12 Current and future products span various compositions 13 and modes of action and there is a central role for 14 the human microbiome in colonization resistance that 15 should be considered in all decolonization and 16 pathogen reduction strategies.</p> <p>17 A tolerable safety margin is impacted 18 by local versus systemic body site distribution and -- 19 of a drug and target versus risk-based implementation 20 strategies. Finally, to achieve effectiveness, it is 21 important to tailor the intervention and its timing to 22 the duration and timing of maximum risk of infection.</p>
<p style="text-align: right;">Page 43</p> <p>1 for regulatory approval for such agents. We think 2 there's still a lot of wisdom in the old adage, an 3 ounce of prevention is worth a pound of cure. Thank 4 you for your attention.</p> <p>5 DR. HEIDI SMITH: Thank you very much, 6 John. We're going to move on to our next speaker who 7 is Clifford McDonald who's going to be speaking about 8 Decolonizing Approaches: Current State and Future 9 Needs. Dr. McDonald is currently associate director 10 for science in the Division Healthcare Quality 11 Promotion at CDC. He's published extensively in 12 healthcare-associated infections, especially C. 13 difficile infections and antibiotic resistance and has 14 led efforts of his division to explore application of 15 microbiome science to public health. Thank you. Dr. 16 McDonald.</p> <p>17 DR. CLIFFORD MCDONALD: Good morning. 18 I will be speaking to you today about decolonizing 19 approaches, including current state and future needs. 20 Next slide, please.</p> <p>21 I have no financial disclosures and the 22 findings and conclusions of this presentation are mine</p>	<p style="text-align: right;">Page 45</p> <p>1 Next slide, please.</p> <p>2 First, decolonization and pathogen 3 reduction is already widespread in some forms of 4 antimicrobial prophylaxis. When we think of 5 antimicrobial prophylaxis, we often think of surgical 6 antibiotic prophylaxis but in practice it involves any 7 localized or systemic administration of an 8 antimicrobial to prevent infection through a range of 9 mechanisms.</p> <p>10 These include decolonization and 11 pathogen reduction but also various combinations of 12 prevention of invasion or translocation and prevention 13 of attachment involved in establishing infection.</p> <p>14 Next slide, please.</p> <p>15 I begin with examples where 16 decolonization and pathogen reduction or pilot 17 pathogen reduction are most clearly their mode of 18 action, as these are also examples of the 19 effectiveness of approach to the point that some are 20 incorporated into evidence-based practice 21 recommendations.</p> <p>22 Chief among these is the preoperative</p>

<p style="text-align: right;">Page 46</p> <p>1 application of nasal mupirocin to prevent staph aureus 2 infections following cardiac and orthopedic surgery. 3 This appears in WHO guidelines as well as relevant 4 U.S. professional society guidelines. Another is 5 preoperative administration of non-absorbed 6 antimicrobials along with mechanical bowel preparation 7 to prevent surgical infection and anastomotic leaks 8 following bowel surgery. Again, this is recommended 9 in WHO and relevant professional society guidelines. 10 There are also recommendations to 11 prevent secondary cases of meningococcal disease using 12 oral antibiotics. Finally, another other form of 13 antimicrobial decolonization or pathogen reduction is 14 the use of selective digestive decontamination and 15 oral decontamination to prevent infections and reduce 16 mortality in intensive care unit or ICU patients. 17 This is currently a nationally recommended practice in 18 the Netherlands. Next slide, please. 19 Here's a diagram that outlines the use 20 of selective digestive decontamination and the types 21 of agents used. These are administered from the first 22 day of admission to an intensive care unit in any</p>	<p style="text-align: right;">Page 48</p> <p>1 such as the Netherlands. However, in settings with 2 moderate to high resistance such as other parts of 3 Europe, the benefits are less clear. 4 I would note that the main negative 5 study that led to the second sentence was a multisite 6 European study in which the systemic cephalosporin was 7 not administered over fear that it might drive 8 infections with gram-negative bacteria possessing 9 extended spectrum beta-lactamases which were prevalent 10 in many of the study locations. Again, I refer the 11 audience to my supplementary slides about the measured 12 impacts of this practice on resistance. 13 There has also been one in vitro study 14 demonstrating the colistin use as part of the 15 decontamination regimen can drive microevolution of 16 resistance. There has only been one study to date of 17 the microbiome of patients receiving these regimens 18 which did, not unexpectedly, demonstrate a degree of 19 microbiome disruption relative to healthy controls. 20 However, the status of microbiome disruption relative 21 to usual ICU care has not been studied. 22 Before moving to my next slide, I will</p>
<p style="text-align: right;">Page 47</p> <p>1 patient expected to stay longer than two to three days 2 during which they are expected to receive ventilator 3 care. Systemic antibiotics included in the regimen 4 consists most commonly of a third generation 5 cephalosporin continued for four days. The idea 6 behind both the topical and systemic antibiotics is 7 that these regimens have relatively little impact on 8 the largely anaerobic microbiota of the large 9 intestine and oropharynx. 10 I would refer the audience to the 11 narrative review referenced here to read more about 12 the evolution of this practice. Based upon this 13 review, I have prepared my first two supplementary 14 slides to assist the audience in understanding some of 15 the issues encountered in studying this practice, as 16 well as evidence for the practice from cluster 17 randomized trials. Next slide, please. 18 The conclusions of the authors of this 19 narrative review is that the practice of selective 20 digestive decontamination is consistently associated 21 with less resistance and improved patient outcomes in 22 settings with low prevalence of antibiotic resistance</p>	<p style="text-align: right;">Page 49</p> <p>1 note that my third supplementary slide highlights 2 examples of antimicrobial prophylaxis with currently 3 little role for decolonization and pathogen reduction 4 and ask the question whether these may be missed 5 opportunities for future advanced methods of 6 decolonization and pathogen reduction. Next slide, 7 please. 8 Let's now turn our attention to two 9 areas where there are unfolding failings of 10 antimicrobial prophylaxis and in which decolonization 11 and pathogen reduction plays a variable role. Both 12 involve the use of fluoroquinolones and are shown on 13 this slide. The first is use of oral systemic 14 fluoroquinolones to prevent infections following 15 transrectal biopsies. The fact that some studies 16 indicate improved prevention with administration 17 beginning one day before the procedure provides some 18 evidence the fluoroquinolone alone acts in part 19 through decolonization and pathogen reduction. 20 Regardless, there are now recent 21 worldwide increases in breakthrough post-biopsy 22 infections with intestinal colonization by</p>

<p style="text-align: right;">Page 50</p> <p>1 fluoroquinolone-resistant gram-negative pathogens 2 increasing the risk of these breakthrough infections. 3 The other unfolding failing after a long period of 4 successful use is the systemic use of fluoroquinolones 5 to prevent bloodstream infections in neutropenic 6 patients. 7 There are now increasing reports of 8 clusters of breakthrough infections and in subsequent 9 slides I will provide evidence how these reflect the 10 role of decolonization and pathogen reduction as well 11 as how fluoroquinolone were poorly designed for this 12 purpose. Next slide, please. 13 First, we have heard previously of the 14 phenomenon of intestinal domination when a single 15 species or group of species over grows the microbiome, 16 most commonly that of the lower intestine or gut. 17 Here we see results of a study in which 113 18 hematopoietic stem cell transplant recipients 19 underwent serial stool sampling and microbiome 20 analysis, associating results of these analyses with 21 various exposures and subsequent bacteremias. 22 In this study domination was defined by</p>	<p style="text-align: right;">Page 52</p> <p>1 So in summary, intestinal domination by 2 gram-negative pathogens is associated with subsequent 3 bloodstream infection and fluoroquinolone prophylaxis 4 normally reduces the risk of intestinal domination by 5 gram-negative pathogens and colonization with 6 fluoroquinolone-resistant gram-negative pathogens 7 increases risk for breakthrough infection. Therefore, 8 the protection from fluoroquinolone prophylaxis is 9 mediated at least in part through pathogen reduction 10 and fluoroquinolone resistance leads to breakthrough 11 infections through breakthrough intestinal dominance. 12 Next slide, please. 13 So what can we learn in here about 14 possibly improved approaches? Fluoroquinolones were 15 developed for short-term treatment of local infection 16 through systemic administration and not specifically 17 for decolonization or pathogen reduction. Some key 18 characteristics make them well suited for the former 19 use and not so well suited for the latter. First, 20 fluoroquinolones are highly absorbed following oral 21 administration and have excellent body site 22 distribution and tissue penetration. Reflecting this</p>
<p style="text-align: right;">Page 51</p> <p>1 greater than 30 percent of the composition of gut 2 microbiota and as highlighted by the red box on the 3 slide, domination by gram-negative pathogens of 4 proteobacteria, but bacteria was a predictor of 5 subsequent gram-negative bacteremia. Although not 6 highlighted, you can also see that enterococcus 7 domination was a predictor for vancomycin-resistant 8 enterococcus or VRE bacteremia. Next slide, please. 9 Also from the same study, we can see 10 how receipt of fluoroquinolones was normally 11 protective against intestinal domination caused by 12 gram-negative bacteria or proteobacteria with a hazard 13 ratio of 0.09 shown in the right columns. Next slide, 14 please. 15 Finally, from another study of 234 16 hematopoietic stem cell transplant recipients, 17 or 17 31 percent of the 54 who were colonized with 18 fluoroquinolone-resistant Enterobacterales developed 19 gram-negative bloodstream infection despite 20 fluoroquinolone prophylaxis, compared to only two or 1 21 percent of the 180 who were not so colonized. Next 22 slide, please.</p>	<p style="text-align: right;">Page 53</p> <p>1 tissue penetration, fluoroquinolones have increasingly 2 recognized toxicity. Despite their high absorption, 3 they do achieve high fecal levels. However, 4 resistance when it develops commonly leads to 5 relatively high minimum inhibitory concentrations or 6 MICs that likely exceed fecal levels. 7 Finally, although initially thought to 8 have little impact on anaerobic microbiota and the gut 9 microbiome, the selection of resistance in key 10 anaerobes and microbiome disruption are both now 11 increasingly recognized. Next slide, please. 12 This brings us to what may be specific 13 attributes that future decolonization should possess. 14 First, direct acting agents such as small molecules 15 should have a narrow microbiological spectrum targeted 16 to specific pathogens or groups of pathogens and 17 limited body site distribution. Together these 18 attributes may improve drug safety and reduce 19 collateral damage to the human microbiome. Examples 20 include non-absorbable narrow-spectrum agents for 21 enteral, topical, or other local applications. 22 Second, agents and strategies should</p>

<p style="text-align: right;">Page 54</p> <p>1 have favorable pharmacokinetics to reduce emergence of 2 resistance through local evolution. For example, 3 applications should achieve high drug levels relative 4 to the minimum inhibitory concentration or even the 5 bactericidal concentration. 6 Ideally, agents should be unlikely to 7 evoke cross resistance to clinically important 8 antibiotics used for treatment of infection usually 9 through markedly different mechanisms of action. For 10 example, antiseptics are generally less likely to 11 evoke cross resistance to therapeutic antimicrobials, 12 although co-selection may still occur. 13 We will want to say more about 14 leveraging colonization resistance afforded by the 15 human microbiome, and finally we need to think about 16 the durability of effect beyond duration of 17 application. For example, phage or live 18 biotherapeutics may expend -- extend duration of 19 decolonization or colonization resistance through 20 their replication. Next slide, please. 21 Current and future product categories 22 are listed here along with some examples. These span</p>	<p style="text-align: right;">Page 56</p> <p>1 recurrent <i>C. difficile</i> infection under FDA enforcement 2 discretion. However, this enforcement discretion does 3 not extend to FMT use specifically for decolonization 4 or pathogen reduction. Under development are drugs 5 such as pathogen reduced or otherwise processed FMT or 6 derivatives, also more defined microbiota consortia. 7 Finally, phage is a promising avenue 8 for decolonization given its potential to be 9 relatively narrow spectrum and propagate, possibly 10 extending its duration of action. Next slide, please. 11 There is a central role for the human 12 microbiome and colonization resistance that should be 13 considered in all decolonization strategies. The 14 microbiome resist colonization by pathogens via 15 several mechanisms shown here, including the direct 16 inhibition via naturally produced molecules such as 17 bacteriocins and metabolites. 18 Metabolites and protein messaging from 19 the microbiome assist the host by maintaining the 20 mucosal barrier that prevents invasion and participate 21 in cross talk with the host to favorably modulate the 22 host immune system. Finally, the normal microbiome</p>
<p style="text-align: right;">Page 55</p> <p>1 various compositions and modes of action. Mupirocin 2 is an example of a small molecule agent, as are the 3 agents used for gut decontamination. Bacteriocins are 4 proteins produced by bacteria that inhibit or kill 5 pathogens and along with local application of 6 monoclonal antibodies can be quite narrow in spectrum. 7 Lysostaphin is an example of a 8 bacteriocin that has been studied over the past 20 9 years with several notable development advancements, 10 but yet to be made clinically available. Topical 11 antiseptics or decontaminating agents such as alcohol 12 or chlorhexidine are used in combination with other 13 agents to decolonize. There are various drugs under 14 development that act indirectly to decolonize or 15 prevent colonization by protecting the microbiome from 16 antibiotics, for example, an activated charcoal 17 product to absorb antibiotics or beta-lactamase enzyme 18 to destroy antibiotics that may make their way into 19 the GI tract. 20 In addition, there are microbiome 21 restoratives such as fecal microbiota transplantation 22 or FMT which is currently in clinical use for</p>	<p style="text-align: right;">Page 57</p> <p>1 utilizes nutrients in the microenvironment, denying 2 the pathogen's use of those same nutrients. Next 3 slide, please. 4 The powerful effect of the human 5 microbiome in providing colonization resistance may be 6 grasped from early data such as this, comparing 7 patients who had their recurrent <i>Clostridioides</i> 8 <i>difficile</i> infections managed via fecal microbiota 9 transplantation versus usual antibiotics. Though this 10 was a prospective observational study, it was not 11 randomized. However, propensity matching was used to 12 make the cohort more comparable. 13 As highlighted in the red boxes on this 14 slide, in the 90 days following FMT or antibiotics for 15 management of recurrent <i>C. difficile</i> infections, 16 patients treated with FMT were much less likely to 17 develop bloodstream infections, had shorter 18 hospitalizations, and overall improved survival. Next 19 slide, please. 20 This suggests that whatever methods are 21 used to decolonize or pathogen reduce, they should 22 either replicate essential components of the natural</p>

<p style="text-align: right;">Page 58</p> <p>1 functions of the microbiome or spare, protect, or 2 restore the microbiome. I will further point out that 3 the human microbiome is part of a larger microbial 4 ecology and we at CDC are very aware of this. I 5 encourage the audience to read about this at the link 6 shown to the bottom of this slide and listen for Dr. 7 Cal Ham's comments later this morning about how we 8 have considered this in regard to increasing 9 chlorhexidine use. Next slide, please.</p> <p>10 Finally, just a few notes on how a 11 tolerable safety margin may be impacted by local 12 versus systemic body site distribution of a drug and 13 targeted versus risk based implementation strategies. 14 Obviously, local versus systemic body site 15 distribution limits and end-organ exposure to 16 potential toxicities. However, the tradeoff is that 17 the locally acting agent may have a slower onset of 18 action, for example, waiting for GI motility to bring 19 a non-absorbed antibiotic to the active site in the 20 large bowel.</p> <p>21 Meanwhile there are targeted versus 22 risk-based strategies to apply decolonization and</p>	<p style="text-align: right;">Page 60</p> <p>1 Still, some decolonization strategies 2 may have inherently slower onset. For example, when 3 selective digestive decontamination was extended to a 4 multi-country study across Europe, its effectiveness 5 may have been compromised by the removal of the third 6 generation cephalosporin from the regimen that 7 normally protected patients while the oral agents 8 transferred to the gut and began to protect through 9 direct decolonization and pathogen reduction.</p> <p>10 Finally, one needs an intervention that 11 is durable for the duration of increased risk and 12 overall we need more durable decolonization 13 strategies. Although not an example of HAI 14 prevention, the main reason that prepartum 15 decolonization versus intrapartum antibiotics was 16 historically not pursued as a means of Group B strep 17 prophylaxis of early onset neonatal bacteremia is 18 because durable decolonization strategies were not 19 available. Next slide, please.</p> <p>20 So this concludes my comments to you 21 today. Although many of these take home points can be 22 made into standalone presentations, I've tried to span</p>
<p style="text-align: right;">Page 59</p> <p>1 pathogen reduction. Targeted application involves 2 rapid screening for colonization and directing 3 decolonizing and pathogen reduction therapy based on 4 that. The results in -- this results in a generally 5 smaller population being exposed to the decolonizing 6 therapy.</p> <p>7 In contrast, risk-based strategies 8 focus on specific patient risk factors to minimize the 9 population being decolonized. While targeted 10 application would appear to be favorable from a risk- 11 benefit standpoint, there can be serious 12 implementation challenges to screening for 13 colonization. Next slide, please.</p> <p>14 In addition to tailoring interventions 15 to safety considerations, one needs to tailor to 16 achieve effectiveness. Here, one needs to think about 17 the onset of action in the intervention and will it be 18 fast enough to protect the patient as they experience 19 increased risk. If it is to be a targeted application 20 and the patient has increased risk during the 21 screening process, the turnaround on that screening 22 needs to be also considered.</p>	<p style="text-align: right;">Page 61</p> <p>1 a broad horizon of our current state and future needs 2 in decolonization strategies. Thank you.</p> <p>3 DR. HEIDI SMITH: Thank you for that 4 presentation. Our next speaker will be Maroya Walters 5 who is going to be talking about Multidrug-resistant 6 Gram-negative Bacilli, Epidemiology and Decolonization 7 Considerations. Dr. Walters is an epidemiologist and 8 leads the antimicrobial resistance team in the 9 Prevention and Response Branch in the CDC Division of 10 Healthcare Quality Promotion. Her interests include 11 strategies to prevent the spread of multidrug- 12 resistant bacteria, especially carbapenem-resistant 13 gram-negative bacilli, and outbreak response. Dr. 14 Walters, thanks for your presentation.</p> <p>15 DR. MAROYA WALTERS: Good morning. 16 Next slide, please.</p> <p>17 I am leading off four pathogen focused 18 presentations that will each cover epidemiology, 19 asymptomatic colonization, and decolonization and 20 pathogen reduction approaches for an organism or group 21 of organisms. Before delving into the details of 22 multidrug-resistant gram-negative bacilli, I want to</p>

<p style="text-align: right;">Page 62</p> <p>1 emphasize key areas of need for prevention. These 2 include developing novel approaches for decolonization 3 and pathogen reduction, primarily focusing on the 4 gastrointestinal tract but potentially including other 5 sites and high risk population, and symptomatic 6 evaluation of these approaches to understand their 7 impact on colonization, infection, and transmission. 8 Among decolonization and source control 9 measures currently under investigation, the 10 heterogeneity and how decolonization approaches are 11 assessed and in what populations, the use of different 12 endpoints to establish decolonization, and the lack of 13 control groups in some studies compromises our ability 14 to evaluate these approaches and move forward. Next 15 slide. Next slide. 16 Gram-negative bacilli encompass a large 17 number of organisms that cause a diverse array of 18 infection. They are responsible for approximately 19 one-third of all healthcare-associated infections 20 reported to the national Healthcare Safety Network. 21 Among these, most infections are associated with 22 Enterobacterales species and the lactose non-</p>	<p style="text-align: right;">Page 64</p> <p>1 healthcare settings, these are transmitted by a direct 2 and indirect contact with infected or colonized 3 individuals or the contaminated healthcare 4 environment. And finally, horizontal transfer of 5 resistance elements plays an important role in 6 facilitating spread of these organisms. Next slide. 7 There are also important 8 epidemiological differences among these organisms, 9 including between ESBL producing and carbapenem 10 resistant Enterobacterales. ESBLs are endemic in the 11 United States and approximately half of cases occur in 12 community dwellers who have not had recent 13 hospitalization, long-term care stays, or invasive 14 procedures. Risk factors in the community include 15 recent antibiotic therapy and international travel, 16 and food and water are increasingly recognized 17 reservoirs. 18 In contrast CRE are still emerging in 19 the United States. CRE primarily occur in patients 20 who have extensive healthcare exposures. Indwelling 21 devices, severe underlying illness, long-term care 22 facility admission, and antibiotic exposure are all</p>
<p style="text-align: right;">Page 63</p> <p>1 fermenters, pseudomonas and acinetobacter. Next 2 slide. 3 Today, I will focus on the four 4 healthcare-associated multidrug-resistant gram- 5 negative bacilli listed by CDC as urgent or serious 6 threats. These are carbapenem-resistant and extended- 7 spectrum beta-lactamase producing Enterobacterales 8 which are enteric organisms and multidrug-resistant 9 Pseudomonas aeruginosa and carbapenem-resistant 10 Acinetobacter, which are non-enteric organisms. 11 I want to note that Enterobacterales is 12 a taxonomic order that represents over 70 different 13 genera. Some of the genera most often identified in 14 clinical microbiology laboratories are listed on this 15 slide. Next slide. 16 And although they represent a diversity 17 of organisms, these MDR gram-negative bacilli have 18 several common characteristics. They are 19 opportunistic pathogens that can colonize multiple 20 mucosal surfaces such as the gastrointestinal tract, 21 lung, and wound, contributing to the variety of 22 infections with which they are associated. In</p>	<p style="text-align: right;">Page 65</p> <p>1 associated with CRE acquisition. Patient to patient 2 transmission accounts for the majority of CRE 3 acquisitions, although environmental reservoirs such 4 as healthcare facility wastewater plumbing also 5 contribute. Next slide. 6 A distinguishing feature of MDR-P. 7 aeruginosa and carbapenem-resistant acinetobacter is 8 the ability to form biofilm, which contributes to 9 colonization of indwelling medical devices, persistent 10 wound and respiratory tract colonization, and the 11 contamination of shared medical equipment. Risk 12 factors are similar to those for CRE. 13 Infections occur almost exclusively in 14 patients with substantial healthcare exposure, 15 including in patients with chronic underlying 16 conditions resulting in dysbiosis, such as cystic 17 fibrosis. And although I won't address cystic 18 fibrosis patients specifically, I want to note that 19 they are an important group to include when discussing 20 P. aeruginosa colonization and infection, as shown on 21 my supplementary slide, and we will hear from Dr. 22 Whitney Brown of the CF Foundation later this morning.</p>

<p style="text-align: right;">Page 66</p> <p>1 Intrinsic resistance of these non-</p> <p>2 enteric gram-negatives combined with the remarkable</p> <p>3 ability to acquire new resistance mechanisms means</p> <p>4 that there are limited treatment options despite the</p> <p>5 many new antibiotics for gram-negatives that have</p> <p>6 recently come to market. Next slide.</p> <p>7 Overall, how common are MDR gram-</p> <p>8 negative bacilli? This graph shows the number of</p> <p>9 clinical cultures with MDR gram-negative identified in</p> <p>10 hospitalized patients in 2019 and the 90-day</p> <p>11 attributable mortality. Case numbers vary</p> <p>12 substantially from 6,000 cases of carbapenem-resistant</p> <p>13 acinetobacter to over 194,000 cases of ESBL producing</p> <p>14 Enterobacterales.</p> <p>15 The number of cases should not be</p> <p>16 confused with relative importance as these organisms</p> <p>17 are in different stages of emergence and the</p> <p>18 carbapenem-resistant gram-negatives are associated</p> <p>19 with limited treatment options and higher mortality</p> <p>20 relative to the total number of cases than ESBLs.</p> <p>21 Also, these cases are just the tip of the iceberg</p> <p>22 because most individuals with gram-negative bacilli</p>	<p style="text-align: right;">Page 68</p> <p>1 slide.</p> <p>2 Now let's look more closely at the</p> <p>3 characteristics of colonization. The gastrointestinal</p> <p>4 tract is the primary and Enterobacterales colonization</p> <p>5 site, although MDR Enterobacterales can also be found</p> <p>6 elsewhere on the body of colonized patients including</p> <p>7 on the skin. Estimates for the duration of</p> <p>8 colonization vary. Factors that contribute to this</p> <p>9 variability include differences in patient</p> <p>10 populations, decolonization criteria, and laboratory</p> <p>11 testing approaches.</p> <p>12 Despite the heterogeneity in the exact</p> <p>13 estimate, colonization is generally prolonged, with</p> <p>14 one meta analysis estimating that 35 percent of</p> <p>15 colonized individuals remained colonized with ESBL</p> <p>16 Enterobacterales or CRE one year after initial</p> <p>17 detection. Median time to decolonization or negative</p> <p>18 culture in three exemplar studies ranged from 144 to</p> <p>19 295 days. In general, community dwellers are found to</p> <p>20 be colonized at higher rates and more rapidly than</p> <p>21 those admitted to healthcare setting, possibly owing</p> <p>22 to more rapid restoration of a healthy microbiome or</p>
<p style="text-align: right;">Page 67</p> <p>1 are colonized, not infected. Next slide.</p> <p>2 Carbapenem-resistant gram-negatives</p> <p>3 have been the focus of targeted public health</p> <p>4 detection, response, and prevention efforts in</p> <p>5 healthcare settings. Perhaps in part due to these</p> <p>6 efforts, during 2017 to 2019, cases of carbapenem-</p> <p>7 resistant acinetobacter among hospitalized patients</p> <p>8 remained steady while cases of CRE and MGR-P.</p> <p>9 aeruginosa declined.</p> <p>10 In contrast, ESBL-producing</p> <p>11 Enterobacterales increased, illustrating challenges in</p> <p>12 controlling spread once these pathogens move into</p> <p>13 community settings. Since ESBLs and CRE encompass the</p> <p>14 same organisms with spread driven by mobile resistance</p> <p>15 elements, the trajectory of ESBL Enterobacterales</p> <p>16 could presage the future for CRE in the absence of new</p> <p>17 approaches to prevent transmission. Next slide.</p> <p>18 And this is especially important in</p> <p>19 light of case trajectories during the COVID-19</p> <p>20 pandemic during which we observed increases in</p> <p>21 carbapenem-resistant acinetobacter cases and halting</p> <p>22 of prior declines for CRE and MDR-P. aeruginosa. Next</p>	<p style="text-align: right;">Page 69</p> <p>1 reduced risk of becoming recolonized.</p> <p>2 And some strains and organisms are</p> <p>3 associated with increased duration of colonization,</p> <p>4 including certain strains associated with epidemic</p> <p>5 spread such as ESBL producing ST131 E. coli. Next</p> <p>6 slide.</p> <p>7 Colonization with MDR Enterobacterales</p> <p>8 is strongly associated with increased risk of</p> <p>9 infection with the highest risk among intensive care</p> <p>10 unit patients. In studies of ICU patients, those who</p> <p>11 were CRE colonized at admission had two- to tenfold</p> <p>12 higher risk of infection than those who were not</p> <p>13 colonized.</p> <p>14 In another study, 95 percent of ESBL</p> <p>15 Enterobacterales infections in ICU patients occurred</p> <p>16 in those with a history of colonization. The risk of</p> <p>17 CRE infection among colonized hospitalized patients is</p> <p>18 substantial. In a meta analysis, 16.5 percent of CRE</p> <p>19 colonized patients were estimated to develop</p> <p>20 subsequent CRE infection. The mortality in patients</p> <p>21 who develop infection is over 30 percent. As Dr.</p> <p>22 Jernigan described earlier, not just the presence of</p>

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<p>1 the organism, but the abundance plays a role in 2 pathogenesis.</p> <p>3 Among long-term acute care hospital 4 patients colonized with KPP producing Klebsiella 5 pneumoniae, a type of CRE, higher abundance in the 6 gastrointestinal tract was independently associated 7 with increased risk of bacteremia with this organism, 8 reinforcing the concept that reducing organism burden 9 even without complete eradication has potential 10 benefit. Next slide.</p> <p>11 In contrast to MDR Enterobacterales, 12 there is no gold standard screening site for MDR-P. 13 aeruginosa or carbapenem-resistant acinetobacter. 14 These bacteria can colonize the skin, upper and lower 15 respiratory tract, wounds, and digestive tract. The 16 figure illustrates the wide range of reported 17 sensitivities for detection of carbapenem-resistant A. 18 baumannii at different body sites.</p> <p>19 Similar to MDR Enterobacterales, 20 colonization can be prolonged. One study found that 21 17 percent of patients with a prior carbapenem- 22 resistant A. baumannii clinical culture remained</p>	<p>1 transmission to other patients, as Dr. Jernigan so 2 nicely illustrated. In a study of long-term acute 3 care hospitals in Chicago, which had achieved a 4 greater than 30 percent reduction in KPC-producing 5 Klebsiella pneumoniae prevalence and infections after 6 implementing a bundle of prevention intervention that 7 included active surveillance, daily chlorhexidine 8 bathing, contact isolation, and healthcare personnel 9 education, a 1 percent increase in colonization 10 pressure was associated with a 2 percent increase in 11 acquisition risk.</p> <p>12 The figure shows that if colonization 13 pressure increases, so do the odds of KPC acquisition, 14 even in settings where intensive infection control 15 measures have been implemented. Next slide.</p> <p>16 These characteristics can lead to very 17 high prevalence of patients colonized with multidrug- 18 resistant organisms, especially in high acuity, long- 19 term care settings. This is a schematic of the 20 ventilator unit of a skilled nursing facility in which 21 each circle is a resident. The purple circles 22 represent patients colonized only with the yeast</p>
<p>1 colonized after six months, although as the author 2 stated, this is likely an underestimate due to the low 3 sensitivity of screening methods used.</p> <p>4 Among hospitalized kidney transplant 5 patients, carbapenem-resistant P. aeruginosa 6 colonization persisted for a median 42 days. Next 7 slide.</p> <p>8 Like for MDR Enterobacterales, 9 colonization with acinetobacter and pseudomonas 10 typically proceeds infections with the same strain 11 with higher risk of infection and higher acuity 12 patients. ICU patients with carbapenem-resistant A. 13 baumannii bloodstream infections were colonized with 14 the same strain prior to developing infections, and 15 among patients colonized with P. aeruginosa at 16 admission, 23 to 43 percent developed infection during 17 their hospitalization and their risk of having a 18 clinical culture with P. aeruginosa was six times 19 higher than those who were not colonized at admission. 20 Next slide.</p> <p>21 Colonization is not only a risk for 22 infection in the colonized individual, but a risk for</p>	<p>1 Candida auris, which Dr. Sexton will cover later this 2 morning, and the other colors represent residents 3 colonized with different combinations of carbapenem- 4 resistant organisms, some of whom also carry C. auris.</p> <p>5 Note the high prevalence which leads to 6 sustained transmission and creates a reservoir that, 7 through patient sharing, can amplify spread throughout 8 healthcare facilities in a region. Next slide.</p> <p>9 Multiple products have been assessed 10 for pathogen reduction or decolonization of MDR gram- 11 negative bacilli and I have attempted to summarize 12 them in this table. However, there are currently no 13 FDA approved decolonization agents for these 14 organisms. Skin antiseptics with chlorhexidine, 15 abbreviated CHG on the slide, has been found to reduce 16 skin concentrations of CRE and may also reduce the 17 skin burden of carbapenem-resistant acinetobacter, 18 which theoretically can prevent infections and reduce 19 transmission.</p> <p>20 In the next presentation Dr. Ham will 21 highlight the success of chlorhexidine bathing for 22 preventing gram-positive infection. However, it's</p>

<p style="text-align: right;">Page 74</p> <p>1 important to note that substantially higher 2 concentrations of chlorhexidine are needed to reduce 3 the growth of gram-negatives compared to gram- 4 positives, and these may be difficult to achieve in 5 clinical practice.</p> <p>6 This may be in part why in two meta 7 analyses of chlorhexidine bathing in ICU patients, 8 this practice was not found to impact gram-negative 9 infection. The use of non-absorbable oral antibiotics 10 for selective digestive decontamination during periods 11 when patients are at high risk of infection such as in 12 the ICU was described by Dr. McDonald. Across 13 multiple randomized controlled trials, SDD reduced the 14 gastrointestinal carriage rate of ESBL 15 Enterobacterales, CRE, and carbapenem-resistant 16 acinetobacter.</p> <p>17 The effect is temporary, suggesting 18 that this may serve more to suppress these organisms 19 than to eliminate them from the gut. SDD fails to 20 meet several of the specific attributes of a 21 decolonizing agent through its use of therapeutic 22 agents, typically polymyxins and aminoglycosides, with</p>	<p style="text-align: right;">Page 76</p> <p>1 antibiotic resistant organisms which included both VRE 2 and MDR Enterobacterales. A small number of reports 3 in case series have documented decolonization of 4 carbapenem-resistant P. aeruginosa and acinetobacter 5 following FMT, suggesting that this strategy may not 6 be limited to the enteric gram-negatives.</p> <p>7 However, more well controlled studies 8 including randomized controlled trial with clearly 9 defined endpoints for decolonization or pathogen 10 reduction are needed. Finally, the literature 11 contains several case reports of successful treatment 12 of acinetobacter, P. aeruginosa, and Enterobacterales 13 infections with bacteriophage under compassionate use, 14 including cure of wound infections and eradication of 15 P. aeruginosa from cystic fibrosis patient lungs. 16 This may be a promising approach for decolonization 17 due to the narrow spectrum and durability of phage 18 action. Next slide.</p> <p>19 So where do we go from here? First, 20 let's recap where we are. These are highly resistant 21 organisms with limited treatment options. 22 Colonization increases the risk of infection and</p>
<p style="text-align: right;">Page 75</p> <p>1 the potential to both evoke resistance to these 2 therapies and to disrupt the intestinal microbiome.</p> <p>3 The next two approaches, probiotics and 4 fecal microbiota transplant are intestinal microbiome 5 restoratives. By restoring the natural colonization 6 resistance of a healthy microbiome, these modalities 7 could potentially protect against colonization with 8 MDR gram-negatives or function as decolonization or 9 pathogen reduction agents.</p> <p>10 Among two randomized controlled trials 11 in which a probiotic was administered to hospitalized 12 patients, MDR Enterobacterales acquisition and loss 13 were not altered. Similarly, randomized controlled 14 trials to assess decolonization of MDR 15 Enterobacterales carriers did not show reductions in 16 carriage after probiotic treatment.</p> <p>17 The current evidence for fecal 18 microbiota transplant assessed across multiple case 19 studies and primarily uncontrolled case series is more 20 optimistic. A meta analysis of three studies 21 estimated that one month post fecal microbiota 22 transplant, 46 percent of patients decolonized</p>	<p style="text-align: right;">Page 77</p> <p>1 creates a reservoir for transmission to other 2 patients. Current infection control methods slow but 3 do not stop transmission, as illustrated in our LTACH 4 example.</p> <p>5 Therefore, MDR gram-negative 6 decolonization or pathogen reduction has the potential 7 to positively impact both the individual and the 8 population by reducing infections and preventing 9 transmission, but there are currently no FDA-approved 10 agents for these purposes.</p> <p>11 Hence there is a critical need for 12 novel approaches that satisfy the specific attributes 13 of decolonization and pathogen reduction agents and to 14 systematically evaluate these approaches including 15 randomized control trials in order to understand their 16 effect on colonization, infection, and transmission. 17 Thank you.</p> <p>18 DR. HEIDI SMITH: Thank you for that 19 presentation. And so we're going to move on to our 20 last presentation of the first half of this session. 21 Cal Ham is going to be speaking on Gram Positives: 22 Staph aureus and Vancomycin-resistant Enterococci.</p>

<p style="text-align: right;">Page 78</p> <p>1 Dr. Ham is the deputy lead of the Antimicrobial 2 Resistance Team in the Division of Healthcare Quality 3 Promotion at CDC. He serves there as a subject matter 4 expert on antibiotic-resistant gram-positive bacteria. 5 He oversees a broad portfolio of projects focused on 6 the prevention of antimicrobial-resistant pathogens in 7 the healthcare setting. On to your presentation, Dr. 8 Ham. Thanks.</p> <p>9 DR. CAL HAM: Good morning, everyone. 10 Thank you very much for that introduction and I am 11 pleased to be speaking with you all today about 12 decolonization and pathogen reduction for two 13 important gram-positive bacteria, Staphylococcus 14 aureus and vancomycin-resistant Enterococci. I have 15 no financial disclosures to report.</p> <p>16 So as with the previous talk, I will 17 begin today with the description of key areas of need 18 for prevention. For Staphylococcus aureus, 19 decolonization and pathogen reduction strategies have 20 proven effective as demonstrated by a number of large 21 clinical trials; however, despite these excesses, 22 there remains work to be done first in evaluating and</p>	<p style="text-align: right;">Page 80</p> <p>1 exposures. However, transmission of a highly fit 2 clone, USA300 in the community subsequently led to 3 large increases in infections among those without 4 healthcare-related risk factors in the United States. 5 Staph aureus also remains a major cause 6 of healthcare-associated infections, with it being the 7 number one cause of surgical site infections and 8 overall the second most common cause of HAIs in 9 hospitals. Next slide, please.</p> <p>10 Diving a little bit deeper into the 11 epidemiology of MRSA, in 2020 there were an estimated 12 279,300 MRSA infections among hospitalized patients in 13 the United States, representing a significant burden 14 of disease. And as with other HAIs, the COVID-19 15 pandemic had a major impact on hospital-onset MRSA 16 infections.</p> <p>17 This table is taken from a recent 18 publication and shows national estimates of hospital 19 onset MRSA bacteremia by quarter in 2020 compared to 20 respective quarters in 2019. You can see that in 21 quarter one 2020, hospital onset MRSA bacteremia 22 estimates were down 7.2 percent compared to quarter</p>
<p style="text-align: right;">Page 79</p> <p>1 expanding decolonization and pathogen reduction 2 strategies for staph aureus to additional settings and 3 high risk populations, and second in the development 4 of additional products and novel approaches that can 5 be incorporated into our prevention arsenal.</p> <p>6 In contrast, while we have seen great 7 successes in decolonization and pathogen reduction for 8 staph aureus, for VRE there are currently no approved 9 decolonization products. As such, there is a great 10 need to develop and investigate promising and novel 11 agents with the potential for large impacts on patient 12 outcomes. Next slide, please. And next slide, 13 please.</p> <p>14 So staph aureus is a common cause of 15 infections in both community and healthcare settings. 16 We categorize staph aureus based on resistance 17 patterns into two types: methicillin susceptible 18 staph aureus or MSSA and methicillin resistant staph 19 aureus or MRSA, which is commonly resistant to many 20 commonly used first line antibiotics.</p> <p>21 When MRSA first emerged, it was 22 primarily identified in patients with healthcare</p>	<p style="text-align: right;">Page 81</p> <p>1 one 2019.</p> <p>2 However, this dramatically changed 3 beginning in quarter two 2020 with increases noted in 4 each subsequent quarter compared to their respective 5 2019 quarters, highlighting the need for continued 6 prevention efforts to combat the increases we have 7 seen in these invasive infections. Next slide, 8 please.</p> <p>9 Continuing with some background 10 information, staph aureus is transmitted by direct or 11 indirect contact with infected or colonized 12 individuals or contaminated surfaces. The primary 13 site of colonization is the nares, but it can also 14 colonize other anatomic sites including the axilla, 15 groin, perineum and pharynx.</p> <p>16 It is estimated that approximately one- 17 third of the population is colonized with staph aureus 18 and about 1 percent with MRSA; although, this MRSA 19 estimate is based on older data and may be higher now, 20 particularly in certain high risk groups such as long- 21 term care facility residents, healthcare personnel, 22 and individuals with extensive healthcare exposures.</p>

<p style="text-align: right;">Page 82</p> <p>1 The duration of colonization by MRSA is 2 highly variable, but can be prolonged. Reports in the 3 literature range from weeks to years; however, one 4 systematic review that I reference here reported a 5 median duration of MRSA colonization of 88 weeks. 6 And finally, as has been mentioned in 7 previous talks, colonization is a driver of 8 transmission but also increases the risk of developing 9 an infection. In fact, among hospitalized patients 10 who are newly colonized with MRSA, about 15 percent 11 will progress to clinical infection. Next slide, 12 please. 13 Next, I'll provide some background 14 information on VRE which like staph aureus is a common 15 cause of HAIs. In 2020, there were an estimated 16 50,300 infections caused by VRE among hospitalized 17 patients in the United States. VRE is also spread by 18 direct or indirect contact with infected or colonized 19 individuals or contaminated surfaces; however, I do 20 want to highlight that environmental contamination 21 plays a much greater role in VRE transmission than for 22 staph aureus. Next slide, please.</p>	<p style="text-align: right;">Page 84</p> <p>1 So for MRSA, we are fortunate to have a 2 number of different decolonization and pathogen 3 reduction agents available. Decolonization or 4 pathogen reduction is typically done using an 5 intranasal anti-staphylococcal agent in combination 6 with a topical antiseptic. For intranasal agents, 7 mupirocin, which is an antibiotic, has been most 8 commonly investigated, but there is also iodophor or 9 povidone iodine and alcohol-based agents that have 10 been employed. 11 For topical antiseptics, chlorhexidine 12 gluconate is the most commonly used and is applied 13 directly to a patient's skin. I did want to note that 14 a mupirocin and chlorhexidine decolonization regimen 15 has been shown to be superior to an iodophor 16 chlorhexidine based regimen for staph aureus 17 prevention based on results from the Swap Out Trial. 18 And while there have been reports in 19 mupirocin resistance in the literature which bears 20 careful monitoring, no significant increases in 21 mupirocin resistance were observed in a large clinical 22 trial for decolonization, the reduce MRSA trial, which</p>
<p style="text-align: right;">Page 83</p> <p>1 Unlike staph aureus, the primary site 2 of VRE colonization is the gastrointestinal tract and 3 it can occasionally colonize the urinary tract. VRE 4 colonization among hospitalized patients is common and 5 one meta analysis found that the prevalence of 6 colonization at time of admission to an ICU was 12.3 7 percent among U.S. patients. 8 Similar to MRSA, the duration of 9 colonization for VRE is highly variable but ranges 10 from weeks to years with a median of 26 weeks. And 11 risk factors include prolonged healthcare exposures, 12 invasive devices, antibiotic receipt, and long-term 13 care residence. 14 As with MRSA, colonization by VRE can 15 drive transmission but also increases the risk of 16 developing an infection. Certain groups at high risk 17 for progression to clinical infection include cancer 18 patients where an estimated one out of eight who are 19 colonized go on to develop a VRE bloodstream 20 infection, and ICU patients where rates of progression 21 to clinical infection may also be very high. Next 22 slide, please. And next slide, please.</p>	<p style="text-align: right;">Page 85</p> <p>1 I'll talk about more in just a minute. 2 We have also investigated chlorhexidine 3 resistance in collaboration with academic partners and 4 in a convenience sample of just over 500 antibiotic- 5 resistant isolates, we did not observe increases in 6 chlorhexidine MICs over time from 2005 to 2019. 7 In a separate evaluation at healthcare 8 facilities with longstanding chlorhexidine patient 9 bathing, no increases in chlorhexidine 10 nonsusceptibility or deleterious changes to microbial 11 ecology were identified in the chlorhexidine bathing 12 period compared to the pre-chlorhexidine bathing 13 period. 14 Now the existing intranasal agents 15 listed on the slide have a broad spectrum of activity 16 which can affect the entire nasal microbiota, but are 17 there ways that we can be more targeted with nasal 18 decolonization? One potential class of decolonizing 19 agents that are often narrow spectrum are bacteriocins 20 which are antibacterial peptides that are produced by 21 competing bacteria, including in the nares. 22 One of these, lysostaphin, targets</p>

<p style="text-align: right;">Page 86</p> <p>1 staphylococcus species including staph aureus and has 2 shown promise in animal models. Other approaches such 3 as phage therapy and monoclonal antibodies targeting 4 staphylococcus protein A also show promise and have 5 narrow spectrum activity that is likely to have 6 minimal impact on the nasal microbiota.</p> <p>7 In addition, further study of the nasal 8 microbiome itself and how other bacteria compete with 9 staph aureus in the nares may yield additional 10 decolonization targets. Next slide, please.</p> <p>11 So next I'm going to spend a few 12 minutes talking about the evidence supporting 13 decolonization and pathogen reduction for staph aureus 14 to give you a sense of how successful these approaches 15 have been. One of the seminal trials that I'll go 16 into a bit of detail on is to Reduce MRSA Trial and 17 you'll hear more from the study's lead author Dr. 18 Susan Huang later today.</p> <p>19 This study was supported by CDCs 20 Prevention Epicenters and was a cluster randomized 21 trial of 74 adult ICUs that involved three arms: Arm 22 1, which is what I'll call the routine care arm where</p>	<p style="text-align: right;">Page 88</p> <p>1 in MRSA clinical cultures or all cause bloodstream 2 infections. However, for the targeted decolonization 3 arm, there was a 25 percent reduction in MRSA clinical 4 cultures and a 22 percent reduction in all cause 5 bloodstream infections, both of which were 6 statistically significant.</p> <p>7 And for the universal decolonization 8 arm, there was an even greater impact with a 37 9 percent reduction in MRSA clinical cultures and a 44 10 percent reduction in all cause bloodstream infections, 11 both of which were statistically significant. These 12 large reductions, particularly those in the universal 13 arm are truly remarkable and demonstrate that 14 decolonization is one of the most effective prevention 15 tools we have available for staph aureus. Next slide, 16 please.</p> <p>17 Now, in addition to REDUCE MRSA, there 18 are several other studies which have evaluated the 19 impact of decolonization and pathogen reduction 20 interventions for staph aureus in various patient 21 populations and in the next two slides, I'll summarize 22 some of the key findings. While I can't discuss each</p>
<p style="text-align: right;">Page 87</p> <p>1 patients were screened on admission to ICUs and MRSA 2 carriers were isolated; Arm 2, which was a which was a 3 targeted decolonization arm where they screened 4 patients on admission, isolated MRSA carriers, and 5 decolonized those who were MRSA positive with 6 intranasal mupirocin and chlorhexidine bathing; and 7 finally Arm 3 or the universal decolonization arm 8 where there was no screening on admission, but rather, 9 they decolonized all ICU patients with intranasal 10 mupirocin and chlorhexidine bathing as well as 11 isolating previously known in MRSA carriers.</p> <p>12 It is important to note that practices 13 in Arm 1 where the standard of care during the 14 baseline period for all arms and therefore results 15 from this arm are an indication of the secular trend. 16 Next slide, please.</p> <p>17 Now, getting to the results which are 18 presented as reductions in outcomes observed during 19 the intervention period relative to the baseline 20 period. Statistically significant reductions are 21 noted by an asterisk. You can see that for the 22 routine care arm, there were no significant reductions</p>	<p style="text-align: right;">Page 89</p> <p>1 of these in detail, the main takeaway I want you to 2 have is that these interventions have proven 3 successful in reducing infections across a number of 4 different populations.</p> <p>5 These included hospitalized patients 6 outside the ICU with indwelling devices, as shown in 7 the ABATE Infection Trial, MRSA carriers following 8 hospital discharge from Project CLEAR, nursing home 9 residents in the Protect Trial -- I've included some 10 updated results from that trial here -- surgical 11 patients as seen in studies from Bode et al. and 12 continuing to the next slide, the MARS Study and STOP 13 SSI, and finally neonatal ICU patients.</p> <p>14 Again, the results from these studies 15 as well as several others, point to how impactful 16 decolonization and pathogen reduction strategies for 17 staph aureus can be, particularly for high risk 18 patients during high risk periods, such as during an 19 ICU admission, when indwelling devices are present, or 20 when undergoing high risk surgeries.</p> <p>21 They have resulted in national 22 recommendations from both CDC and the Society for</p>

<p style="text-align: right;">Page 90</p> <p>1 Healthcare Epidemiology of America or SHEA, and these 2 strategies have been widely implemented in acute care 3 hospitals with 37 percent of U.S. hospitals in 2021 4 reporting routine use of an intranasal anti- 5 staphylococcal agent in combination with chlorhexidine 6 bathing. Next slide, please.</p> <p>7 Now, for VRE, we have a very different 8 story. As I mentioned earlier, there are currently no 9 approved products for VRE decolonization. Now, 10 chlorhexidine bathing can be effective for pathogen 11 reduction, but will not impact colonization of the 12 gastrointestinal tract. Several other approaches have 13 been investigated and generally fall into the 14 categories of antibiotics, repurposing of other drugs 15 with activity against VRE, gut microbiome-modifying 16 therapies, or combination approaches.</p> <p>17 In general, these have been small case 18 series or trials that have yielded mixed results, had 19 limited follow-up time, and commonly reported 20 colonization rebound. Next slide, please.</p> <p>21 Now, on the next two slides, I'll 22 highlight just a few findings from the literature for</p>	<p style="text-align: right;">Page 92</p> <p>1 its effectiveness. Next slide, please.</p> <p>2 Next, it is known that certain 3 commensal bacteria inhibit VRE growth in the GI tract, 4 such as <i>Barnesiella</i> species which prevent intestinal 5 domination by VRE and may reduce the risk of 6 subsequent infection. As such, probiotics have been 7 investigated for MDRO decolonization including for 8 VRE.</p> <p>9 These studies have shown mixed results 10 and I'll highlight one small randomized control trial 11 assessing VRE clearance following the use of 12 <i>Lactobacillus rhamnosus</i> GG, which showed 100 percent 13 clearance at four weeks in the treatment arm compared 14 to just 8 percent clearance in the control arm. I 15 will however note that another recently published 16 study showed no effect of <i>Lactobacillus rhamnosus</i> on 17 VRE clearance.</p> <p>18 Finally, fecal microbiota 19 transplantation or FMT is a promising new approach 20 that may prove effective. However, as with other 21 approaches to VRE decolonization, many reports on FMT 22 have been case series and have shown mixed results.</p>
<p style="text-align: right;">Page 91</p> <p>1 these different approaches. First, the use of 2 antibiotics for VRE decolonization has shown mixed 3 results with reports of poor tolerance and gut 4 microbiome disruption. Oral bacitracin is one of the 5 more commonly investigated and one review article 6 reported here -- sorry -- reported between 43 and 100 7 percent initial clearance. However, only 33 to 53 8 percent of individuals remained decolonized at three 9 weeks.</p> <p>10 Another antibiotic, rampolanin, was 11 investigated in a small randomized control trial with 12 68 participants which showed 85 percent clearance at 13 day seven in the treatment arms compared to zero 14 present in the placebo arm. However, there were no 15 significant differences between treatment and placebo 16 arms at day 21.</p> <p>17 In terms of repurposing other drugs 18 with activity against VRE, ebselen, a synthetic 19 organoselenium compound, has been demonstrated to have 20 potent activity against enterococcus in vitro, in a 21 mouse model reduced VRE fecal burden by 99 percent. 22 However, clinical trials are still needed to determine</p>	<p style="text-align: right;">Page 93</p> <p>1 One that I'll highlight here came from France where 2 they successfully decolonized seven out of eight 3 carriers during a hospital outbreak of VRE. Next 4 slide, please.</p> <p>5 So to summarize, decolonization and 6 pathogen reduction for MRSA carriers has proven 7 successful with several large trials among different 8 populations demonstrating effectiveness which have 9 resulted in national recommendations. Universal 10 approaches such as universal decolonization of ICU 11 patients as was done in the REDUCE MRSA Trial also 12 have the potential to impact MSSA infections as well. 13 These decolonization and pathogen reduction strategies 14 play a major role in the prevention of staph aureus 15 infections.</p> <p>16 However, as I pointed out earlier, we 17 still have more work to do both in terms of expanding 18 the use of these in populations where they have proven 19 to be effective, but also in evaluating their impact 20 in other high risk populations or settings. There is 21 also the need to investigate the effectiveness of 22 other agents for staph aureus decolonization, and</p>

<p style="text-align: right;">Page 94</p> <p>1 pathogen reduction and some promising new approaches 2 including bacteriocins, phage therapy, and the use of 3 monoclonal antibodies may add additional tools to our 4 prevention arsenal. Next slide, please. 5 For VRE, there remains a major need for 6 effective decolonization and pathogen reduction 7 regimens. While several strategies have been 8 investigated with mixed results, we need a more 9 systematic approach and larger clinical trials to 10 determine the effectiveness of these agents as well as 11 the development and evaluation of other novel 12 products. 13 Given the burden of VRE infections 14 among hospitalized patients, the development of 15 effective decolonization and pathogen reduction 16 regimens truly has the potential to greatly impact 17 patient outcomes in the United States. Next slide, 18 please. 19 Thank you very much, and I will turn it 20 back over to the moderators. 21 DR. HEIDI SMITH: Thank you very much, 22 Dr. Ham, for that presentation. And I want to thank</p>	<p style="text-align: right;">Page 96</p> <p>1 lead for the Mycotic Diseases Branch Laboratory at 2 CDC. I'm really grateful to be here today and have 3 fungi be included in this important conversation. 4 Like many bacterial pathogens, we're 5 also really concerned about increasing antimicrobial 6 resistance in fungi and healthcare-associated 7 infections. Today, I'm going to talk to you about 8 <i>Candida auris</i>, an emerging fungal pathogen of 9 increasing public health concern. Next slide, please. 10 <i>Candida auris</i> was first reported in 11 2009 but has rapidly spread across the globe and USA. 12 Using whole genome sequencing, we've learned that this 13 is not simply recent detection, but is true emergence 14 and essentially the spread of just a few highly clonal 15 groups or clades. Unlike most fungal pathogens, 16 <i>Candida auris</i> has proven to be unique in its ability 17 to heavily colonize patients' skin and cause outbreaks 18 in healthcare settings that are hard to control. 19 To date, there are no decolonization or 20 pathogen reduction strategies for <i>Candida auris</i>. In 21 2019, <i>Candida auris</i> was identified as an urgent threat 22 in CDC's 2019 AR Threat Report. Next slide, please.</p>
<p style="text-align: right;">Page 95</p> <p>1 all the speakers for the first half of session one for 2 some great presentations and also for staying on 3 schedule. So we are on time to take a break. We will 4 be taking a break now and we'll be back at 10:25 for 5 the second half of session one. Thanks very much and 6 see you then. 7 (Break) 8 TIMOTHY BENSMAN: Welcome back 9 everyone. My name is Tim Bensman from FDA and I'll be 10 moderating the second half of the morning session. 11 We're going to begin with Dr. Joe 12 Sexton who will present on the topic of <i>Candida auris</i> 13 colonization and the implications for public health. 14 Dr. Sexton is a microbiologist and a team lead for the 15 Mycotic Disease Branch Laboratory at CDC. Dr. Sexton 16 has specific subject matter expertise in the detection 17 and control of <i>Candida auris</i> including diagnostics, 18 colonization, transmission, and environmental control. 19 Dr. Sexton, the floor is yours. 20 DR. JOE SEXTON: Good morning, 21 everyone. Thank you so much for tuning into this talk 22 and workshop. My name is Joe Sexton and I'm the team</p>	<p style="text-align: right;">Page 97</p> <p>1 I'd like to highlight that much of what 2 we know about <i>Candida auris</i> right now in the United 3 States is thanks to the AR Lab Network, seven highly 4 specialized public health laboratories who have the 5 unique capacity to provide <i>C. auris</i> colonization 6 screening which is performed by testing ES swabs 7 collected from the axilla, groin, and sometimes 8 interior nares. The AR Lab Network also performs 9 antifungal susceptibility testing and plays an 10 important role in helping us track AR. Next slide, 11 please. 12 So why are we concerned about <i>Candida</i> 13 <i>auris</i>? I'm going to go through three main reasons. 14 First is antimicrobial resistance, high rates of 15 antimicrobial resistance, and for a little bit of 16 context I think it's important to appreciate that 17 because fungi are eukaryotic organisms like ourselves, 18 it is challenging to find unique drug targets that can 19 hurt the fungal pathogen without having side effects 20 on us. And for this reason, we really just don't have 21 a lot of antifungals to work with in the beginning and 22 that really makes antifungal resistance highly</p>

<p style="text-align: right;">Page 98</p> <p>1 concerning to us.</p> <p>2 Just to paint a picture of what we're</p> <p>3 seeing with Candida auris, we're seeing that over 80</p> <p>4 percent of isolates are resistant to one class of</p> <p>5 antifungal. Over 25 percent of isolates in the United</p> <p>6 States are resistant to two classes and we're really</p> <p>7 concerned to now see isolates popping up that are</p> <p>8 resistant to all three classes of antifungals that are</p> <p>9 currently available.</p> <p>10 Colonization also amplifies the</p> <p>11 problem. We're learning that 5 to 10 percent of</p> <p>12 colonized patients go on to develop invasive</p> <p>13 infections and of those we're seeing over 45 percent</p> <p>14 mortality within the first 30 days. Candida auris</p> <p>15 also causes large outbreaks in healthcare settings</p> <p>16 that are hard to control and we see colonization</p> <p>17 prevalence go very high. In some cases, it can -- in</p> <p>18 some units it can be equal to or even greater than 70</p> <p>19 percent of the patients are colonized by Candida</p> <p>20 auris. Next slide, please.</p> <p>21 Unfortunately, Candida auris cases are</p> <p>22 increasing. This figure shows case counts from data</p>	<p style="text-align: right;">Page 100</p> <p>1 Candida auris is not easy under even normal</p> <p>2 circumstances. Caring for colonized patients requires</p> <p>3 increased resources to adhere to transmission based</p> <p>4 precautions, enhance communication across units and</p> <p>5 between other facilities, and investing in enhanced</p> <p>6 IPC practices across the board.</p> <p>7 One example includes special attention</p> <p>8 to disinfectants. We learned early on that many</p> <p>9 hospital disinfectants with general fungicidal claims</p> <p>10 are often not effective against Candida auris. This</p> <p>11 prompted a collaborative effort between CDC and EPA to</p> <p>12 generate additional data and clarified guidance. This</p> <p>13 resulted in the release of List P which is an easily</p> <p>14 referenceable list of disinfectant products that have</p> <p>15 met EPA's five log reduction performance thresholds</p> <p>16 for Candida auris. We often get the question, how do</p> <p>17 we de colonize patients.</p> <p>18 It's often dissatisfying to have to</p> <p>19 communicate that there's really not a lot of options</p> <p>20 right now, and I think that one of the things that</p> <p>21 we're concerned about is that we're hearing from</p> <p>22 healthcare facilities that they're struggling to</p>
<p style="text-align: right;">Page 99</p> <p>1 generated by the AR Lab Network as well as other</p> <p>2 sources showing colonization screening cases in green</p> <p>3 and the clinical cases in blue. I'd like to draw your</p> <p>4 attention to early 2020 that coincides with the start</p> <p>5 of the COVID-19 pandemic. As you can see, cases have</p> <p>6 increased substantially during the pandemic. The</p> <p>7 reasons for this are not fully understood, but are</p> <p>8 likely related to increased patient movement during</p> <p>9 the pandemic as well as other logistical challenges</p> <p>10 experienced by healthcare facilities such as PPE</p> <p>11 shortages, turnovers, and other challenges just doing</p> <p>12 the work that they're trying to do. Next slide,</p> <p>13 please.</p> <p>14 So who gets colonized by Candida auris?</p> <p>15 Known risk factors are actually pretty similar to</p> <p>16 other MDROs, things like mechanical ventilation and</p> <p>17 recent exposure to prior acute healthcare. Antibiotic</p> <p>18 exposure is also a risk factor as well as systemic</p> <p>19 fluconazole, a commonly used antifungal that C. auris</p> <p>20 is typically resistant to. Next slide, please.</p> <p>21 It's important to highlight that</p> <p>22 providing healthcare for patients colonized with</p>	<p style="text-align: right;">Page 101</p> <p>1 transfer colonized patients out of their unit to the</p> <p>2 appropriate level of care because some facilities and</p> <p>3 units will not accept patients known to be colonized</p> <p>4 by Candida auris. This means some patients are</p> <p>5 getting stuck at the incorrect level of care, in some</p> <p>6 cases for prolonged periods of time. Next slide,</p> <p>7 please.</p> <p>8 So what do we know, what tools do we</p> <p>9 have? I think this is a good opportunity to</p> <p>10 communicate something a little different between</p> <p>11 Candida auris and some of the other pathogens we're</p> <p>12 hearing about, simply because Candida auris is so new.</p> <p>13 We still have a lot to learn. We don't have a large</p> <p>14 body of literature to reference, but we have learned</p> <p>15 certain things that I think are relevant and helpful</p> <p>16 to this conversation.</p> <p>17 One thing we've learned is that</p> <p>18 environmental contamination can be extensive in the</p> <p>19 healthcare environment around colonized patients and</p> <p>20 C. auris can persist on inanimate surfaces for at</p> <p>21 least weeks. So let's talk a little bit about what we</p> <p>22 know about Candida auris colonization and how that</p>

<p style="text-align: right;">Page 102</p> <p>1 relates to environmental contamination and subsequent 2 transmission. Next slide, please.</p> <p>3 First we and others have noted very 4 high concentrations of <i>Candida auris</i> in the swabs 5 we've received for colonization screening. We're 6 talking about millions and even tens of millions of 7 viable cells in a single colonization swab. For those 8 who can't see the Y axis clearly, this figure is in a 9 logarithmic scale going up to 10 to the ninth CFUs per 10 swab. This was surprising to our lab. We actually 11 had to continually revise our laboratory methods to 12 incorporate additional serial dilutions to finally get 13 countable colonies. Next slide, please.</p> <p>14 And perhaps not surprisingly, we've 15 also observed that patients with more <i>Candida auris</i> on 16 their skin also have more <i>Candida auris</i> in their 17 environment. Here on the left, you can see a look at 18 environmental contamination on the Y axis plotted 19 against skin colonization burden on the X axis, 20 showing the positive relationship between those two 21 variables.</p> <p>22 On the right, you can see individual</p>	<p style="text-align: right;">Page 104</p> <p>1 <i>auris</i> colonization in the interior nares observed in 2 this study and corroborated by others, emphasizes the 3 importance of considering the interior nares in any 4 strategy intended to decolonize or reduce pathogen 5 burden. Next slide, please.</p> <p>6 One interesting observation in the same 7 cohort of patients, the patients who were not 8 colonized by <i>Candida auris</i> tended to have mycobiome is 9 dominated by <i>Malassezia</i>. <i>Malassezia</i> is another yeast 10 species that is generally thought to be a part of a 11 normal healthy mycobiome. In contrast, in colonized 12 patients, <i>C. auris</i> was really dominating the mycobiome 13 and we saw very little <i>Malassezia</i>.</p> <p>14 We certainly have a lot more to learn 15 about what a healthy fungal mycobiome looks like, but 16 these observations at minimum suggest further 17 investigation is warranted and additional insights 18 would be relevant to considerations about how to 19 decolonize or reduce pathogen burden for <i>Candida</i> 20 <i>auris</i>. Thank you.</p> <p>21 Unfortunately <i>Candida</i> or is 22 colonization appears to last a very long time and may</p>
<p style="text-align: right;">Page 103</p> <p>1 patients organized along the X axis and the 2 concentration of <i>C. auris</i> detected on their left and 3 right handrails of their bed with a horizontal line, 4 showing the average between those two values. What 5 you can see is that the left and right handrails for a 6 given patient have remarkably similar levels of 7 <i>Candida auris</i> contamination, again indicating a common 8 source from the patient shedding to the environment.</p> <p>9 So we know that colonized patients can 10 serve as a reservoir and contribute to environmental 11 contamination in the healthcare setting. Next slide, 12 please.</p> <p>13 So what else have we learned about 14 <i>Candida auris</i> colonization? This figure highlights a 15 study looking more comprehensively at what body sites 16 can be colonized in a cohort of 57 residents at a 17 ventilated skilled nursing facility that was 18 previously known to have high <i>Candida auris</i> 19 colonization prevalence. This study demonstrated <i>C.</i> 20 <i>auris</i> can colonize many body sites, literally from 21 head to toe.</p> <p>22 In particular, the high frequency of <i>C.</i></p>	<p style="text-align: right;">Page 105</p> <p>1 be indefinite without some kind of intervention. To 2 date, there are some patients that have been tracked 3 being colonized consistently for over four years now. 4 It probably can go longer, but this is the longest 5 that we've been able to track people to date. Thank 6 you.</p> <p>7 So let's talk a little bit about CHG, 8 chlorhexidine, because again, we're still -- there's 9 still a lot more data to have, but there are patients 10 who are colonized with <i>Candida auris</i> that are 11 receiving CHG bathing as a part of care for other 12 MRDOs or other IPC interventions. However, we don't 13 have a lot of data that speaks to its efficacy against 14 <i>Candida auris</i> specifically.</p> <p>15 In this work, CHG concentrations were 16 measured on patient skin and correlated with their 17 colonization status. Although colonization was less 18 common when CHG levels were greater than 625 19 micrograms per mil, this concentration was rarely 20 observed, suggesting it can be difficult to achieve 21 necessary CHG concentrations in practice. And of 22 course CHG bathing would not be expected to impact</p>

<p style="text-align: right;">Page 106</p> <p>1 Candida auris populations in the interior nares. Next 2 slide, please. 3 I'd also like to highlight that there 4 is some very interesting work happening right now with 5 mouse models and other new model systems including pig 6 skin and other artificial models. This field is still 7 young, but I think it's already producing interesting 8 results. One study by Julie Segre's group shown on 9 the left indicated C. auris may be able to colonize 10 even the base of the hair follicles, which again, is 11 relevant to considerations of what it would take 12 technically to access Candida auris to effectively 13 decolonize or reduce burden. 14 The figure on the right shows 15 additional data from Mahmoud Ghannoum's group at Case 16 Western demonstrating that they were successful at 17 achieving a stable colonization model and observed 18 pathogen reduction with an antifungal cream. I think 19 just highlighting that they were able to achieve 20 stable colonization is worth noting because that's 21 been a practical challenge for several groups 22 establishing these models.</p>	<p style="text-align: right;">Page 108</p> <p>1 Healthcare facilities often ask us 2 about decolonization treatments and it's dissatisfying 3 and disappointing when we have to communicate that 4 there's just not a lot of options right now. Patients 5 colonized with Candida auris are increasingly stuck at 6 the wrong level of care because other facilities 7 refuse to accept them. 8 And so there's a public health need for 9 decolonization or pathogen reduction strategies that 10 can specifically address C. auris colonization, and I 11 think that further advancing and standardizing 12 laboratory models to help evaluate new approaches will 13 be an important piece of that puzzle. Next slide, 14 please. 15 And so that -- with that, I'd like to 16 give some special thanks in particular to the AR Lab 17 Network who've done a lot of work to help us keep 18 track of Candida auris. Of course, our colleagues in 19 the Division of Healthcare and -- Quality and 20 Promotion for collaborating with us so consistently on 21 Candida auris, many of which are presenting before and 22 after me.</p>
<p style="text-align: right;">Page 107</p> <p>1 Others are also doing really 2 interesting work in this area, so this slide isn't 3 necessarily intended to be comprehensive, but I do 4 want to highlight while both of these studies were 5 done very well in independence, just to point out that 6 they did use different mouse models and for that it's 7 hard to kind of compare apples to apples and I think 8 I'm highlighting that because that's kind of a current 9 need I think in the field. 10 Whether you're talking about a mouse 11 model, a skin model, or some other artificial model, 12 it will be helpful as the field grows to see consensus 13 develop around common model systems that can be 14 standardized to best support robust evaluations of 15 products before moving to patient populations. 16 So what do we need? Just to briefly 17 review some of the things and takeaways from today, I 18 hope you guys have learned and come to appreciate that 19 C. auris can asymptotically colonize patients' skin 20 and that increases their risk of developing an 21 infection and it contributes to environmental 22 contamination and transmission to others.</p>	<p style="text-align: right;">Page 109</p> <p>1 And I'd like to thank my home branch, 2 the Mycotic Diseases Branch, for doing a lot of work 3 on this, but also other fungi. We always like to 4 point out that we are a small but dynamic group. 5 We're the only group at CDC responsible for an entire 6 kingdom of life and we couldn't do that without a 7 really strong and dynamic team. 8 And I'd also like to thank other 9 groups, the Wadsworth Laboratory, Chicago Department 10 of Health, Mary Hayden and Rush University, Julie 11 Segre and NIH, Susan Huang and UCI, and others that 12 we've collaborated with on these special studies to 13 learn what we've learned. 14 With that, I want to conclude with one 15 of our mottoes is think fungus and save lives. And 16 thanks again to the organizers for including fungi in 17 this important conversation. And with that, I will 18 conclude my talk and turn it back over to the 19 moderators. Thank you. 20 TIMOTHY BENSMAN: Wonderful. Well thank 21 you Dr. Sexton and a very nice presentation. Our next 22 speaker is Dr. Alice Guh who will present on</p>

<p style="text-align: right;">Page 110</p> <p>1 Clostridioides difficile: Epidemiological Risks and 2 Decolonization Strategies. Dr. Guh is a U.S. public 3 health service medical officer in the Division of 4 Healthcare Quality Promotion at the CDC. She leads 5 the Clostridioides difficile infection and multisite 6 gram-negative surveillance initiative team within the 7 Epidemiology Research and Innovations Branch in DHQP. 8 Dr. Guh, the microphone is yours.</p> <p>9 DR. ALICE GUH: Thank you. Good 10 morning, everyone. I will be presenting on 11 Clostridioides difficile or C. diff, the Epidemiologic 12 Risks and Decolonization Strategies. Next slide, 13 please.</p> <p>14 I have no financial disclosures. Next 15 slide.</p> <p>16 What we need for C. diff is an 17 effective decolonization strategy to prevent 18 transmission of C. diff from infected patients and 19 asymptomatic carriers and to prevent primary and 20 recurrent C. diff infection. We also need an approved 21 microbiome-based therapeutic for C. diff infection. 22 There are currently several</p>	<p style="text-align: right;">Page 112</p> <p>1 outbreak settings with one study reporting 51 percent 2 during an outbreak involving a long-term care 3 facility.</p> <p>4 Among persons in the community, about 2 5 to 10 percent can be asymptotically colonized with 6 C. diff. For most healthy individuals with intact 7 microbiota, C. diff carriage is transient but for some 8 they can remain persistently colonized for several 9 months. Next slide, please. Next slide.</p> <p>10 In a meta analysis of hospitalized 11 patients, previous CDI, hospitalization in the 12 previous six months, tube feeding, gastric acid 13 suppression, and corticosteroid use in the previous 14 eight weeks were all found to be risk factors for C. 15 diff colonization. Interestingly, prior antimicrobial 16 use was not found to be a risk factor for C. diff 17 colonization among hospitalized patients, but this may 18 be due to the pooling of all antibiotic classes in the 19 meta analysis, which may have diminished any class- 20 specific effect.</p> <p>21 In addition, it's possible that even 22 without prior antimicrobial use, a patient's</p>
<p style="text-align: right;">Page 111</p> <p>1 biotherapeutics and clinical trials, some of which I 2 will be highlighting later in my presentation, but 3 first I'd like to provide some background on C. diff 4 and associated colonization risks. Next slide, 5 please. Next slide.</p> <p>6 C. diff is an anaerobic gram-positive 7 spore-forming gastrointestinal pathogen. Transmission 8 usually occurs via the oral-fecal route. Clinical 9 spectrum ranges from asymptomatic colonization to 10 severe disease with fulminant colitis and death. C. 11 diff is the leading cause of healthcare-associated 12 diarrhea and is increasingly reported in the 13 community.</p> <p>14 It's been estimated that there were 15 462,000 incident C. diff infections or CDI in the 16 United States in 2017 with an estimated close to 17 224,000 cases and almost 12,800 associated deaths 18 among hospitalized patients. Next slide, please.</p> <p>19 Asymptomatic colonization of C. diff 20 can occur in about 7 to 18 percent of hospitalized 21 patients and 15 percent of long-term care facility 22 residents. Colonization rate can be higher during</p>	<p style="text-align: right;">Page 113</p> <p>1 microbiome might be disrupted from acute illness or 2 from dietary changes of hospitalization that might 3 predispose the patient to being colonized with D. 4 diff. Among long-term care facility residents, risk 5 factors for C. diff colonization include prior CDI 6 outbreaks in the facility, previous CDI, prior 7 hospitalization, and prior antimicrobial use. Next 8 slide.</p> <p>9 It's been shown that 10 to 60 percent 10 of hospitalized patients who are colonized with 11 toxigenic C. diff may develop CDI. The risk of CDI 12 increases with gut microbiome disruption and 13 immunosuppression. The primary risk factor for CDI is 14 antibiotic use which can directly impact the gut 15 microbiome. Other risk factors that can affect the 16 microbiome and/or cause immunosuppression include 17 proton pump inhibitor use, advanced age, and 18 chemotherapy.</p> <p>19 Certain strains of C. diff may also be 20 more likely to cause disease. One study found that 21 ribotype 027, which is the epidemic strain and 22 produces more toxin than most other C. diff strains</p>

<p style="text-align: right;">Page 114</p> <p>1 was found in 25 percent of CDI cases versus 3 percent 2 of asymptomatic carriers. Next slide, please. 3 Asymptomatic carriers can transmit C. 4 diff to other patients since they can shed the 5 organism on their skin and in the environment, 6 although to a lesser degree than symptomatic patients. 7 Certain patients who are colonized might be a higher 8 risk of transmission, including those who were 9 recently infected and might still have a high burden 10 of the organism. 11 In one study, patients with recent CDI 12 accounted for 22 percent of hospitalized asymptomatic 13 carriers. Patients with a higher burden of C. diff 14 colonization might also shed greatly on their skin and 15 in the surrounding environment. Next slide, please. 16 In fact, several studies have 17 demonstrated the transmission of C. diff by 18 asymptomatic patients. In the study on the left by 19 Curry et al., they found that incident CDI cases among 20 hospitalized patients were as frequently linked to 21 transmission from asymptomatic carriers as from 22 symptomatic patients. They also identify four</p>	<p style="text-align: right;">Page 116</p> <p>1 spores are ingested, it can remain in the dormant form 2 or they can germinate to form vegetative cells that 3 cause disease. The homeostasis of the gut microbiome 4 is essential in preventing the overgrowth of the 5 vegetative form of C. diff and along with an intact 6 immune system can help keep the patient in a 7 asymptotically colonized state and not develop 8 disease, although shedding can still occur. 9 In contrast, when the microbiota is 10 disrupted, C. diff can thrive in the gut causing 11 disease and lead to significant shedding, hence the 12 reason why there is great interest in therapeutic 13 strategies for CDI that can help restore the normal 14 gut microbiota. Next slide, please. Next slide. 15 Currently microbiome-based therapy for 16 C. diff is primarily focused on the treatment of 17 recurrent disease. They include traditional fecal 18 microbiota transplantation or FMT and novel 19 biotherapeutics. To date, there is a lack of studies 20 evaluating microbiome-based therapy for the prevention 21 and treatment of primary CDI, and as of yet there is 22 no effective decolonization strategy of asymptomatic</p>
<p style="text-align: right;">Page 115</p> <p>1 transmission events that may have occurred from 2 environmental exposures where transmission may have 3 occurred from prior room occupants who had CDI or who 4 were asymptomatic carriers. 5 In a more recent study by Donskey et 6 al., they investigated transmission of C. diff from 7 asymptotically colonized or infected long-term care 8 facility residents. Using whole genome sequencing, 9 they found that 19 percent of healthcare-associated 10 CDI cases could be linked to long-term care facility 11 residents with CDI or who were asymptomatic carriers. 12 They also found that almost three- 13 quarters of the asymptomatic carriers had positive 14 cultures of their groin, skin, and/or surrounding 15 environment for toxigenic C. diff, indicating the 16 potential for transmission due to shedding. In fact, 17 among asymptomatic carriers who were linked to 18 transmission, they found a high burden of C. diff with 19 more than 25 colonies per perirectal swab. Next 20 slide, please. 21 This figure shows the important role of 22 the gut microbiota in CDI development. When C. diff</p>	<p style="text-align: right;">Page 117</p> <p>1 carriers. Next slide, please. 2 FMT, which you heard mentioned by 3 several of the other CDC speakers, is probably one of 4 the most well studied microbiome-based therapy for 5 CDI. It involves the transplantation of the gut 6 microbiota from a healthy donor to a patient to 7 restore normal diversity and function. It's usually 8 administered endoscopically or through the nasogastric 9 or nasoduodenal tube. Several randomized controlled 10 trials and meta analyses have demonstrated the 11 efficacy of FMT for recurrent CDI. 12 The first randomized control trial to 13 be published was by Nood, et al. in 2013. They 14 assigned 43 patients with recurrent CDI to receive 15 either a standard course of oral vancomycin, oral 16 vancomycin with bowel lavage, or four-day course oral 17 vancomycin followed by bowel lavage and FMT. 18 The study was ended early after interim 19 analysis showed that FMT was significantly more 20 effective than vancomycin with resolution of CDI in 81 21 percent who received FMT versus 31 percent who 22 received vancomycin alone versus 23 percent who</p>

<p style="text-align: right;">Page 118</p> <p>1 received vancomycin with bowel lavage. Next slide, 2 please.</p> <p>3 There are, however, some challenges 4 with traditional FMT. Although generally considered a 5 safe procedure, there some risks such as possible 6 aspiration and bowel perforation. Most of the safety 7 data that we have come from short-term studies. So 8 far, associated adverse events are generally self- 9 limited and infectious complications have been rarely 10 recorded, although they have included two 11 immunocompromised patients who developed bacteremia 12 from extended-spectrum beta-lactamase-producing E. 13 coli.</p> <p>14 More recently, there has Shiga toxin- 15 producing E. coli from a single donor to four patients 16 who developed self-limited diarrheal illness. Another 17 challenge with FMT Is the heterogeneity and its 18 practice. Although we now have stool banks, there is 19 the variability in donor recruitment and screening as 20 well as stool preparation methods. Next slide, 21 please.</p> <p>22 Therefore, there's a need for</p>	<p style="text-align: right;">Page 120</p> <p>1 showed similar efficacy with a polled cure rate of 92 2 percent for capsule-based FMT and 94.8 percent for FMT 3 using colonoscopy. Next slide, please.</p> <p>4 As Phase 3 clinical trials completed 5 for some of the novel biotherapeutics, there's the 6 potential for an approved product that can replace 7 traditional FMT and be effective in preventing further 8 recurrence of C. diff as well as transmission of C. 9 diff to other patients. Over the next decade or so, 10 we hope to have data from longitudinal follow-up 11 studies that can provide more insight on long-term 12 safety as well as the durability of FMT and other 13 microbiome restoration therapies.</p> <p>14 We also need continued advancements in 15 developing defined microbial consortia to help improve 16 the safety of these products. In addition, we should 17 explore the role of FMT for the management of primary 18 CDI. A few years ago there was a proof of concept 19 clinical trial that enrolled 20 patients with primary 20 CDI and signed to receive either FMT or treatment with 21 metronidazole. A full clinical response was observed 22 in 78 percent of the FMT group versus 45 percent of</p>
<p style="text-align: right;">Page 119</p> <p>1 standardized microbiome restoration therapies. In 2 recent years there's been a development of several 3 capsule- and enema-based products. Several these 4 products have many potential benefits. For example, 5 they're easier to administer and especially the 6 capsule-based product they're more aesthetically 7 pleasing to patients. And both capsule- and enema- 8 based products are less invasive than traditional FMT.</p> <p>9 Many of these novel products are now in 10 clinical trial. They include whole stool or defined 11 FMT as well as a product containing fecal bacterial 12 spores specifically purified firmicutes spores known 13 as SER-109. A Phase 3 double-blinded randomized 14 control trial was completed for SER-109 and the 15 results were published earlier this year.</p> <p>16 They had enrolled 182 patients with 17 three or more episodes of CDI to receive either SER- 18 109 or placebo following standard care antibiotic 19 therapy. Twelve percent of the SER-109 group versus 20 40 percent of the placebo group developed recurrent 21 CDI. A recent meta analysis compared capsule-based 22 FMT with FMT given endoscopically. Both treatments</p>	<p style="text-align: right;">Page 121</p> <p>1 the metronidazole group. A Phase 3 clinical trial is 2 currently underway. Next slide, please.</p> <p>3 I also want to mention the use of 4 nontoxicogenic C. diff strains to prevent recurrent CDI. 5 In a Phase 2 double-blinded randomized control trial, 6 173 patients with CDI were signed to receive one of 7 three treatments with a nontoxicogenic C. diff strain, 8 M3, or to receive placebo. The three treatments 9 consisted of either 10 to the fourth or 10 to the 10 seventh spores of M3 per day for seven days each or 10 11 to the seven spores per day for 14 days each.</p> <p>12 This figure on the slide shows the 13 proportion of patients of positive C. diff cultures 14 from day one of the study through week 26. The shaded 15 color represents toxigenic C. diff and the nonshaded 16 color represents nontoxicogenic C. diff. The top 17 lefthand quadrant shows the results of the placebo 18 group. We can see that there was a high rate of 19 colonization with toxigenic C. diff versus the 20 remaining three quadrants each showing the results of 21 one of the three treatments with M3.</p> <p>22 You can see that they all had high rate</p>

<p style="text-align: right;">Page 122</p> <p>1 of colonization when nontoxigenic <i>C. diff</i> compared to 2 the placebo group. In fact, CDI recurrence was 3 observed in only 11 percent of patients who received 4 the nontoxigenic <i>C. diff</i> strain M3 versus 30 percent 5 of the placebo group. The likely mechanism by which 6 M3 might be preventing recurrent CDI is that patients 7 are colonized with it, thereby decolonizing or out 8 competing toxigenic <i>C. diff</i> strains from the 9 microbiome.</p> <p>10 The investigators noted that M3 11 colonization was likely transient as it was 12 undetectable after week 22 of follow up, possibly due 13 to restoration of the normal gut microbiota. Next 14 slide, please.</p> <p>15 To date, there is no effective strategy 16 for decolonizing asymptomatic carriers. This study 17 was conducted in the early '90s and was unfortunately 18 unsuccessful. They randomized 30 asymptomatic 19 carriers to receive either 10 days of oral vancomycin 20 or metronidazole or placebo. This figure shows the 21 percent of positive stool cultures among the 22 asymptomatic carriers.</p>	<p style="text-align: right;">Page 124</p> <p>1 versus 12 percent in the no prophylaxis group 2 developed healthcare facility onset CDI.</p> <p>3 No new colonization of vancomycin 4 resistant enterococci was detected among the oral 5 vancomycin prophylaxis group. However only a portion 6 of the patients had a follow up swab done. A recent 7 meta analysis assessed the efficacy of oral vancomycin 8 prophylaxis for primary and secondary CDI prevention 9 in patients treated with systemic antibiotics. This 10 analysis included 11 studies, including one randomized 11 controlled trial and several studies immunocompromised 12 patients, and they found that oral vancomycin 13 prophylaxis is protective against CDI and that its use 14 was not associated with high risk of VRE.</p> <p>15 While these results are promising and 16 more randomized controlled trials are needed, I do 17 want to note that there are some major shortcomings 18 with the strategy namely that vancomycin is an 19 antibiotic and it's used to treat an infection, and as 20 I mentioned earlier it can leave -- it can affect the 21 microbiome leaving it in an even more impaired state 22 and that's failing in an attribute of decolonization</p>
<p style="text-align: right;">Page 123</p> <p>1 Treatment with metronidazole shown by 2 the dashed line and treatment shown by dotted line did 3 not suppress <i>C. diff</i> colonization; whereas, oral 4 vancomycin shown by the solid line suppressed 5 colonization during treatment, but you can see that 6 this effect was only temporary since the carriage rate 7 increased subsequently after vancomycin was stopped. 8 Next slide, please.</p> <p>9 And lastly, I want to mention the use 10 of oral vancomycin prophylaxis for primary and 11 secondary CDI prevention. As I alluded to in my last 12 slide, vancomycin has potent activity against <i>C. diff</i> 13 but it can profoundly affect the microbiome resulting 14 reduced colonization resistance to <i>C. diff</i> that can 15 persist for weeks after vancomycin has stopped, 16 potentially increasing a patient's risk for CDI.</p> <p>17 There's been at least one randomized 18 control trial that has assessed the use of oral 19 vancomycin prophylaxis. The trial enrolled 100 20 patients to receive either oral vancomycin prophylaxis 21 while systemic antibiotics or no prophylaxis. Zero 22 percent in the oral vancomycin prophylaxis group</p>	<p style="text-align: right;">Page 125</p> <p>1 or pathogen reduction agent, many of these attributes 2 that you heard earlier in Dr. McDonald's presentation. 3 Next slide, please. Next one.</p> <p>4 So in conclusion, I'd like to reiterate 5 that for the future of <i>C. diff</i>, we need an effective 6 decolonization strategy that can help prevent 7 transmission of <i>C. diff</i> from infected patients and 8 asymptomatic carriers and prevent primary and 9 recurrent <i>C. diff</i> infection. We also need an approved 10 microbiome-based therapeutic for <i>C. diff</i> infection, 11 which I believe will not be too far off in the future 12 since there are several biotherapeutics that are 13 currently in clinical trials. Next slide.</p> <p>14 Thank you. I'd like to turn it back to 15 the moderators.</p> <p>16 TIMOTHY BENSMAN: Wonderful. Well 17 thank you, Dr. Guh. We will now hear presentations on 18 patient impact and perspectives. Dr. Whitney Brown 19 will share with us the impact of infection on the 20 lives of people with cystic fibrosis. Dr. Brown is 21 currently at Inova advanced lung disease and 22 transplant program, and helped create the Inova Cystic</p>

<p style="text-align: right;">Page 126</p> <p>1 Fibrosis Center.</p> <p>2 In July of 2021, Dr. Brown joined the</p> <p>3 clinical affairs department with a focus on supporting</p> <p>4 the care center network and the evolving cystic</p> <p>5 fibrosis care model. She continues to care for adults</p> <p>6 with cystic fibrosis at Inova which energizes and</p> <p>7 informs her work at the Cystic Fibrosis Foundation.</p> <p>8 Dr. Brown, the stage is yours.</p> <p>9 DR. A. WHITNEY BROWN: Thank you so</p> <p>10 much and good morning. Yes, I have the pleasure of</p> <p>11 speaking today on behalf of people with cystic</p> <p>12 fibrosis to give us a little insight into the impact</p> <p>13 of infection on their lives. Next slide.</p> <p>14 So as many of you know, cystic fibrosis</p> <p>15 is really characterized by a lifetime of infections,</p> <p>16 and I'll be primarily talking about the respiratory</p> <p>17 tract today but what we can see in this schematic is</p> <p>18 because of the underlying defect in cystic fibrosis,</p> <p>19 the result is sticky, dehydrated mucous down in the</p> <p>20 lungs and that really sets the stage for inflammation</p> <p>21 and infection and the cycle goes round and round.</p> <p>22 And in fact, really repeated or</p>	<p style="text-align: right;">Page 128</p> <p>1 bottom, denoted in gray. Next slide.</p> <p>2 So because the acquisition of</p> <p>3 infections occurs so early in life and because there's</p> <p>4 repeated exposure to the healthcare system for people</p> <p>5 with cystic fibrosis, we struggle with antimicrobial</p> <p>6 resistance. And here again, we have more data from</p> <p>7 our patient registry, this time from 2020. And I can</p> <p>8 show you here in the bottom left field, we see the</p> <p>9 distribution of gray, that's the age distribution, the</p> <p>10 number of individuals at each age in our registry.</p> <p>11 Superimposed on that are the people in</p> <p>12 2020, individuals that grew staph aureus. And the</p> <p>13 subset in red are those who grew methicillin-resistant</p> <p>14 staph aureus. So clearly -- and we can see that staph</p> <p>15 is again more prevalent at early ages and decreases</p> <p>16 and stabilizes later in life.</p> <p>17 Likewise, up with pseudomonas, same</p> <p>18 kind of figure with gray being all individuals in the</p> <p>19 registry and then we see the distribution of those who</p> <p>20 grew pseudomonas in the registry from a respiratory</p> <p>21 culture, and then the subset growing multidrug-</p> <p>22 resistant pseudomonas. So clearly, we struggle with</p>
<p style="text-align: right;">Page 127</p> <p>1 persistent airway infection over the course of a</p> <p>2 lifetime is what leads to progressive loss of lung</p> <p>3 function in people with cystic fibrosis. And</p> <p>4 unfortunately respiratory failure is the leading cause</p> <p>5 of death. Next slide.</p> <p>6 So this acquisition of respiratory</p> <p>7 infections really occurs early in life and what I'm</p> <p>8 showing you here is a schematic from our 2019 cystic</p> <p>9 fibrosis patient registry data report. And so what we</p> <p>10 can see on the X axis is this is the patient age and</p> <p>11 years and on the Y axis, the percentage of individuals</p> <p>12 that culture from the respiratory tract one or more of</p> <p>13 these organisms.</p> <p>14 And so early, on by age one and age</p> <p>15 two, you can see a variety of different colors meaning</p> <p>16 that even infants have acquired respiratory tract</p> <p>17 infections and early on it's primarily staph aureus,</p> <p>18 but as kids aged through adolescence, it becomes more</p> <p>19 predominant with pseudomonas or staph aureus and</p> <p>20 pseudomonas in combination. But what you definitely</p> <p>21 notice is the percentage of the population that</p> <p>22 escapes respiratory infections is very small at the</p>	<p style="text-align: right;">Page 129</p> <p>1 antimicrobial resistance. Next slide.</p> <p>2 And we have learned some difficult</p> <p>3 lessons over time, and this is just to highlight.</p> <p>4 This is a timeline of reported publications or reports</p> <p>5 of transmissible strains of, in this case we're</p> <p>6 focusing on pseudomonas and burkholderia that were</p> <p>7 published in the literature and made known over time,</p> <p>8 and this really heightened our awareness that these</p> <p>9 pathogens don't just come from the environment but</p> <p>10 there can be patient-to-patient transmission occurring</p> <p>11 in nosocomial settings as well as in community</p> <p>12 settings like even the CF summer camps that used to</p> <p>13 occur. Next slide.</p> <p>14 And this -- these events and these</p> <p>15 reporting really lead to a revamping of our infection</p> <p>16 prevention and control guidelines for cystic fibrosis.</p> <p>17 And these were put out in 2013 and are specific to our</p> <p>18 population. Really, the most fundamental one is the</p> <p>19 first year that all people with CF are placed on</p> <p>20 contact precautions in healthcare settings, regardless</p> <p>21 of what they have grown in the past. And</p> <p>22 historically, this was gown and gloves, as you see in</p>

<p style="text-align: right;">Page 130</p> <p>1 the picture.</p> <p>2 Of course, now with universal or almost</p> <p>3 universal masking in healthcare settings, the mask has</p> <p>4 been added. And speaking of masks, we've asked our</p> <p>5 patients to wear masks themselves in healthcare</p> <p>6 settings since the publication of these updated</p> <p>7 guidelines and also to keep 6-foot distance between</p> <p>8 other patients and themselves.</p> <p>9 And so this distance is not only in the</p> <p>10 healthcare setting but also in social settings. So</p> <p>11 for example, at Cystic Fibrosis Foundation events or</p> <p>12 other social settings, only one person with CF is</p> <p>13 usually invited to indoor events to be extremely</p> <p>14 cautious on this basis. We also have in this reported</p> <p>15 guideline standards for reducing risk with pulmonary</p> <p>16 function testing and also for cleaning and</p> <p>17 disinfecting environmental services. Next slide.</p> <p>18 So naturally I think most healthcare</p> <p>19 providers and patients and families would agree that</p> <p>20 these guidelines are really for their protection, but</p> <p>21 I wanted to share some terms or thoughts that have</p> <p>22 been shared with me from patients over the years in</p>	<p style="text-align: right;">Page 132</p> <p>1 requiring intravenous antibiotic use. So this is the</p> <p>2 number of times people get sick and need IV</p> <p>3 antibiotics. And this is a time span from the</p> <p>4 beginning of 2019 looking at almost to the end of</p> <p>5 2020.</p> <p>6 And what we see up here in red is for</p> <p>7 people 12 years and older and the number of monthly</p> <p>8 exacerbations and down here in blue is 11 and younger.</p> <p>9 And what we can see at the beginning of 2019 was</p> <p>10 really there was a high level of intravenous</p> <p>11 antibiotic use for pulmonary exacerbation treatment</p> <p>12 each month, a little bit of up and down but high level</p> <p>13 in those 12 and older.</p> <p>14 And then something transformative</p> <p>15 happened in our community in October of 2019 which was</p> <p>16 the approval of elexacaftor/tezacaftor/ivacaftor, and</p> <p>17 this is an oral CFTR modulator medication that helps</p> <p>18 the CF protein work better in almost 90 percent of</p> <p>19 individuals with CF. But initially it was approved</p> <p>20 for 12 and up.</p> <p>21 So what do we see in this 12 and up</p> <p>22 group? We see a marked decline in the subsequent</p>
<p style="text-align: right;">Page 131</p> <p>1 terms of really how these guidelines impact their</p> <p>2 lives.</p> <p>3 So as I mentioned, two people with CF</p> <p>4 can't be within 6 feet of each other, so really that</p> <p>5 has resulted in a heavy social media presence, lots of</p> <p>6 virtual friendships. And in the healthcare setting,</p> <p>7 although there are upsides to getting private rooms</p> <p>8 with contact precautions, you know, naturally there in</p> <p>9 some settings is the feeling of isolation and</p> <p>10 stigmatism, particularly for healthcare settings that</p> <p>11 are outside of the typical CF team.</p> <p>12 And indeed, patients I think complain</p> <p>13 that procedures and surgeries are often scheduled at</p> <p>14 the end of the day or postponed unnecessarily in some</p> <p>15 cases because of this contact precaution status, which</p> <p>16 results in prolonged fasting. It really can be a</p> <p>17 problem for those with CF-related diabetes. Next</p> <p>18 slide.</p> <p>19 So what about the burden of getting</p> <p>20 sick? So we know these bacteria are down in the</p> <p>21 lungs, and what I'm showing you here is, this is a</p> <p>22 graph showing us the number of pulmonary exacerbations</p>	<p style="text-align: right;">Page 133</p> <p>1 months in the need for IV antibiotics in this</p> <p>2 population, which was very, very encouraging. We</p> <p>3 don't see it as notably in the pediatric population,</p> <p>4 because the medication was only approved initially for</p> <p>5 12 and up.</p> <p>6 Then of course we have COVID coming on</p> <p>7 the scene in March of 2020, which led to a further</p> <p>8 decrease in both populations now of IV antibiotic use,</p> <p>9 and that of course is partially a result of social</p> <p>10 distancing and more universal masking. Next slide.</p> <p>11 And then this slide is just to catch us</p> <p>12 up on what happened last year. And really last year</p> <p>13 is a continuation of the really good pattern we saw</p> <p>14 early in the in the pandemic after the approval of</p> <p>15 elexacaftor/tezacaftor/ivacaftor, which is only 14</p> <p>16 percent of adults needing IV antibiotics last year,</p> <p>17 only 10 percent of children which are markedly reduced</p> <p>18 from the rates seen pre-pandemic.</p> <p>19 Likewise, we have this chart here.</p> <p>20 This is based on surveillance respiratory cultures</p> <p>21 that were done in 2019 and then compared to those done</p> <p>22 last year, again from our patient registry. And we</p>

<p style="text-align: right;">Page 134</p> <p>1 see encouraging trends that there may be less 2 infections being detected with -- in terms of these 3 key bacteria for us and non-tuberculous mycobacteria 4 when you compare the two years.</p> <p>5 However, there are two caveats to this, 6 which is our clinic attendance and therefore 7 surveillance culture data has not returned to pre- 8 pandemic levels. So we are -- we have a sampling 9 bias. There are less cultures being collected. And 10 secondly, because of the new medication, many people 11 with CF are living healthier lives, having less cough 12 and sputum, and therefore the cultures that we are 13 getting, they may be more oropharyngeal or throat 14 swabs because patients cannot cough up sputum on 15 command during their visits. So we take these data 16 with a grain of salt, but some encouraging trends. 17 Next slide.</p> <p>18 But still, infection remains a deep 19 concern for our community and this -- and many 20 patients express to me that they are afraid that they 21 will run out of antibiotic choices over the course of 22 their lifetime due to resistance and due to repeated</p>	<p style="text-align: right;">Page 136</p> <p>1 pseudomonas also on non-tuberculous mycobacterium, and 2 then multiple organisms accounting for another body of 3 funding. And more recently, really also interested in 4 bacteriophage therapy. Next slide.</p> <p>5 So we have many unanswered questions 6 when it comes to the infection landscape in cystic 7 fibrosis, but I hope I've convinced you that during 8 the pandemic time period with the approval of the 9 transformative new therapy, things are looking up for 10 our population. But questions remain and one of those 11 would be with less antibiotic use, if this trend 12 continues, will we see less antimicrobial resistance 13 in our population?</p> <p>14 Secondly we're all very concerned about 15 the impact of masking. I think it has had a positive 16 impact on the incidence of pulmonary exacerbations. 17 And we're -- you know, I think it would be quite 18 beneficial to continue masking in healthcare settings 19 for the protection of our community.</p> <p>20 And then lastly, with less -- if people 21 are healthier with CF, if they're lucky enough to be 22 on this therapy and are benefiting, they're not</p>
<p style="text-align: right;">Page 135</p> <p>1 use of oral, inhaled, and intravenous antibiotics.</p> <p>2 So we conducted a survey in quarter 3 three of last year asking the patients and families in 4 our community what they're -- what they saw the CF 5 Foundation's priorities in the field of infection- 6 related research. And not surprisingly, the top one 7 here was the development of new treatments. And 8 again, that's to answer that concern about 9 antimicrobial resistance.</p> <p>10 Also optimizing current treatments was 11 notable in the top three, and then again improving 12 detection and diagnosis, which I would argue is 13 becoming even more important now that less individuals 14 are coughing up sputum cultures. Next slide.</p> <p>15 So in our research portfolio that we 16 fund at the CF Foundation, we're trying to mirror our 17 community's priorities, and this you can see is the 18 number of studies that we are funding divided up into 19 those in industry, those in academics, and looked at 20 over time and by pathogen type.</p> <p>21 And what we can see is that really 22 heavy emphasis, not surprisingly, on the burden of</p>	<p style="text-align: right;">Page 137</p> <p>1 coughing and having as much sputum. Will their 2 pathogens be as transmissible and will there be a 3 point at which we can revisit infection control 4 practices and allow people with CF to be safely 5 together in person?</p> <p>6 These are very provocative questions 7 and really they're going to take time to answer. And 8 to get these answers, we're going to continue to 9 perform surveillance respiratory cultures. We're 10 going to continue to collect clinical data in our 11 registry. And we're going to continue to invest in 12 infection-related research. Thank you.</p> <p>13 TIMOTHY BENSMAN: Thank you, Dr. Brown. 14 We'll now hear from Ms. Jeanine Thomas on the 15 aftermath of living with having healthcare-associated 16 infections. Ms. Thomas was the first patient advocate 17 to raise the alarm concerning methicillin-resistant 18 staph aureus and healthcare-associated infections in 19 2002 and founded the MRSA Survivors Network in 2003. 20 She's a survivor of MRSA sepsis and C. difficile. Ms. 21 Thomas, the floor is yours.</p> <p>22 JEANINE THOMAS: First, I would like to</p>

<p style="text-align: right;">Page 138</p> <p>1 commend and give gratitude to the healthcare workers 2 who have worked tirelessly and selfishly through the 3 last couple of years to save patients from COVID-19. 4 Your commitment to save patients from COVID is highly 5 appreciated and all the sacrifices that you made from 6 yourself and from your family. We applaud you. 7 The healthcare system was pushed to its 8 limit and beyond, but now we have more protocols in 9 place that can combat healthcare-acquired infections 10 and so many more patients now know what a nasal swab 11 is and how it can help them from acquiring an 12 infection. 13 It has been over 20 years since I was 14 infected with MRSA. My story is like many patients 15 who came into a hospital for surgery that should have 16 not been life threatening and ended up fighting for 17 their lives and were forever changed by this 18 experience. The sad thing is that now we have soaring 19 rates of MRSA infections. 20 My journey started in December of 2000 21 when I slipped on black ice and fractured my ankle. I 22 had multiple fractures and -- which required a plate</p>	<p style="text-align: right;">Page 140</p> <p>1 could not. My body was shutting down. I didn't want 2 to die. I still had more -- so many more things to do 3 in life. My culture had come back positive for MRSA, 4 but when I was not given vancomycin, so the broad- 5 spectrum antibiotic was not working on me. 6 On the fifth night of being in the 7 hospital, I suddenly woke up in the night and the 8 night nurse was checking my temp and laid the box on 9 my chest. I happened to see for a second the digital 10 readout, 105. I thought, oh my God, no wonder I'm 11 burning up. I heard the nurses screaming in the hall 12 to page my doctor and then carts rattling down the 13 hall as they worked on trying to save me. I was near 14 death. 15 I had a near death experience, the one 16 you had when you were close to crossing over. I felt 17 relieved that I was not burning up anymore and a 18 serene calmness came over me. I saw the nurses 19 working on me and they were very distraught and 20 anxious. I wanted to tell them that I was going to be 21 -- not going to die, that I was going to be okay. It 22 was not my time.</p>
<p style="text-align: right;">Page 139</p> <p>1 and two screws. During surgery, I was infected with 2 MRSA and it went into my bone marrow giving me 3 osteomyelitis and later it would be sepsis. 4 I went home a couple of days after 5 surgery and was recovering, but then I began to feel 6 nauseous but didn't have a fever. I paged my surgeon 7 and he said, come to the ER. And of course, it was a 8 Friday night. When the doctors took my cast off, my 9 - I was horrified by the sight and smell of my leg. I 10 could not have surgery that night because I had eaten 11 during the day. 12 The next day, I had surgery and I don't 13 remember it. By then, I had a high fever and was in a 14 lot of pain and sedated. The next few days were also 15 a blur and I had another surgery to clean the wound 16 and I could no longer speak or communicate with 17 anyone. I knew I was gravely ill and I felt that I 18 was dying, and I don't know why the staff didn't 19 realize that because I know sepsis is hard to 20 diagnose. 21 I was burning up with fever. I felt 22 utterly helpless and afraid, desperate to speak but</p>	<p style="text-align: right;">Page 141</p> <p>1 I was finally given vancomycin. I 2 remember being semiconscious later the next day. I 3 could not open my eyes. Later I could not even see 4 anything. All I saw was dark gray. I did not know if 5 I was alive or in some other space of time or reality. 6 I could hear faintly voices around me. I fought as 7 hard as I could to open my eyes and I was able to for 8 a second. I knew that I was alive but would find out 9 later that I was septic and had the beginnings of 10 multiple organ failure. 11 The next few weeks were a blur of 12 surgeries and unbearable pain as they tried to save my 13 leg from amputation. I spent Christmas in the 14 hospital and finally my infection stabilized. I went 15 home and did not recognize myself. I had lost over 30 16 pounds and I had no color in my skin, so sickly 17 looking with excruciating pain and total fatigue. 18 I had a couple of more surgeries on my 19 leg but was not able to have a bone, muscle, or skin 20 graft. I then developed C. diff which was another 21 trip to the ER and more antibiotics. I was on a 22 cocktail of antibiotics for many months and after a</p>

<p style="text-align: right;">Page 142</p> <p>1 year I had the hardware taken out. I was diagnosed 2 and treated with posttraumatic stress disorder and 3 depression. I never had these disorders before. 4 Over the next couple of years, I would 5 have fevers, more antibiotics and feel like I was just 6 surviving. I would have breakouts and I was 7 constantly vigilant and I was the lucky one, though. 8 I had survived, though the pain was so increased in my 9 leg that many times I wish that they had amputated it. 10 But I was wondering how could I have died nearly from 11 ankle surgery. There was barely any information about 12 MRSA on the internet. 13 In 2003, I founded my organization MRSA 14 Survivors Network to educate and raise the alarm to 15 the epidemic and we also established the first crisis 16 hotline in the U.S. I worked with former Illinois 17 State Senator Barack Obama to pass the Hospital Report 18 Card Act to mandate MRSA and other HAIs be publicly 19 reported. 20 It was the first legislation of its 21 kind in the U.S. I was placed on an Illinois State 22 advisory board and saw that more needed to be done and</p>	<p style="text-align: right;">Page 144</p> <p>1 immunocompromised. 2 For many, MRSA and HAIs are a 3 dehumanizing experience and diminishes a person's 4 personal health. I know I felt like a leper. And we 5 also lose our wellbeing, quality of life, and for so 6 many, financial futures. There's still a stigma for 7 MRSA patients and this we've worked very hard at but 8 it still is acquiring this. 9 If we have learned anything from COVID, 10 the pandemic, it is the screening is essential along 11 with contact precautions, contamination -- 12 decontamination, strict hygiene, and more. More 13 healthcare facilities suspended screening for MRSA and 14 reporting infection rates during the pandemic. MRSA 15 has proliferated into a bigger epidemic in the past 16 two years. 17 We must remember patient safety should 18 come first. It is time to laser focus needless pain 19 and suffering should not happen anymore. We patients 20 want a desire for superior antibiotics and therapies, 21 not inferior products. So we must invest in the 22 advanced technology, fully staffing of infection</p>
<p style="text-align: right;">Page 143</p> <p>1 initiated legislation, the MRSA Screening and 2 Reporting Act, which passed unanimously in Illinois 3 and enacted in 2007. It was the first in the country 4 and more states followed the legislation. 5 From this 50 -- the next couple of 6 years, 50 percent of the healthcare facilities were 7 screening high risk patients and infection rates were 8 dropping. My health over the years was never the same 9 and I have to be careful of contracting viruses and if 10 I do, I'm sometimes ill for several months. This is 11 very common with MRSA patients. 12 In 2015, I had a surgery and contracted 13 staph aureus and pseudomonas. I was devastated and 14 realized that very little had changed for patient 15 safety as SSIs are still very high and contamination 16 in healthcare facilities needed so much more 17 attention, along with other measures. 18 I contracted COVID-19 in February of 19 2020 and was seriously ill and had long time -- long 20 COVID for over a year. But I was able to heal myself 21 and have had two more COVID infections since then, and 22 of course I'm fully boosted. I am forever</p>	<p style="text-align: right;">Page 145</p> <p>1 control, along with continued training. 2 We can never get to zero, but we can 3 get close to that. So this should be our goal. 4 Remember, prevention saves lives. Thank you. Back to 5 the monitor. 6 TIMOTHY BEHSMAN: And thank you, Ms. 7 Thomas, for your story. The burden you bear is truly 8 humbling and something I think we will keep with us as 9 we work through this workshop. 10 We'll now begin presentations by our 11 public comment speakers. Our first speaker is Dr. 12 Michael Woodworth, who will talk about microbiome 13 approaches to treat colonization with antibiotic- 14 resistant bacteria. Dr. Woodworth is an assistant 15 professor of medicine, infectious diseases at Emory 16 University School of Medicine. 17 Dr. Woodworth's research is primarily 18 focused on the translational study of microbiome 19 therapies like fecal microbiota transplantation to 20 treat colonization with antibiotic-resistant bacteria 21 and leads two microbiome clinical trials as an 22 investigator with the CDC funded Prevention Epicenter</p>

<p style="text-align: right;">Page 146</p> <p>1 of Emory. Dr. Woodworth, the stage is yours.</p> <p>2 DR. MICHAEL WOODWORTH: Good morning,</p> <p>3 everyone. My name is Michael Woodworth. I'm an</p> <p>4 assistant professor at Emory University School of</p> <p>5 Medicine, and I'm excited to speak to you today about</p> <p>6 microbiome therapies to treat colonization with</p> <p>7 antibiotic-resistant bacteria. I'd like to thank the</p> <p>8 organizers for the opportunity to speak today.</p> <p>9 As talks have so clearly elaborated</p> <p>10 earlier today, antibiotic resistance is a true global</p> <p>11 threat and this is chiefly due to diminishing numbers</p> <p>12 of effective therapies. As an infectious disease</p> <p>13 physician, I frequently see isolates that are</p> <p>14 resistant to many if not all antibiotics on first</p> <p>15 round susceptibility testing, and this is a true and</p> <p>16 present threat.</p> <p>17 Others have said earlier that nothing</p> <p>18 in biology makes sense except in the light of</p> <p>19 evolution, and I would like to suggest today that</p> <p>20 nothing in antimicrobial resistance makes sense except</p> <p>21 in the light of colonization. Simply put, we must</p> <p>22 increase our focus on colonization to address the</p>	<p style="text-align: right;">Page 148</p> <p>1 day 36 by stool culture, proceeded to get an FMT. In</p> <p>2 this way, everyone in the study was eligible to</p> <p>3 receive up to two FMTs. What you can see in the</p> <p>4 observation column, is that five out of five</p> <p>5 participants who received a bowel prep but did not</p> <p>6 receive an FMT were still positive at day 36.</p> <p>7 Those patients who were randomized to</p> <p>8 start with an FMT or proceeded to get an FMT after an</p> <p>9 observation period, you can see that six out of ten of</p> <p>10 these participants were MDRO negative after one FMT.</p> <p>11 And of those who proceeded to get a second FMT, two</p> <p>12 out of three were MDRO negative at day 36.</p> <p>13 In a pooled analysis, eight out of ten</p> <p>14 patients who received at least one FMT were MDRO</p> <p>15 negative at their last stool culture. Shown in the</p> <p>16 time to event analysis in a Kaplan-Meier style plot,</p> <p>17 you can see that in the Y axis, the proportion of</p> <p>18 patients who had a positive MDRO stool culture. The</p> <p>19 green trace shows those patients who were randomized</p> <p>20 to start with FMT and the blue trace shows those</p> <p>21 patients who were randomized to start with an</p> <p>22 observation period followed by FMT at a later date.</p>
<p style="text-align: right;">Page 147</p> <p>1 mounting threats of global resistance.</p> <p>2 So then what can be done for patients</p> <p>3 who are colonized with multidrug or even pan-resistant</p> <p>4 organisms? And the honest answer is that today,</p> <p>5 nothing can be done for these patients, because there</p> <p>6 are no -- as outlined earlier today, intestinal</p> <p>7 microbial communities are well established as being</p> <p>8 critical to MDRO colonization resistance.</p> <p>9 So to further evaluate the safety and</p> <p>10 efficacy of directly applying these microbes in a</p> <p>11 procedure called fecal microbiota transplantation, we</p> <p>12 conducted a small clinical trial in renal transplant</p> <p>13 recipients who are colonized with MDROs after</p> <p>14 infection called PREMIX.</p> <p>15 This slide shows you the culture</p> <p>16 results from the first 11 patients who were enrolled</p> <p>17 and treated in PREMIX, and on the bottom five rows you</p> <p>18 can see the participants who were randomized to start</p> <p>19 with the bowel prep alone without an FMT followed by</p> <p>20 an observation cycle of visits.</p> <p>21 As you can see in the following</p> <p>22 columns, that all patients who were MDRO positive at</p>	<p style="text-align: right;">Page 149</p> <p>1 And what you can see is patients who</p> <p>2 were randomized to start with an FMT were those who</p> <p>3 were in MDRO negative first. Put in a slightly</p> <p>4 different way, all of those who were in the</p> <p>5 observation group were MDRO positive until they</p> <p>6 received an FMT.</p> <p>7 Now, because all patients in our study</p> <p>8 were eligible to receive an FMT, we had to turn to a</p> <p>9 different cohort of patients at Emory. This large</p> <p>10 cohort of over 4,000 renal transplant recipients</p> <p>11 contained 16 patients who would have been eligible for</p> <p>12 PREMIX, but were not enrolled and did not receive an</p> <p>13 FMT for any other reason. This group is shown in the</p> <p>14 purple trace. They're compared to our patients in the</p> <p>15 PREMIX study in the brown trace on the top, and what's</p> <p>16 shown on the Y axis is the proportion of agents who</p> <p>17 are free from MDRO infection.</p> <p>18 And what you can see is that the</p> <p>19 patients in the PREMIX study in the brown trace on top</p> <p>20 had a much longer time of being free from MDRO</p> <p>21 infection from the time of their initial eligibility.</p> <p>22 Now, this slide summarizes all of the</p>

<p style="text-align: right;">Page 150</p> <p>1 studies that have been published to date, evaluating 2 the safety and efficacy of FMT for MDRO 3 decolonization. And what you can see are strong 4 signals for efficacy, but the other signal that you 5 can see in this table is that none of these studies 6 were designed or conducted in the United States and I 7 believe that as a country, we're starting to fall 8 behind.</p> <p>9 So then how do we move beyond the crude 10 application of microbes to try to treat or even 11 prevent an infectious disease? Well, you may remember 12 that this was the humble beginning of vaccinology when 13 Edward Jenner applied a live virus to try to prevent 14 small pox in a small boy, and how far we've come in 15 vaccinology since that time, such that we could 16 develop an entirely novel vaccine within less than a 17 year of the emergence of a global pandemic.</p> <p>18 So then I had two suggestions for how 19 to accelerate the development of microbiome therapies 20 for MDRO colonization. First, we need to do the 21 studies. We need to design and conduct prospective 22 clinical trials of decolonization as an indication and</p>	<p style="text-align: right;">Page 152</p> <p>1 therapeutics. Thank you for your time and attention 2 and for the invitation to speak. Good morning 3 everyone.</p> <p>4 TIMOTHY BENSMAN: Thank you, Dr. 5 Woodworth. Our next speaker is Carl Genberg, who will 6 speak about Preventing Biofilm Fouling of Indwelling 7 Medical Devices to Reduce Healthcare-Associated 8 Infections and Antimicrobial Resistance.</p> <p>9 Mr. Genberg is a chief scientist and 10 development officer at N8 Medical. Mr. Genberg is 11 involved in the development and commercialization of 12 patented technology designed to prevent bacteria, 13 fungi, and viruses from forming biofilms on medical 14 devices and resulting healthcare-associated 15 infections. Dr. Genberg, the floor is yours.</p> <p>16 CARL GENBERG: Thank you very much. 17 Good morning. My name is Carl Genberg. I'm with N8 18 Biosciences, also known as N8 Medical. I'd like to 19 thank the organizers for allowing me to speak to you 20 this morning. I'll be speaking on three points: 21 HAIs, the role that biofilms play in HAIs, and how we 22 may prevent such biofilm-related HAIs with our</p>
<p style="text-align: right;">Page 151</p> <p>1 as a primary endpoint.</p> <p>2 Second, we must require data sharing 3 and open science for microbiome clinical trials.</p> <p>4 Almost everything that we've come to learn about the 5 human microbiome, much less interventional studies, 6 had its beginning in the Human Microbiome Project and 7 many of the sub-studies that followed. So much was 8 gained from an open data approach that we need to 9 carry this forward with academic and industry 10 partnerships going forward to accelerate the 11 translation of these therapies.</p> <p>12 Finally, in conclusion I would like to 13 point out that it was the boldness of the FDA to 14 exercise enforcement discretion in 2013 that really 15 facilitated and accelerated so much of what we've 16 learned since that time about the use of fecal 17 microbiota transplantation. So much has been gained 18 from secondary study of FMT for other indications 19 since that time. This is another one of these moments 20 when the FDA can again listen to public comment from 21 providers and patients and to facilitate more rapid 22 translation and development of microbiome</p>	<p style="text-align: right;">Page 153</p> <p>1 CeraShield coated medical devices potentially save 2 lives and billions of dollars in the process. Next 3 slide, please.</p> <p>4 Just as water may exist in various 5 physical forms, liquid, gas, and solid -- ice -- with 6 dramatically different properties, bacteria also exist 7 in two forms, free living single planktonic cells 8 which are highly susceptible to conventional 9 antibiotics and biofilms which are slime-like 10 aggregates of millions of CFUs of bacterial cells 11 which are highly tolerant of conventional antibiotics.</p> <p>12 Next slide.</p> <p>13 We are losing the war against HAIs. 14 The situation is likely to get worse. Most of the 15 funding efforts to date have gone to develop new drugs 16 to cure infections. We need to invest more 17 technologies to prevent colonization and infection. 18 Next slide.</p> <p>19 Twenty years ago, Dr. Bell highlighted 20 the need for a fundamental shift in thinking to focus 21 on biofilm-related infections. New technology, our 22 biofilm-resisting coating called CeraShield, now makes</p>

<p style="text-align: right;">Page 154</p> <p>1 that possible. Next.</p> <p>2 It has been observed in the recent</p> <p>3 literature that one factor that's been consistently</p> <p>4 overlooked in these types of discussions is biofilm.</p> <p>5 Biofilm fouling accounts for 65 percent of hospital</p> <p>6 acquired infections. According to the NIH, HAIs add</p> <p>7 \$30 billion annually to the annual healthcare</p> <p>8 expenditures in the U.S. Next slide.</p> <p>9 FDA has also called for a focus on</p> <p>10 preventing infections and the best way, according to</p> <p>11 Dr. Gottlieb, to prevent a resistant microbe from</p> <p>12 becoming resistant was to prevent patients from</p> <p>13 getting infection in the first place. Next slide.</p> <p>14 Biofilms are responsible for over half</p> <p>15 in some cases 65 percent of all HAI bacterial</p> <p>16 infections such as VAP, CAUTIs, urinary tract</p> <p>17 infections, and surgical site infections. The biofilm</p> <p>18 growth on these medical devices in the case of gram-</p> <p>19 negative pathogens secrete endotoxin and these</p> <p>20 endotoxins lead to inflammatory cytokine cascade</p> <p>21 driven primarily by IL6. This can be prevented along</p> <p>22 with the adverse events that are associated with this</p>	<p style="text-align: right;">Page 156</p> <p>1 U.S., which may be largely preventable if new</p> <p>2 technology can prevent biofilm growth on endotracheal</p> <p>3 tubes. Next.</p> <p>4 We've developed a new technology based</p> <p>5 on insights from research and innate immunity,</p> <p>6 specifically the role of antimicrobial peptides as a</p> <p>7 first line of defense in the innate immune system. We</p> <p>8 have developed a lead compound CSA-131 which is active</p> <p>9 against all escape pathogens, fungi, lipid enveloped</p> <p>10 viruses, COVID, and monkeypox.</p> <p>11 There's been some very interesting</p> <p>12 discussion on the role of Candida auris. We co-</p> <p>13 published a study with CDC's Dr. Sean Lockhart on the</p> <p>14 activity of CSA-131 active against all tested isolates</p> <p>15 including pan-resistant. FDA has designated our</p> <p>16 device as a breakthrough device. It's already</p> <p>17 approved in Canada and Brazil and other countries in</p> <p>18 the near term. We're working with the NCDC in</p> <p>19 Tbilisi, Georgia for an upcoming VAP study in high</p> <p>20 risk patients where the VAP rates may exceed 50</p> <p>21 percent. Next.</p> <p>22 Prevention of VAP is a good first</p>
<p style="text-align: right;">Page 155</p> <p>1 type of cytokine cascade. Next.</p> <p>2 Dr. Donlan of the CDC's Biofilm</p> <p>3 Research Center has also opined that biofilm plays a</p> <p>4 key role in antimicrobial resistance and that</p> <p>5 antimicrobial concentrations sufficient to inactivate</p> <p>6 planktonic organism are generally inadequate to</p> <p>7 inactivate biofilm organisms. Next.</p> <p>8 Recent editorial in The Lancet, also</p> <p>9 focusing on the need to prevent infections in the</p> <p>10 first place. Next.</p> <p>11 Of the various infections, ventilator</p> <p>12 associated pneumonia is high incidence and high</p> <p>13 mortality and is the leading biofilm-related medical</p> <p>14 device infection. Within hours after intubation of</p> <p>15 the patient with an endotracheal tube, the surfaces of</p> <p>16 the tube begin to grow biofilm and these biofilm act</p> <p>17 as a reservoir in infectious disease, leading to VAP</p> <p>18 in some cases.</p> <p>19 A patient who develops VAP spends on</p> <p>20 average eight additional days mechanical ventilation</p> <p>21 in the ICU with an estimated cost of \$4,000 a day,</p> <p>22 total estimated cost of \$6.4 billion annually in the</p>	<p style="text-align: right;">Page 157</p> <p>1 target because it can have a dramatic impact on</p> <p>2 healthcare and expenditures as well. And this is a</p> <p>3 technology that is available worldwide at a reasonable</p> <p>4 cost because we'll be saving the share -- share the</p> <p>5 savings of what preventable cases of VAP lead to.</p> <p>6 Even in India, LMIC, we're looking at \$6,000 added</p> <p>7 costs for VAP.</p> <p>8 Money saved on treating VAP can be</p> <p>9 used, redirected to develop and purchase expensive</p> <p>10 antibiotics and to address other critical healthcare</p> <p>11 concerns. A solution that is only applicable in</p> <p>12 wealthy countries is suboptimal. We're dealing with</p> <p>13 an international crisis. Next.</p> <p>14 This is a scanning electron microscopy</p> <p>15 image of endotracheal tubes challenged with a</p> <p>16 combination of pseudomonas and Candida auris. On the</p> <p>17 lefthand side, you see dense biofilm. On the</p> <p>18 righthand side, with our coated endotracheal tube</p> <p>19 segment, you see clean surface. Next.</p> <p>20 Of critical importance is that the</p> <p>21 active is a mimic of antimicrobial peptides which has</p> <p>22 been in nature for millions of years. And serial</p>

<p style="text-align: right;">Page 158</p> <p>1 passaging studies show that CSA-131 does not induce 2 mutation resistance, even after 30 serial passages, in 3 contrast to colistin who's MICs rise above 300 and 4 close to 400. Next.</p> <p>5 We've done a small study in Canada with 6 Professor John Muscedere at Kingston General Hospital. 7 We looked at endotracheal tube aspirates from the 8 mechanically ventilated patients looking at bacterial 9 colonization and we dramatically reduced colonization 10 and of significant importance, not a single gram- 11 negative pathogen was detected. This compared to 12 historical controls from a prior published study, 13 looking at 75 and 80 percent even with a sub-glottic 14 suctioning device. Next.</p> <p>15 Ceragenins have broad spectrum activity 16 -- there are over 100 peer reviewed journal articles - 17 - active against all escape pathogens, MDR strains, C. 18 auris, Candida, aspergillosis, and lipid enveloped 19 viruses such as COVID-19 and monkeypox.</p> <p>20 When you're dealing with a lipid 21 enveloped virus, the virus mutates, the lipid does 22 not. So we expect that this would be broad spectrum</p>	<p style="text-align: right;">Page 160</p> <p>1 Trial Task Force for Diseases of the Elderly. Biofilm 2 prevention is highly cost effective and will 3 significantly reduce the need for antibiotic therapy 4 while potentially saving billions. Next.</p> <p>5 Thank you. I look forward to hearing 6 from you.</p> <p>7 TIMOTHY BENSMAN: Wonderful. Thank 8 you, Dr. Genberg, for the nice presentation. Our last 9 speaker is Dr. Christopher Lehmann who will talk on 10 the topic of Microbiome, Liver Transplant, and 11 Hospital Acquired Infections. Dr. Lehmann is an adult 12 and pediatric infectious disease clinical fellow at 13 the University of Chicago. His research is focused on 14 describing the interactions between stool microbiota 15 and multiple drug resistant organisms, as well as 16 identifying possible microbiome therapies to prevent 17 multidrug resistant infections. I'll now turn it over 18 to you, Dr. Lehmann.</p> <p>19 DR. CHRISTOPHER LEHMANN: Yes, thank 20 you for the introduction and thank you to the 21 organizers for inviting us to this presentation and 22 for putting the presentation together. Next slide.</p>
<p style="text-align: right;">Page 159</p> <p>1 in these viruses or the lipid enveloped viruses. 2 We're also developing this active as an inhaled drug. 3 given the presence of biofilm in cystic fibrosis 4 patients with support from the Cystic Fibrosis 5 Foundation.</p> <p>6 So this is able to prevent and 7 eradicate biofilm. Prevention on medical devices that 8 is a very low concentration. Also able to bind 9 endotoxin and sequester LPS and most importantly does 10 not induce mutational resistance. Next.</p> <p>11 Current drug developments are focused 12 on free living planktonic cells, acute infections. 13 However, more than half the problem is by biofilm and 14 conventional antibiotics are not effective. The only 15 way we can deal with this problem is to prevent the 16 growth on the first place. There's new technology, 17 CeraShield coating that has been developed and can 18 achieve this without inducing mutational resistance.</p> <p>19 We're about to start a large 800- 20 patients study in Canada, funded by governmental 21 agencies in Canada with Professor Muscedere as the 22 lead PI, who is the head of the Canadian Clinical</p>	<p style="text-align: right;">Page 161</p> <p>1 I have no disclosures to make it this 2 time. Next slide.</p> <p>3 Before we get into the microbiome 4 discussion, I just wanted to briefly mention liver 5 transplantation. You know, liver transplantation is 6 often the only curative therapy for many liver 7 diseases affecting many people and hospital acquired 8 infection is a very significant contributor to this 9 course, occurring in up to 25 percent of patients.</p> <p>10 These infections are very morbid and 11 oftentimes deadly. Further, these infections are 12 often linked to the microbiome. And then finally, you 13 know, we view this opportunity to study the microbiome 14 in this patient population but likely would be 15 generalizable to other patient populations reaching 16 thousands and thousands of people. Next slide.</p> <p>17 So to assess the microbiome in this 18 patient population and its contribution to infection, 19 we performed shotgun metagenomic sequencing of stool 20 samples in the postoperative period and we organized 21 them based on infection and no infection. Each 22 vertical column you see here is a single stool sample</p>

<p style="text-align: right;">Page 162</p> <p>1 collected from a patient and each color within each 2 vertical column is a unique organism. 3 You'll see immediately the dark green 4 color that represents enterococcus. The bright red 5 color that you see represents proteobacteria. This 6 contains the family Enterobacterales, things like E. 7 coli and klebsiella, and then many of the other 8 colors, the pinks, the cyans, the purples, and the 9 browns, these are obligate anaerobic bacteria that are 10 generally regarded as healthy members of the 11 microbiome. 12 If you look sort of in the middle of 13 the right side, you'll see some stool samples that 14 have sort of a rainbow of appearance of multiple 15 different colors of these anaerobes and these stool 16 samples would be the closest to what we would consider 17 to be normal microbiome. 18 And then finally at the bottom each one 19 of these colored squares, the green colored squares 20 represents an enterococcus infection and the red 21 colored squares represents an Enterobacterales 22 infection. And to determine the association between</p>	<p style="text-align: right;">Page 164</p> <p>1 be necessary for infection, it might not be sufficient 2 raising hypotheses that perhaps other residual 3 microbiota may be preventing infection and defending 4 these patients from infection. Next slide, please. 5 So to better determine the exact 6 association between the colonization, expansion, and 7 then subsequent infection, we created two receiver 8 operator curves with Enterobacterales and enterococcus 9 colonization and then associating that with infection. 10 And here we see a very strong association with areas 11 under the curve approaching 90 percent and then 80 12 percent for Enterobacterales. 13 We then optimized the cut point at the 14 degree of expansion necessary to highest predisposed 15 towards infection, and here we see that an expansion 16 at a level of between 5 and 6 percent is actually 17 associated with that significant increase in risk for 18 infection. While those 90 percent expansions are 19 impressive, perhaps the 5 percent threshold is what's 20 important. And finally at these thresholds we found 21 an odds for infection to be significantly elevated in 22 the expanded patient populations, reaching an odds</p>
<p style="text-align: right;">Page 163</p> <p>1 colonization and infection in this group, we ordered 2 these stool samples based on relative abundance of 3 enterococcus where on the far left you see stool 4 samples that have a normal microbiome essentially 5 completely replaced with a single organism of 6 enterococcus and then gradation from there. 7 And then if you draw your attention to 8 the enterococcus infection column, you'll see that 9 nearly every single enterococcus infection experienced 10 in our study occurred in patients who have expansion 11 of these enterococci within their stool microbiota. 12 Next slide, please. 13 We then did the same reordering, but 14 now focusing on Enterobacterales, and we see a similar 15 trend where Enterobacterales expansion sometimes even 16 complete domination of the microbiome occurs and is 17 associated with an infection caused by these 18 Enterobacterales. 19 The other thing that you may have 20 noticed is there are patients in the no infection 21 group who also experience expansion and domination 22 with these taxa, suggesting that while expansion may</p>	<p style="text-align: right;">Page 165</p> <p>1 ratio of up to 50 in the enterococcus group, and 2 again, that's a 50-fold increase in risk for 3 infection. 4 Now these numbers are somewhat 5 disconcerting in terms of risk for infection with 6 colonization, but if you flip this on its head and 7 view this as an opportunity where we can use 8 microbiome therapies to suppress expansion of these 9 taxa down below this 5 percent threshold, we have the 10 opportunity to reduce the risk for infection up to 50- 11 fold in these patients. And again that's a reduction 12 that would be really revolutionary compared to other 13 therapies with much less magnitude for benefit. Next 14 slide, please. 15 So next steps within our research 16 endeavors is to recognize that these organisms aren't 17 just existing within the colons and the stool of our 18 patient, but that these organisms are active. They're 19 doing things. They're competing with each other and 20 they're interacting with the host. 21 So here we looked at the microbiome 22 derived metabolites in the stool and you'll see here</p>

<p style="text-align: right;">Page 166</p> <p>1 on the top right of this figure, these are metabolites 2 that are enriched in our patients who managed to 3 escape getting infected. And while we don't have time 4 to discuss each of these individual metabolites, we 5 know that they are produced by the microbiome and many 6 of these compounds have been implicated in health. 7 Notably the top five on the right, indole, 8 desaminotyrosine, and tryptamine have been implicated 9 in boosting enterocytes mucosal barrier, inducing host 10 production of antimicrobial peptides, and then finally 11 immunomodulation and avoiding excess inflammation 12 within the gut. Next slide, please.</p> <p>13 So you know as we move forward on 14 understanding the relationship between the microbiome 15 and hospital acquired infections and multiple drug 16 resistant infections, these questions rise. Who are 17 they? How many? What are they doing? But I think 18 most importantly is how can we return to normal, how 19 can we suppress these pathogens back to low levels and 20 reestablish those anaerobic consortias, and at the 21 University of Chicago, the Duchossois Family 22 Institute, we are currently working on developing a</p>	<p style="text-align: right;">Page 168</p> <p>1 informative, and thoughtful which is no small feat 2 with the time restrictions you all faced.</p> <p>3 It's now time for the lunch break, so 4 feel free to answer the poll questions as it comes up, 5 but do rejoin us at 12:30 for Session 2 talks.</p> <p>6 (Break)</p> <p>7 DR. JOHN JERNIGAN: -- get started with 8 our first afternoon session which will be covering the 9 regulatory perspective and trial design challenges and 10 considerations. My name is John Jernigan, chief of 11 the Epidemiology Research and Innovations Branch in 12 the Division of Healthcare Quality Promotion at CDC, 13 and I'll be co-moderating this session along with Dan 14 Rubin from FDA and I'll turn it over to Dan now to get 15 it started. Dan.</p> <p>16 DR. DAN RUBIN: Good afternoon. My 17 name is Dan Rubin. I'm a co-moderator for this 18 session, and I'm a statistical team leader in the 19 Office of Biostatistics at CDER FDA.</p> <p>20 Our first speaker for this session is 21 Heidi Smith. Dr. Smith is a clinical team leader in 22 the division of anti-infectives in the Center for Drug</p>
<p style="text-align: right;">Page 167</p> <p>1 discrete healthy microbiome consortia using good 2 manufacturing practices that will engraft into our 3 high risk patients, will restore their microbiota, 4 will reestablish colonization resistance, will 5 suppress pathogen abundance, and will ultimately 6 prevent infection. And with that, thank you so much 7 for all of your time. Next slide, please.</p> <p>8 I'd like to thank the Duchossois Family 9 Institute, University of Chicago, my mentor Dr. Pamer, 10 and so many other mentors, collaborators who have 11 helped progress this work and are continuing to work 12 on those future projects. I thank the CDC and FDA for 13 organizing this presentation, this workshop, and to 14 all of the audience for your thoughts and 15 considerations. And with that, I will turn it back to 16 the moderators.</p> <p>17 TIMOTHY BENSMAN: Wonderful. Well 18 thank you, Dr. Lehmann for sharing some of your 19 clinical research findings. This concludes this 20 morning's session. Dr. Smith and I want to thank all 21 the speakers this morning for their excellent 22 presentations. They were very comprehensive,</p>	<p style="text-align: right;">Page 169</p> <p>1 Evaluation and Research at FDA, where she is involved 2 in the review and regulation of products intended for 3 the treatment and prevention of infectious diseases. 4 Over.</p> <p>5 Heidi, I think you're on mute.</p> <p>6 DR. HEIDI SMITH. Thank you. Double 7 muted. We can go ahead and move on to the next slide.</p> <p>8 All right, a brief outline of the 9 presentation. So I'm going to start with some context 10 on HAIs and the clinical context of what we'll be 11 covering, standards for approval. We'll delve into 12 the characteristics of adequate and well-controlled 13 trials and then go through some illustrative examples 14 of drugs to prevent surgical site infections, drugs to 15 reduce the incidence of catheter-related bloodstream 16 infections, and then talk a little bit about safety 17 database confederations. Next slide, please.</p> <p>18 So as was discussed in much more detail 19 this morning, healthcare-associated infections are 20 broadly defined as infections that develop while 21 receiving healthcare or shortly thereafter, and it 22 includes catheter associated bloodstream infections,</p>

<p style="text-align: right;">Page 170</p> <p>1 catheter associated UTIs, surgical site infections, 2 and ventilator associated pneumonia. 3 And as I've also noted the pathogens 4 responsible frequently develop antimicrobial 5 resistance. The drugs developed to prevent or reduce 6 the incidence of HAIs may have different clinical 7 development pathways. Next slide, please. 8 So before we talk more details about 9 the statutory standards for drug approval, it 10 sometimes helps to take a step back and recall where 11 these statutes came from. So this photo is actually 12 showing President Kennedy signing the 1962 amendment 13 to the food -- the federal Food Drug and Cosmetic Act, 14 and these were also known as the Kefauver-Harris 15 amendments. 16 They established the framework that 17 required drug manufacturers to prove scientifically 18 that a drug was not only safe but also effective. I 19 also like this picture because the only woman in the 20 room in this picture is Frances Kelsey, who was the 21 FDA medical officer who was very instrumental in 22 preventing thalidomide from coming to the market in</p>	<p style="text-align: right;">Page 172</p> <p>1 a valid comparison with a control in order to affect a 2 drug's effect. Next slide, please. 3 In the CFR, there's these seven 4 characteristics laid out of adequate and well- 5 controlled trials. These trials have a clear 6 statement of objectives and a proposed method of 7 analysis. They permit valid comparison with a control 8 so that a quantitative assessment of the drug's 9 effects can be made. They have a method of selecting 10 subjects that provides assurance that they have the 11 disease that's being studied or in the case of a 12 preventative treatment, that there's evidence of 13 susceptibility and exposure to the disease to be 14 prevented. 15 The method of assigning -- assignment 16 to study arm minimizes bias and is intended to ensure 17 comparability between the treatment groups. Measures 18 to minimize bias on the part of the subject, 19 observers, and analysts of the data are incorporated 20 into the trial design. There's a method for assessing 21 treatment response that's well defined and reliable. 22 And the analysis of the results is adequate to assess</p>
<p style="text-align: right;">Page 171</p> <p>1 the U.S. because she had over its data. Next slide, 2 please. 3 Okay, so what do these standards state? 4 So a drug's effectiveness must be established by 5 substantial evidence of effectiveness defined as 6 evidence consisting of adequate and well controlled 7 investigations including clinical investigations. And 8 this is generally interpreted as requiring two 9 adequate and well-controlled trials, each of which is 10 convincing on its own. 11 Now the Food and Drug Administration 12 Modernization Act amended the provisions to add that 13 the FDA may consider data from one adequate and well- 14 controlled clinical investigation with confirmatory 15 evidence. Next slide, please. 16 So let's talk a bit about the 17 definition of adequate and well-controlled trials. So 18 the purpose of these trials is to distinguish the 19 effect of the drug from other influences, spontaneous 20 change, placebo effect, observational biases, and the 21 Code of Federal Regulations describes the trial design 22 elements that are intended to minimize bias and permit</p>	<p style="text-align: right;">Page 173</p> <p>1 the drug's effect, the analytical methods used, the 2 comparability of the test and control groups, and the 3 effects of any interim analyses. 4 Next slide, please. Can I have the 5 next slide? Is it an anything on your end, because 6 I'm not seeing -- there we go. Perfect. Thanks. 7 That's the one. 8 So since adequate and well-controlled 9 trials has control, let's talk a little bit about some 10 different types of controls that we might see in these 11 trials. So, placebo concurrent control is a 12 comparison to an inactive preparation that's designed 13 to resemble the test drugs. A dose comparison 14 concurrent control has a comparison of at least two 15 different doses of a test drug. 16 A no treatment concurrent control has a 17 comparison of the test drug with no treatment, but it 18 usually still includes randomization and it's usually 19 only used in situations where the outcome measure is 20 objective and the placebo effect is negligible. An 21 active treatment concurrent control is a comparison 22 with a known effective therapy. And this is usually</p>

<p style="text-align: right;">Page 174</p> <p>1 used in situations where placebo or no treatment is 2 contrary to the interests of the patient. 3 It's worthwhile noting here though that 4 with this type of control, the similarity of the test 5 drug and the active control can mean either that both 6 drugs are effective or that neither drug was 7 effective. An analysis of the study should reference 8 the evidence for the effectiveness of the control. 9 And then finally, historical control of 10 the comparison with experience historically derived 11 from natural history of disease or results from active 12 treatment in a comparable population. This is usually 13 reserved for special circumstances such as diseases 14 with high predictable mortality or studies where 15 effect is self-evident. Next slide, please. 16 So trial endpoints. So these -- the 17 methods that are assessing the response to the drug 18 should be well defined and reliable and the endpoints 19 should be clinically meaningful. The most common type 20 of endpoint that we're dealing with is a clinical 21 endpoint, as referenced by Dr. Farley early on in the 22 workshop, these are characteristics or variables that</p>	<p style="text-align: right;">Page 176</p> <p>1 validated surrogate endpoint and this endpoint would 2 have data including some clinical trials and 3 epidemiologic studies that demonstrates its ability to 4 predict a clinical benefit. 5 Accelerated approval, on the other 6 hand, can be supported by adequate and well-controlled 7 trials establishing an effect on a surrogate endpoint 8 that is reasonably likely to predict clinical benefit 9 based on epidemiologic, therapeutic, pathophysiologic, 10 or other evidence or on the basis of an effect on the 11 clinical endpoint other than survival or irreversible 12 morbidity. 13 Now, in the case of accelerated 14 approval, this requires that the applicant study the 15 drug further, can vary and describe its clinical 16 benefit where there is uncertainty as to the 17 relationship of the surrogate endpoint to the clinical 18 benefit or the observed clinical benefit to the 19 ultimate patient outcome. 20 The FDA does maintain a public list. 21 Listed in -- the link is in the hyperlink at the 22 bottom of the side of surrogates that have been used</p>
<p style="text-align: right;">Page 175</p> <p>1 directly measure a therapeutic effect, the effect on 2 how the patient feels, functions, or survives. 3 It's important to note in the context 4 of what we're discussing today that medical biologic 5 outcomes are not clinical endpoints. 6 We can also use validated surrogate 7 endpoints. So these are endpoints that are supported 8 by clear mechanistic rationale as well as critical 9 data that provide strong evidence that the effect on 10 the surrogate predicts a specific clinical benefit. 11 Next slide, please. 12 So • 03:18:15 a little bit more detail 13 on surrogate endpoints. So as Dr. Farley had 14 mentioned, surrogate endpoints are used as a 15 substitute of a direct measure of our patients feel, 16 function, or survive. So they must be supported by 17 evidence that show that they can be relied upon to 18 predict a clinical benefit. 19 And in terms of approval based on 20 surrogate endpoints, there's two potential pathways. 21 Traditional approval can be supported by adequate and 22 well-controlled trials that establish an effect on a</p>	<p style="text-align: right;">Page 177</p> <p>1 as a basis of approval. We should note though that 2 the acceptability of these surrogate endpoints for use 3 in a particular drug development program is determined 4 on a case-by-case basis and it is context dependent: 5 the disease, the patient population, the mechanism of 6 action of the drug, and the availability of other 7 approved treatments. Next slide, please. 8 So trial objectives. The two primary 9 types of studies that we'll be evaluating are 10 superiority trial and this would be a study that 11 demonstrates efficacy by showing that the test drug is 12 superior to control. And generally this provides the 13 strongest evidence of effectiveness. 14 The other primary type of trial we 15 evaluated is non-inferiority trials and these 16 demonstrate efficacy by showing that the test drug is 17 not effective less effective than the active control 18 by more than a predefined amount or the NI margin, the 19 non-inferiority margin. But these types of trials 20 rely upon the assumption that's not confirmed in the 21 trial itself that the control had its anticipated 22 effect, which is the basis for the NI margin. Next</p>

<p style="text-align: right;">Page 178</p> <p>1 slide.</p> <p>2 So these are a couple illustrative</p> <p>3 examples starting with drugs to prevent surgical site</p> <p>4 infections or SSI. So did a compare and contrast two</p> <p>5 types of development programs, one for a topical</p> <p>6 antibacterial for staph aureus nasal decolonization</p> <p>7 and another for systemic antibacterial for peri-</p> <p>8 operative prophylaxis.</p> <p>9 So for both of these types of</p> <p>10 development programs, the trial endpoint is likely to</p> <p>11 be surgical site infection incident. But in the case</p> <p>12 of a topical antibacterial for staph aureus nasal</p> <p>13 decolonization, there's inconsistent data on whether</p> <p>14 nasal decolonization alone results in reduction in</p> <p>15 surgical site infection. So this is going to require</p> <p>16 an assessment relative to placebo, because there's no</p> <p>17 active comparator with demonstrated efficacy.</p> <p>18 In contrast, for systemic antibacterial</p> <p>19 for peri-operative prophylaxis, there's multiple</p> <p>20 trials demonstrating reduction in surgical site</p> <p>21 infection when peri-operative antibiotic compared to</p> <p>22 placebo or no treatment. This allows the</p>	<p style="text-align: right;">Page 180</p> <p>1 physical effects of the topical application of the</p> <p>2 product as well as blinding. Patient selection</p> <p>3 considerations would include potential enrichment for</p> <p>4 staph aureus carriers and surgical population, the</p> <p>5 highest risk of surgical site infection.</p> <p>6 Concomitant prophylaxis measures that</p> <p>7 should be controlled for would be things like timing</p> <p>8 and the type of skin decontamination and the use of</p> <p>9 systemic peri-operative antibacterials. Randomization</p> <p>10 could be cultural randomization by hospital or by</p> <p>11 surgical unit or by individual patients.</p> <p>12 Clinical endpoints. Primary endpoints</p> <p>13 would likely be incidence of surgical site infections,</p> <p>14 incidence of all infections due to staph aureus and/or</p> <p>15 mortality. And secondary endpoints that could be</p> <p>16 considered would include hospital length of stay,</p> <p>17 readmission rates, or reoperation rates. And the</p> <p>18 endpoint analysis is likely superiority of the</p> <p>19 treatment to placebo. Next slide, please.</p> <p>20 Looking a little bit deeper at systemic</p> <p>21 antibacterial for peri-operative prophylaxis to</p> <p>22 prevent SSI, there are multiple trials in the</p>
<p style="text-align: right;">Page 179</p> <p>1 justification of an NI margin that can be used for an</p> <p>2 active comparative controlled non-inferiority trial.</p> <p>3 Next slide, please.</p> <p>4 So going into a few more details,</p> <p>5 starting with the example of a topical antibacterial</p> <p>6 for nasal staph aureus decolonization. So the</p> <p>7 published literature regarding the clinical benefit of</p> <p>8 nasal staph aureus decolonization is not conclusive.</p> <p>9 Studies to date have not demonstrated a consistent</p> <p>10 outcome for the prevention of surgical site infection.</p> <p>11 Most of the studies reporting a clinical benefit have</p> <p>12 used bundled nasal and skin decolonization strategies</p> <p>13 so determination of the benefit of the nasal</p> <p>14 decolonization alone is not possible.</p> <p>15 Other limitations have included</p> <p>16 heterogeneity in the patient populations, differences</p> <p>17 in the reported endpoints and treatment effect, and</p> <p>18 variable methodological quality. Next slide, please.</p> <p>19 So some of the trial design</p> <p>20 considerations for the development of a product like</p> <p>21 this would include the choice of control would likely</p> <p>22 be a placebo vehicle which could control for the</p>	<p style="text-align: right;">Page 181</p> <p>1 published literature that demonstrated clinical</p> <p>2 benefit relative to placebo or no treatment in</p> <p>3 surgical procedures with high rates of infection,</p> <p>4 clean-contaminated or contaminated procedures.</p> <p>5 And one example from The Lancet in 1979</p> <p>6 is a randomized double blind placebo controlled single</p> <p>7 center trial where patients undergoing elective</p> <p>8 colorectal surgery were randomized to IV metronidazole</p> <p>9 or placebo dosed immediately prior to surgery and then</p> <p>10 repeated at eight and 16 hours. For both groups, the</p> <p>11 preoperative, bowel preparation was identical and the</p> <p>12 endpoint evaluated was the overall surgical site</p> <p>13 infection incident. They found 34 percent in the</p> <p>14 metronidazole arm and 77 percent in the placebo arm.</p> <p>15 Next slide, please.</p> <p>16 So there are multiple parenteral</p> <p>17 antibacterials that have been FDA approved with an</p> <p>18 indication for surgical site infection prophylaxis in</p> <p>19 clean contaminated and potentially contaminated</p> <p>20 procedures such as those listed here. Next slide,</p> <p>21 please.</p> <p>22 So the types of trial design</p>

<p style="text-align: right;">Page 182</p> <p>1 considerations for the development of a product like 2 this for a selection of a control, an active control 3 could be used for surgical procedures with established 4 efficacy in surgical site infection prevention. A 5 placebo control might be considered for procedures 6 without a demonstrated efficacy. 7 For patient selection, considerations 8 would include the type of surgical procedure, the 9 similarity to the population in which efficacy was 10 demonstrated by the comparator, as well as enrichment 11 strategies for patients at highest risk of surgical 12 site infections. 13 Concomitant prophylaxis measures could 14 include also timing and type of skin decontamination 15 as well as bowel prep. Randomization, again, could be 16 cluster or individual patient. Clinical endpoints, 17 likely incidence of surgical site infection and 18 mortality with consideration of secondary endpoints 19 for length of stay, readmission rates, and reoperation 20 rates. 21 Endpoint analysis would be superiority 22 to control or non-inferiority to an active control,</p>	<p style="text-align: right;">Page 184</p> <p>1 approved anticoagulant catheter lock solution 2 evaluating the antibacterial as add-on therapy or a 3 placebo control with a saline solution. 4 Patient selection. So take in account 5 factors such as the catheter type, whether it's a 6 long-term catheter or short-term catheter use, the 7 catheter function -- hemodialysis, nutrition, chemo 8 (indiscernible) -- and enrichment for patients at 9 highest risk of infection such as those who have past 10 history of infection, more frequent access of the 11 catheter. 12 Concomitant prophylaxis measures to 13 control for would be things like protocols for aseptic 14 technique, whether chlorhexidine-gluconate impregnated 15 sponges or other dressings are used, or 16 standardization of tubing changes. 17 And then clinical endpoints would be 18 catheter-related bloodstream infection incidence, 19 catheter loss, mortality. Consideration of secondary 20 endpoints to evaluate potential effects of clotting, 21 catheter patency. And then finally endpoint analysis 22 would be superiority to control. Next slide, please.</p>
<p style="text-align: right;">Page 183</p> <p>1 without adequate justification for the NI margin. 2 Next slide, please. 3 Then looking at a slightly different 4 illustrative example, we could look at an 5 antibacterial to reduce the incidence of catheter- 6 related bloodstream infections. So we could consider 7 an antibacterial, locally administered in a catheter 8 lock solution. So while there are FDA approved 9 catheter lock solutions that include saline solutions 10 that physically occupy the catheter space to provide a 11 hydraulic lock plus or minus an anticoagulant drugs to 12 reduce the incidence of clotting, and antibacterial 13 could be evaluated as an add-on to the catheter lock 14 solution containing saline plus or minus an 15 anticoagulant and compared to a control lock solution 16 that had an otherwise identical composition. Next 17 slide, please. 18 So the types of trial design 19 considerations for this type of product development 20 could include for selection of control, there's no FDA 21 approved antibacterial catheter lock solution, but 22 once they consider an active control with an FDA</p>	<p style="text-align: right;">Page 185</p> <p>1 Then finally safety database 2 considerations. Approval decisions requires both a 3 finding of substantial evidence of effectiveness and 4 the determination that the drug is safe for its 5 intended use. The benefits of the drug must outweigh 6 its risks under the conditions of use defined in the 7 labeling. 8 For drugs used as prophylaxis or 9 reduction of incidence of infection, the benefit may 10 only be experienced by a fraction of the treated 11 patients, that subset who would have developed the 12 disease without the prophylactic intervention. And in 13 these cases a larger safety database would generally 14 be required for a drug intended for prophylaxis of a 15 serious infection than a drug intended for treatment 16 of a serious infection. 17 And then finally, just to sum up what 18 we've talked about, products developed for prevention 19 of healthcare-associated infections can have diverse 20 modes of delivery and mechanism of action. The 21 approval of an indication for prevention of 22 healthcare-associated infection requires demonstration</p>

<p style="text-align: right;">Page 186</p> <p>1 of efficacy using a clinically meaningful endpoint or 2 validated surrogate and an adequate safety database to 3 determine whether the benefits of the drug outweigh 4 its risk for the use defined in the labeling. Thank 5 you. 6 DR. DAN RUBIN: Great. Thank you, Dr. 7 Smith, for that great review. Our next talk is 8 entitled Regulation of Healthcare Antiseptics and will 9 be presented by Dr. Theresa Michele. Dr. Michele is 10 currently the director of the Office of 11 Nonprescription Drugs in the Center for Drug 12 Evaluation and Research at the FDA. Among other 13 drugs, the ONPD is responsible for regulating 14 healthcare and consumer antiseptics. Dr. Michele. 15 DR. THERESA MICHELE: Thank you so much 16 and good afternoon, everyone. It's really a pleasure 17 to be here today as part of this important workshop on 18 prevention of healthcare-associated infections. Now 19 because topical antiseptics are often considered part 20 of the armamentarium of infection prevention tools, 21 it's useful to understand some of the background on 22 these products when considering development of new HAI</p>	<p style="text-align: right;">Page 188</p> <p>1 Next slide. 2 There are two different ways to bring 3 an OTC drug to market in the U.S.: the new drug 4 application and the abbreviated new drug application 5 or NDA and ANDA process, and then the OTC monograph 6 process. These two processes are quite different. 7 Patient preoperative skin preparations are actually 8 marketed under both processes. So under the NDA 9 process, which is how most prescription drugs come to 10 the market, an application for the drug is submitted 11 to FDA for approval and the application includes 12 information about the safety and effectiveness of the 13 drug, which you just heard about from Dr. Smith. 14 So the drug can't be marketed until FDA 15 approves that application for the drug. The NDA is 16 specific for a particular drug product including its 17 formulation, its dose, its use, and its labeling. In 18 contrast to the NDA process, an OTC monograph drug can 19 be marketed without FDA approval if the drug complies 20 with all of the requirements in section 505(g) of the 21 federal Food Drug and Cosmetic Act which was added by 22 the CARES Act as well as applicable conditions of its</p>
<p style="text-align: right;">Page 187</p> <p>1 prevention strategies. 2 So over the next 15 minutes or so I'll 3 be providing just a very high level overview of the 4 regulation of healthcare antiseptics which is a bit 5 more complicated than the typical prescription drugs. 6 Next slide. 7 This is the usual FDA Disclaimer. 8 So when we talk about antiseptics we 9 typically divide them into categories based on 10 indication which the -- with the two largest area is 11 being consumer antiseptics and healthcare antiseptics. 12 So for the purposes of today's talk, I'll primarily be 13 discussing patient preoperative skin preparations 14 which fall under the healthcare antiseptic category. 15 The other products in this category are primarily 16 intended to be used on the hands of healthcare 17 personnel, not on patients. 18 So despite the indication for use in 19 the healthcare setting, these are all nonprescription 20 drugs; although, the healthcare products are typically 21 marketed to hospitals and to clinicians in other 22 healthcare settings rather than to the general public.</p>	<p style="text-align: right;">Page 189</p> <p>1 therapeutic category-specific OTC monograph. That's a 2 mouthful, and we'll talk about what an OTC monograph 3 is exactly in just a moment. 4 So except for any final formulation 5 testing specified in the relevant monographs, a 6 manufacturer that's following the OTC monograph does 7 not need to provide safety and effectiveness data of 8 each individual drug product. This is because OTC 9 monographs established conditions including the active 10 ingredients under which an OTC drug is considered 11 generally recognized as safe and effective or GRASE, 12 and does not require FDA approval prior to marketing. 13 Next slide, please. 14 So what's a monograph? Well, an OTC 15 monograph is kind of a rule book. It lists the 16 conditions of each therapeutic category that describes 17 the active ingredients, the uses or indications, the 18 doses, route of administration, labeling, and testing 19 for an OTC drug to be recognized as GRASE. So drugs 20 that are GRASE and meet other requirements in Section 21 505(g) of the act can be marketed without a new drug 22 application and FDA premarket approval.</p>

<p style="text-align: right;">Page 190</p> <p>1 The monograph remains one of the 2 largest and most complex regulatory programs ever 3 undertaken at FDA. Over 100,000 different OTC drug 4 products are marketed under the OTC monographs in the 5 U.S. These monographs or rule books cover 6 approximately 800 different active ingredients for 7 over 1,400 different uses. Next slide. 8 This slide compares and contrasts the 9 two systems. I'll give you just a moment to look at 10 this and note that these slides are available on the 11 website after the presentation if you want to read 12 this in more detail. The most important takeaway here 13 is that the NDA process is product specific, while the 14 monograph process is therapeutic category specific. 15 So in order to qualify for monograph 16 status, a product has to fulfill all of the 17 indications laid out in the monograph in terms of its 18 active ingredients, indication, labeling, et cetera. 19 Now while certain flexibilities are permitted under 20 the monograph such as in inactive ingredients, if a 21 product differs in any way from the prescribed 22 monograph conditions, that product requires a product</p>	<p style="text-align: right;">Page 192</p> <p>1 are regulated in the United States. 2 OTC monograph reform changes the 3 process for revising, issuing, amending, and 4 finalizing OTC monographs from the three phase public 5 notice and comment rulemaking process to a new much 6 more facile administrative order process. The 7 administrative order process still involves public 8 comment and is still largely a public process. 9 Under the CARES Act, OTC monograph 10 healthcare antiseptics can continue to be marketed if 11 they follow the 1994 Antiseptics Tentative Final 12 Monograph, as further amended by the 2015 Health Care 13 Antiseptics proposed rule and other applicable 14 requirements. Next slide. 15 So currently all monograph active 16 ingredients require additional data to determine 17 whether they are generally recognized as safe and 18 effective or GRASE for use in healthcare antiseptics. 19 And we're currently working with manufacturers to help 20 ensure they provide the data necessary to make a GRASE 21 determination for these ingredients. 22 It's the manufacturer's responsibility</p>
<p style="text-align: right;">Page 191</p> <p>1 specific NDA or an OTC monograph order request to 2 change the monograph before it can be marketed. Next 3 slide. 4 Currently for patient preoperative skin 5 preparations, there are six active ingredients that 6 may be marketed under the monograph. These include 7 alcohol, povidone iodine, benzalkonium chloride, 8 isopropyl alcohol, benzethonium chloride, and 9 chloroxylenol. 10 Only single-ingredient products are 11 permitted under the monograph, and combination 12 products require an NDA. While it's possible to 13 submit an NDA for a product with any active 14 ingredient, currently the primary active ingredient 15 found in most NDA patient preoperative skin 16 preparations is chlorhexidine. Next slide. 17 Recently the monograph process 18 underwent significant changes. On March 27th of 2020, 19 the Coronavirus Aid, Relief, and Economic Security Act 20 or the CARES Act was enacted and the CARES Act 21 included important statutory provisions that reform 22 and modernize the way over the counter monograph drugs</p>	<p style="text-align: right;">Page 193</p> <p>1 to ensure that their products have been properly 2 tested, comply with applicable -- goodness -- comply 3 with applicable regulations and have inactive 4 ingredients that are safe and suitable for use in an 5 OTC healthcare antiseptic. Next slide. 6 So this is an example of some of the 7 labeling for a patient preoperative skin preparation. 8 Both NDA and monograph products carry similar 9 labeling. I show this to point out that the 10 indication for these products is for preparation of 11 the skin prior to surgery to help reduce bacteria that 12 can potentially cause skin infection. 13 Note that there are no approved 14 antiseptic products for the prevention of other 15 infections or for repeated use. Also note that the 16 products are intended for external use only on intact 17 skin, not in the eyes and the ears and the mouth and 18 the nose or in any other orifice. Next slide. 19 So testing for a preoperative 20 antiseptic is based on the labeled indication and use 21 which again is for use prior to surgery for the 22 reduction of bacteria on the skin that can potentially</p>

<p style="text-align: right;">Page 194</p> <p>1 cause skin infection. So efficacy testing for 2 preoperative antiseptics includes both in vitro tests 3 and in vivo simulation testing. Testing follows the 4 directions from for use, which I just showed you, and 5 these directions generally state to allow the product 6 to dry completely and do not rinse. 7 I'll review the required efficacy 8 testing in a moment, and while I'm not going to review 9 the safety data as part of this presentation, I do 10 want to point out that the data that we have and that 11 we have requested to support safety of these agents is 12 limited to this specific indicated use. 13 It's a common misperception that 14 because these antiseptics have been around for a very 15 long time and that they have a general indication that 16 data supporting approval is extremely broad, which is 17 just not the case. So testing of these products does 18 not currently include viruses, reduction of systemic 19 infections, or prevention of any specific infection, 20 repeated use, use over a large surface area, use in 21 infants and neonates where there are potential issues 22 with absorption, use on other than intact skin, use</p>	<p style="text-align: right;">Page 196</p> <p>1 ATCC reference strains followed by time kill testing 2 of each of the bacteria tested in the MIC or MBC. So 3 a complete list of these strains can be found in the 4 healthcare antiseptic proposed rule at the reference 5 listed on this slide. Next slide. 6 So products that show adequate in vitro 7 testing then go on to clinical simulation efficacy 8 studies. These studies are based on a surrogate 9 endpoint of the number of bacteria removed from the 10 skin rather than on a clinical outcome endpoint such 11 as reduction in the number of infections. 12 This simulation follows a prescribed 13 protocol with a single application of the product on a 14 dry skin site and a moist skin site such as the groin 15 or axilla which generally has higher numbers of 16 resident bacteria than the dry skin sites. The 17 primary endpoint compares the test product to both a 18 vehicle or negative control and a positive control, 19 and it must demonstrate a superiority margin of 1.2 20 log reduction over the negative control in both sites 21 after 30 seconds or 10 minutes. 22 In addition, the bacterial counts may</p>
<p style="text-align: right;">Page 195</p> <p>1 for pre-catheterization or any of a variety of other 2 uses that people use these things for. 3 This isn't to say that doctors cannot 4 use products in clinical practice for things that go 5 beyond the label. We all know this happens every day, 6 especially with these products. That falls under the 7 practice of medicine, which is not regulated by FDA. 8 What I just want everyone to be aware 9 of is the limitations of the data supporting approval 10 of these products, so that as we discuss options for 11 developing tools to reduce HAIs we consider what 12 additional information might be needed to provide 13 specific evidence to support drug approval for such 14 use. Next slide. 15 In vitro efficacy testing for 16 preoperative skin preparation antiseptics is designed 17 to demonstrate the product spectrum and kinetics of 18 antimicrobial activity by looking at the spectrum of 19 activity against recently isolated normal flora and 20 cutaneous bacterial pathogens. 21 Testing is generally for MIC or MBC 22 testing of 25 representative clinical isolates and 25</p>	<p style="text-align: right;">Page 197</p> <p>1 not exceed baseline at six hours. The use of the 2 surrogate endpoint of clinical simulation studies to 3 support this particular indication was discussed at a 4 public advisory committee which agreed with the 5 proposal. Next slide. 6 So this covers a very high overview of 7 the regulation of healthcare antiseptics in general 8 and preoperative skin preparations in particular. Now 9 I glossed over a lot of information so I would 10 encourage anyone who wants to take a deeper dive into 11 this topic to review the rule makings that I pointed 12 out earlier as well as our website on healthcare 13 antiseptics that's listed here. I'll also leave you 14 with some additional resources on related topics that 15 may be of interest, and I thank you very much for your 16 attention. 17 DR. DAN RUBIN: Thank you very much for 18 your presentation, Dr. Michele. Our next speaker is 19 Paul Carlson. Dr. Carlson is a principal investigator 20 in the Laboratory of Mucosal Pathogens and Cellular 21 Immunity, Division of Bacterial, Parasitic, and 22 Allergenic Products, Office of Vaccines Research and</p>

<p style="text-align: right;">Page 198</p> <p>1 Review in CBER, FDA. His researched FDA has focused 2 on infections caused by the enteric pathogens, 3 Clostridioides difficile and vancomycin-resistant. 4 Enterococci species as well as fecal microbiota 5 transplantation and bacteriophage therapeutics. Over. 6 DR. PAUL CARLSON: Hi. Thanks for the 7 introduction and for the invitation to speak today. 8 I'm not going to be talking about any of my research 9 today. I'm going to talk about regulation of these 10 particular product classes that we've lumped together 11 here to call microbiome based therapeutics. Next 12 slide, please. 13 Just my quick disclaimer. My comments 14 are my own. Slides are always approved, but anything 15 I say particularly later in response to questions will 16 not -- id not. 17 Quick outline. I'm going to go over 18 very briefly some aspects of IND or investigational 19 new drug applications that are relevant for these 20 products. And then I'm going to get into CMC 21 considerations for fecal microbiota transplantation or 22 FMT and live biotherapeutic products, both of which</p>	<p style="text-align: right;">Page 200</p> <p>1 develop. 2 So again CGMP has to be done because it 3 ensures that the drug is safe, has adequate identity, 4 strength, meets the quality and purity characteristics 5 that it purports or is represented to possess. 6 However, for Phase 1, CGMP is not the same as what it 7 might be for later phases. And really what this means 8 is you have to have some control over how you're 9 manufacturing the product. But can you manufacture 10 your Phase 1 material in a research laboratory? Yes. 11 Can you do it in my research laboratory with 12 enterococcus and C. diff floating around? No. 13 So, you know, there are ways these 14 things are done and we work with you as part of the 15 IND process and to work on manufacturing and ensure 16 that the product is going to be safe. Next slide, 17 please. 18 All right. So from here, I'm going to 19 move into CMC considerations for these two product 20 classes, starting with FMT. Next slide, please. 21 So this is a brief history of FMT at 22 the FDA, noting that I arrived in 2015 so I can't be</p>
<p style="text-align: right;">Page 199</p> <p>1 have been mentioned previously today. Next slide. 2 And so briefly, IND, as I said, 3 investigational new drug application exempts the 4 investigational drug from premarketing approvals. You 5 can lawfully ship it. Basically, if you want to use a 6 drug that is not licensed in people and as part of a 7 trial or for any other purposes you need an IND. Next 8 slide, please. 9 Our primary objectives throughout all 10 stages of this review is to assure the safety and 11 rights of the subjects that are part of the 12 investigation and in later phases to also include 13 evaluation of effectiveness and safety. Next slide, 14 please. 15 All right, so here's one of the key 16 questions that I get asked all the time. Do we need 17 to use CGMP manufacturing practices? Does it have to 18 be full CGMP? Do you have to pay the CMO, you know, 19 half a million dollars to get into Phase 1 and the 20 answers are yes and no. Everything has to be done 21 under good manufacturing practices; however, what that 22 means could change throughout the course of product</p>	<p style="text-align: right;">Page 201</p> <p>1 blamed for everything. Briefly here, and in May of 2 2013 the FDA and NIH called a public workshop that was 3 attended by just about everyone in the field or all 4 parts of the field were certainly represented. And at 5 this particular the workshop the FDA noted the use of 6 FMT and clinical studies to evaluate its safety and 7 effectiveness were subject to the regulation by FDA. 8 And I've heard a lot of people say in 9 2013 the FDA decided that no that's not how -- it's 10 always been this way. This is a drug. But this was 11 when it was made clear to everyone that INDs were 12 going to be required or have been required. 13 Now there were concerns from many 14 people regarding the situation with C. diff and the 15 use for C. diff and the ability to get an IND in and 16 for it to be allowed to proceed at a reasonable pace 17 and in the sheer number of INDS that would have been 18 coming in. 19 And so in 2013, we issued a finalized 20 guidance issuing a policy of enforcement discretion 21 regarding the IND requirements for use of FMT 22 specifically to C. difficile infections not responding</p>

<p style="text-align: right;">Page 202</p> <p>1 to standard therapies. This only applies to C. diff, 2 to treating C. diff that's not responsive to standard 3 therapies and not any other use of FMT. 4 All other uses still require an IND. 5 This guidance from 2013 is still in effect today and 6 this is still policy that we are functioning under. 7 We issued two draft guidances subsequent to that. 8 Neither of those have been implemented to date. First 9 one would have limited enforcement discretion to 10 situations where the donor is known to the doctor or 11 patient. We received many comments, took those into 12 consideration, and chose not to finalize that 13 guidance. 14 Additionally, in 2016 we issued a 15 guidance that would exclude stool from enforcement -- 16 product enforcement discretion if the stool was 17 obtained from a stool bank. So enforcement discretion 18 only applies to those not purchasing or obtaining 19 product from an entity that would be considered a 20 stool bank. Again, this has not been finalized to 21 date. Next slide, please. 22 All right. So how do we ensure the</p>	<p style="text-align: right;">Page 204</p> <p>1 right? What are the long term effects of these 2 products? And this is much harder to get at and 3 typically beyond the scope of a typical clinical 4 trial. 5 And then the last thing I have on your 6 side, we characterize these products as we're looking 7 for consistency. Are the organisms or consortia that 8 matter, specific functions that matter, what's a good 9 potency assay. And I can say, I don't think the field 10 knows the answers to all of these things right now and 11 the majority of the potency assays that we see are 12 still CFU per mil or per gram of product, and these 13 are estimates of potency because not everything is 14 going to grow on those plates. Next slide. 15 I think it's just holding the previous 16 slide. Next slide again, please. One more. Thank 17 you. 18 All right. So along with the concerns 19 about safety, we have had some safety alerts issued as 20 problems have arisen and infections have occurred. 21 This slide is actually out of date as of last week. 22 We added another one last week. But here you can see,</p>
<p style="text-align: right;">Page 203</p> <p>1 safety of FMTs? Imagine that this is -- this is a 2 challenging product to regulate or even to develop. 3 It's going to be variable depending on the donor and 4 the day, and also has potential significant risks 5 associated with it, primarily in terms of infections 6 that can be carried along with the product. 7 So we look at both intrinsic and 8 extrinsic safety. Our primary handle on safety here 9 is through donor and stool screening. So we need 10 questionnaires to -- and tests to ensure the health of 11 the donor. How often should they be tested? 12 Should we allow off site donations, is 13 one of the things that comes up frequently and I can 14 say right now we do not allow any offsite donations. 15 One, to ensure chain of custody, and two, to make sure 16 we're getting a full handle on the potential symptoms 17 that these individuals may have, particularly during 18 the COVID-19 pandemic. 19 Testing of stool. What should we test 20 for? How good our tests? These are both questions we 21 think about all the time and also research questions 22 in my lab. Intrinsic safety is a little harder,</p>	<p style="text-align: right;">Page 205</p> <p>1 had a safety alert regarding the transmission of two 2 ESBL E. coli infections from FMT into two individuals, 3 one of those two individuals did die as a result of 4 that infection and that led to changes in donor 5 screening that now require both exclusion of donors 6 that are at high risk for carriage of these, of 7 various MDROs and also direct testing for them. 8 Previously it had been one or the other. 9 The next alert after that was one I 10 believe was mentioned earlier also, where we had 11 instances of transmission of enteropathogenic E. coli 12 and Shigatoxin-producing E. coli. The 13 enteropathogenic E. coli, we did -- were not requiring 14 testing for prior to this. We now do, so that was the 15 change that that one pushed us towards. And the 16 Shigatoxin-producing E. coli one, it was an 17 interesting case because of course we require testing 18 for Shigatoxin and for STEC, but now we have to 19 require specific testing because in this case they 20 were testing by EIA and that missed the particular 21 case and so now it's required to be done by nucleic 22 acid amplification testing.</p>

<p style="text-align: right;">Page 206</p> <p>1 The next one was a couple of years ago</p> <p>2 we released the safety alert pertaining to the</p> <p>3 potential risk of SARS-CoV-2 virus being shed in stool</p> <p>4 and the potential -- it's known to be shed in stool,</p> <p>5 but the potential risk of that for FMT products, and</p> <p>6 so additional donor screening was required there.</p> <p>7 And then last week, for those of you</p> <p>8 who have been following this, we did release an</p> <p>9 additional safety alert regarding the potential risk</p> <p>10 of transmission of monkeypox virus after reports the</p> <p>11 virus being isolated from -- viable virus being</p> <p>12 isolated from stool of infected individuals and many</p> <p>13 instances of both rectal swab and stool samples being</p> <p>14 positive. Next slide, please.</p> <p>15 So this is going to be an ongoing and</p> <p>16 dynamic list as we move through time and as new</p> <p>17 pathogens emerge, but this is a list of donor</p> <p>18 screening -- potential donor screening recommendations</p> <p>19 that we published a couple of years ago. Now you can</p> <p>20 see in red that about the timing of when this was</p> <p>21 published, because those were added after. There's a</p> <p>22 long list of things here. Many of them are always</p>	<p style="text-align: right;">Page 208</p> <p>1 treatment, or cure of disease or condition of human</p> <p>2 beings -- so it's a drug -- and three, is not a</p> <p>3 vaccine. Next slide.</p> <p>4 So the CMC for these products needs to</p> <p>5 be such that we have sufficient information to ensure</p> <p>6 that we know what we're dealing with. We have proper</p> <p>7 identification, quality, purity, and strength of the</p> <p>8 drug. And then as development proceeds, we expect</p> <p>9 that that CMC information is going to increase. The</p> <p>10 detail is going to be greater and things like assay</p> <p>11 validations and things are going to be provided later</p> <p>12 on the process of drug development. Next slide.</p> <p>13 So this slide outlines some of the</p> <p>14 things that should be included as part of the CMC</p> <p>15 package for this type of drug. You need to know what</p> <p>16 the strain is that you're working with. Very simple</p> <p>17 and straightforward one. Where did it come from? Is</p> <p>18 there any information on strain and passage history,</p> <p>19 and note there, it says as available.</p> <p>20 You don't necessarily have to have</p> <p>21 this, but it's nice if we can understand where this</p> <p>22 strain is coming from and what the reason for</p>
<p style="text-align: right;">Page 207</p> <p>1 going to be required under every circumstance.</p> <p>2 Some things like say CMV are going to</p> <p>3 be required if we have concerns about the patient</p> <p>4 population. It's a challenging one because many</p> <p>5 people are seropositive but there are ways around that</p> <p>6 as well. Again, we added STEC by nucleic acid</p> <p>7 amplification, EPEC, and COVID later, and we have as</p> <p>8 of today not added a requirement for monkeypox</p> <p>9 testing, however I think that the addition of donor</p> <p>10 screening questions and risk assessment will be</p> <p>11 important in mitigating that risk. Next slide.</p> <p>12 This is just the paper that I mentioned</p> <p>13 from the table from the previous slide came from. So</p> <p>14 if anyone wants to learn a little bit more about that,</p> <p>15 it's just a slightly more extensive version of the</p> <p>16 presentation I've just given here. Next slide.</p> <p>17 So now we're going to move on to live</p> <p>18 biotherapeutics. Next slide.</p> <p>19 And live biotherapeutic for the case --</p> <p>20 for this presentation as defined by CBER is a product</p> <p>21 that contains live organisms such as bacteria, not</p> <p>22 limited to bacteria, is applicable to the prevention,</p>	<p style="text-align: right;">Page 209</p> <p>1 including it the product is, and any relevant genotype</p> <p>2 or phenotype of information, and ideally you're going</p> <p>3 to have a full genome sequence of your organism.</p> <p>4 That's so cheap to do these days that there's really</p> <p>5 no reason that you wouldn't expect that a sponsor</p> <p>6 would have that information.</p> <p>7 We also need to know the antibiotic</p> <p>8 resistance profiles for clinically relevant</p> <p>9 antibiotics both by MIC and potentially looking in the</p> <p>10 genome to see if there's anything of concern. But in</p> <p>11 the end, it's really the phenotypic evaluation, so we</p> <p>12 know what drugs are available to treat these things in</p> <p>13 the event of a breakthrough infection.</p> <p>14 We need information on the cell banking</p> <p>15 systems. Master cell banks, working cell banks,</p> <p>16 research cell banks, et cetera. Description of the</p> <p>17 drug substance and drug product manufacturing</p> <p>18 processes. In these cases a lot of times one product</p> <p>19 has many substances. If you have 5, 10, 15, 100</p> <p>20 strains in the product, each one of those might be</p> <p>21 individual drug substance that is then combined into</p> <p>22 your final drug product.</p>

<p style="text-align: right;">Page 210</p> <p>1 We'll need stability data on your 2 product. This is also required for FMT despite the 3 fact that I didn't mention it earlier. We need to 4 know that the product is stable throughout the course 5 of the trial that you are planning and that you're not 6 going to have any issues with, you know, product dying 7 off, right.</p> <p>8 Just like FMT, you need a potency 9 assay. Also like FMT, many times the potency assay 10 for these things is going to be a measurement of total 11 viable cells. In this case, you can tailor that assay 12 to the strains that you're working with, perhaps get 13 more accurate numbers. I do want to note there for 14 multi-strain products you will need to be able to 15 enumerate all strains.</p> <p>16 And this is an instance of where I'm 17 talking about the CMC information that's required 18 increasing over time. In Phase 1, going to need to 19 show that they're all there and have a big picture 20 measure of overall potency. But as we move into Phase 21 3, you're going to need to be able to enumerate the 22 individual strains in your product and provide potency</p>	<p style="text-align: right;">Page 212</p> <p>1 definition of LBPs when they're being used to treat a 2 disease. You might get it off the shelf. They're 3 meant for safe -- or for healthy populations, not for 4 sick individuals. And so in those instances, we need 5 to have an IND and we need to have the information -- 6 sufficient information to product under IND. Next 7 slide.</p> <p>8 Because there were challenges getting 9 that information and often, you know, the manufacturer 10 is not going to be the sponsor of these INDs and the 11 manufacturer frequently doesn't have incentive to 12 provide the information that we're looking for, we do 13 have a method for getting a waiver from the 14 requirements for CMC information and I'll outline that 15 in this slide and the next slide here, but -- so if 16 you had an IND that's utilizing a commercial product, 17 you can request a waiver and it will or will not be 18 granted.</p> <p>19 If it's not granted, then you have to 20 provide full CMC. If it is, then you just have to 21 provide the label of product. And on the next slide, 22 I will tell you how you get that waiver.</p>
<p style="text-align: right;">Page 211</p> <p>1 information on each of them and that can get 2 complicated, admittedly, as the product size grows.</p> <p>3 Any additional information on 4 biochemical or physiochemical properties of the 5 product can be provided as part of potency assays and 6 will be reviewed as such. Bioburden testing will be 7 required in these cases. These are done typically 8 under USD Protocols 61 and 62 looking for extraneous 9 undesirable bacteria.</p> <p>10 And then additional testing may be 11 required depending on the intended population. 12 They're at high risk for infection for some reason, 13 and any other organisms that are manipulated in the 14 same facility. Again, coming back to my lab as the 15 extreme example, working with C. diff and VRE would 16 not be a good thing for product manufacturing. Next 17 slide.</p> <p>18 All right. So we updated our guidance 19 on LBPs in 2016 to account for commercially available 20 products and the challenges that sponsors were having 21 in getting the CMC information. So commercially 22 available products, probiotics, do in fact fit the</p>	<p style="text-align: right;">Page 213</p> <p>1 So the waiver will be granted -- may be 2 granted if all four of the following conditions are 3 met. So the product and the proposed investigational 4 use -- the product for proposed investigational use 5 must be lawfully marketed as a conventional food or 6 dietary supplement. So it's commercially available. 7 Step one.</p> <p>8 Step two, the route of administration, 9 dose, patient population, or other factors does not 10 significantly increase the risk. It's a pill and the 11 label says you say one per day, then that's what 12 you're going to do in your trial, then you're probably 13 okay as long as there's no reason to be concerned 14 about your patient population.</p> <p>15 The investigation is not intended to 16 support a marketing application of the live 17 biotherapeutic as a drug or biologic product for human 18 use in the future. So this is for research studies, 19 clinical research studies only.</p> <p>20 And then finally, the investigation is 21 otherwise conducted in compliance with IND 22 requirements. And then you can get the waiver and</p>

<p style="text-align: right;">Page 214</p> <p>1 provide us with the label of the product and your 2 clinical trial plan as well as part of your IND, and 3 then you will likely be able to proceed. Next slide. 4 All right, and those things are 5 outlined in this paper that was published a few years 6 ago now in Microbiology Spectrum and some more 7 details. It's really a summary of more up-to-date 8 current thinking regarding the things that are in that 9 guidance document. Next slide. 10 All right. And I will end here with 11 some final thoughts. I think you know this meeting 12 the microbiome and microbiome-based products have been 13 mentioned many times. There are many meetings 14 addressing these things around the country and around 15 the world frequently, so I think it's very safe to say 16 interest in these products is increasing, has 17 increased greatly, and will continue to do so. 18 And they -- from our perspective, 19 CBER's regulatory approach to these products has been 20 science based and will continue to be science based 21 and we feel that we have allowed and will continue to 22 help sponsors get these novel approaches into the</p>	<p style="text-align: right;">Page 216</p> <p>1 and operational challenges for HAI prevention trials. 2 Next slide. 3 So there are some really important 4 common features of HAI prevention trials that are 5 fairly distinctive, and one is a general desire to 6 evaluate what's often a quality improvement strategy. 7 And when this occurs, it often has a group focus; that 8 is, quality improvement is usually applied at a unit 9 level, clinic, hospital, nursing home. Often in this 10 case for HAIs, it is targeting a contagious outcome 11 and it's generally spurred by an urgent common need. 12 Oftentimes, this is because of national 13 reporting requirements that bands hospitals and units 14 together to try to identify effective solutions and 15 therefore it's often under the jurisdiction of 16 operational implementation and that often means that 17 there are resource constrained funds. Next slide. 18 Another key distinction between the 19 difference of classical individual randomized control 20 trials and these types of pragmatic trials is that 21 pragmatic trials are targeting populations and they're 22 usually looking for effectiveness. That is, if any</p>
<p style="text-align: right;">Page 215</p> <p>1 clinic to be safely tested and hopefully moved on to 2 be approved therapeutics in the near future. Next 3 slide. 4 I will just leave this up for a minute. 5 This is just some additional resources. I think the 6 slides are all going to be available after the 7 meeting, too, so you can find these in my slide deck 8 after the meeting. And with that, I'll turn this 9 back over to the moderators. Thank you. 10 DR. DAN RUBIN: Thank you very much, 11 Dr. Carlson. Our next topic is Clinical 12 Considerations and Operational Challenges for 13 Prevention Trials and will be presented by Dr. Susan 14 Huang. Dr. Huang is professor in the Division of 15 Infectious Diseases at the University of California 16 Irvine School of Medicine and medical director of 17 Epidemiology and Infection control at UCI Health. Dr. 18 Huang has led several large randomized clinical trials 19 involving decolonization to prevent MDRO disease and 20 other HAIs across the continuum of care. Dr. Huang, 21 DR. SUSAN HUANG: Thank you. Thanks 22 for the opportunity to talk about design challenges</p>	<p style="text-align: right;">Page 217</p> <p>1 hospital were to adopt this, any clinic, how would 2 they be eight to be assured that this is a typical 3 response that they would see. 4 These trials are often minimal risk. 5 That means they employ controls that don't use 6 placebos and many times they will qualify for a waiver 7 of informed consent. Next slide. 8 One reminder about the difference of 9 these effectiveness types of trials versus efficacy is 10 they're not trying to demonstrate the effect of the 11 intervention under its best conditions. It's actually 12 trying to show what happens under typical conditions, 13 meaning the less selection of a population the better, 14 so everybody that comes into a unit, everybody that 15 comes into the emergency department, everybody that 16 comes into a nursing home. 17 And for that reason it can sometimes 18 lend itself towards an efficient type of recruitment. 19 You can recruit a number of sites that want to 20 participate and it also can use a lot of things that 21 are already in place. So operational infrastructure, 22 it can use staff that are already in place to produce</p>

<p style="text-align: right;">Page 218</p> <p>1 quality improvement campaigns.</p> <p>2 It can use compliance tables or reports</p> <p>3 that are already in place. And often it is trying to</p> <p>4 adopt learning while doing, so the learning health</p> <p>5 system rather than a compensated type of trial or a</p> <p>6 trial where you develop a whole infrastructure with</p> <p>7 staffing just to conduct the trial. Next slide.</p> <p>8 Targets for these types of populations</p> <p>9 can include, as I mentioned, these types of grouped</p> <p>10 locations but of course it can also include special</p> <p>11 populations. So this includes people who undergo</p> <p>12 surgical procedures, have specific medical devices,</p> <p>13 including those that have very specific chronic</p> <p>14 illnesses like people who are going to a dialysis</p> <p>15 center.</p> <p>16 This also applies to those who have</p> <p>17 multidrug-resistant organisms, so those that are</p> <p>18 tagged as carriers and of course those that can be</p> <p>19 followed post discharge for any number of reasons.</p> <p>20 Next slide.</p> <p>21 Often when you think about universal</p> <p>22 versus targeted populations, there are real pragmatic</p>	<p style="text-align: right;">Page 220</p> <p>1 individuals. You can recruit and randomize ICUs in a</p> <p>2 cluster randomized way. Those ICUs can just receive</p> <p>3 standard order sets or standard protocols that adopt a</p> <p>4 new practice. And usually the unit based surveillance</p> <p>5 are things that are normally being collected so</p> <p>6 hospital onset, multidrug-resistant organisms,</p> <p>7 bloodstream infections.</p> <p>8 And on the other hand, you could design</p> <p>9 a trial that would decolonize MDRO carriers. That is,</p> <p>10 you would find them with some sort of flag that's in</p> <p>11 the electronic health record. You then recruit them.</p> <p>12 You consent them. You randomize them. And then you</p> <p>13 follow them up on whether they're in the hospital or</p> <p>14 out for any sort of clearance or infection outcomes.</p> <p>15 Next slide.</p> <p>16 So depending on the question under</p> <p>17 study you can design your trial to be very, very</p> <p>18 temporary. That is, you find these high-risk periods.</p> <p>19 Some of these were mentioned in prior talks, and you</p> <p>20 can find these high-risk moments like being in an ICU</p> <p>21 or being in a nursing home, in a dialysis center, and</p> <p>22 you can focus all of your intervention right at that</p>
<p style="text-align: right;">Page 219</p> <p>1 considerations on how to actually roll out the</p> <p>2 intervention. When you do something in a group, a</p> <p>3 whole unit, a whole clinic, often it's easier to train</p> <p>4 and implement. These are changes in protocols and</p> <p>5 practices that are constantly occurring and usually</p> <p>6 institutions have a way in which we roll out new</p> <p>7 protocols and new adopted guidelines.</p> <p>8 Often these types of outcomes again are</p> <p>9 already tracked because many of them are under</p> <p>10 national reporting. Targeted populations, on the</p> <p>11 other hand, require either a flag in the medical chart</p> <p>12 or some sort of detection algorithm to find them. We</p> <p>13 then require some sort of way to track them to be able</p> <p>14 to reach them to find out whether or not they've</p> <p>15 actually had a good outcome, so detailed chart review,</p> <p>16 and many times if we're looking at longitudinal</p> <p>17 effects, then we require special sampling. Next</p> <p>18 slide.</p> <p>19 This is just an example of two</p> <p>20 different ways in which you can study decolonization.</p> <p>21 You can have a population target that's at a unit</p> <p>22 level. So this is a population of critically ill</p>	<p style="text-align: right;">Page 221</p> <p>1 moment.</p> <p>2 So when they leave those areas, the</p> <p>3 follow-up stops. And in those settings, because these</p> <p>4 areas generally have a high amount of staffing and a</p> <p>5 high ability to track, usual surveillance outcomes may</p> <p>6 suffice and may in fact be the actual outcome that is</p> <p>7 of high interest for changing during a quality</p> <p>8 improvement endeavor.</p> <p>9 On the other hand, you might be looking</p> <p>10 for something that is long standing. That is, you</p> <p>11 want to find something that is going to benefit this</p> <p>12 individual for a very, very long period of time, not</p> <p>13 just during this temporary high-risk period and then</p> <p>14 you need to follow them up post discharge in other</p> <p>15 clinics, sometimes have special home visits, and then</p> <p>16 of course either sample them, and this could include</p> <p>17 swabbing or blood draws or any other thing that would</p> <p>18 be required to demonstrate a benefit. Next slide.</p> <p>19 Often when you're doing these types of</p> <p>20 trials for reducing HAIs, it's really important to</p> <p>21 have health system partners. This can be important</p> <p>22 for recruitment. A lot of times health systems have</p>

<p style="text-align: right;">Page 222</p> <p>1 multiple sites that can be leveraged to actually have 2 efficient recruitment and often it's actually better 3 if the system leaders reach out and there's a rapport 4 that actually encourages participation in a trial. 5 It also means that health systems often 6 are asked to make special IT solutions. So they're 7 asked to either build reports to find certain people 8 who might have certain characteristics or certain 9 clinics with certain characteristics. They may be 10 asked to actually implement certain order sets or 11 adherence tracking reports and do feedback. And then 12 of course, system leadership may be very much asked to 13 avoid competing interventions at the time for the 14 duration of the trial. Next slide. 15 These trials, as I mentioned, often do 16 meet the rules for minimal risk and by both OHRP 17 guidance as well as FDA guidance, and one of the 18 questions that's going to be important when we think 19 about waiver of informed consent is who normally 20 consents in the first place. 21 For example if we're talking about a 22 soap that a hospital uses or even something as</p>	<p style="text-align: right;">Page 224</p> <p>1 a baseline before they enter into the intervention 2 period and that particular baseline for every hospital 3 allows it to account for unmeasured confounding; that 4 is, a hospital compared to itself probably has a 5 fairly stable population that they tend to see. 6 They have a fairly stable set of 7 providers. Those providers interact and prescribe a 8 certain way. They influence one another. So having 9 both a baseline period and then an intervention period 10 can be really, really helpful. 11 It's also important to have 12 contemporaneous controls. So a lot of times you want 13 controls at the same time as the intervention is 14 happening so that you can account for secular trends, 15 new changes in guidance, and so oftentimes you may 16 want to employ what's called a difference-in- 17 differences approach. That means you have two groups. 18 One is the control group. One is the intervention 19 group. Each of them compares its intervention period 20 performance to its own baseline performance. And 21 those differences are compared across the two groups. 22 Next slide.</p>
<p style="text-align: right;">Page 223</p> <p>1 significant as what drugs on the formulary, what 2 devices are implanted, what devices are used for 3 intubation, many times these types of things, central 4 lines, are not actually under the choice of the 5 patient. 6 The facility, the clinic, the hospital 7 actually chooses what they purchase. They have a 8 certain supply and those supplies are then used for 9 implantation as needed during the course of medical 10 care. Next slide. 11 Controls are really, really important. 12 It's going to be a big complexity as you think about 13 these types of trials that are not typical of the 14 individual randomized trial. If you're looking at 15 these types of group type of studies, that is looking 16 at let's say 30 hospitals, that's a pretty big sizable 17 trial for a group randomized trial, and yet you only 18 randomize 30 different individual sites. 19 So it's going to be important that you 20 have really important controls. You can imagine that 21 every hospital, every clinic is slightly different. 22 And so it may be particularly wise to have a baseline,</p>	<p style="text-align: right;">Page 225</p> <p>1 That is one way of course to address 2 confounders, and another way is to make sure that we 3 randomize well. This can be particularly challenging 4 when you're randomizing 30 hospitals instead of 30,000 5 people. When you are faced with having to randomize 6 that, it's really important that you use the methods 7 that are most unlikely to achieve balance in key 8 variables. 9 There are specialized approaches to do 10 this. We and others have published on this. We've -- 11 the one I highlight here is called the Goldilocks 12 approach and you basically take a whole bunch of 13 baseline characteristics or outcomes that are present 14 in your particular population, your hospitals, your 15 units, whatever you're going to use, your clinics, and 16 then you use those baseline values and you assign 17 specific weights to them based upon your clinical 18 judgment and then you run a whole bunch of simulations 19 of different ways in which you can randomize and you 20 look at the style of randomization scheme that 21 actually gives you the most likely chance that you 22 will always have balance.</p>

<p style="text-align: right;">Page 226</p> <p>1 And so if you use that a lot of times 2 you can push the button once and you can pick a schema 3 that actually maximizes your chance of having a 4 balanced draw. This is also important when you look 5 at analysis. Of course it's going to be important to 6 look at confounders, so in addition to the as- 7 randomized analysis, often as-treated or adjusted 8 analyses are going to be important. Next slide. 9 This is a particularly important 10 consideration for things that occur in acute 11 healthcare, but also in long-term care and these would 12 be competing interventions. We all know that 13 hospitals, clinics are incredibly driven to always 14 improve, and because of that, there are a myriad of 15 quality improvement activities that are being 16 launched, being maintained, and being dismantled at 17 almost any given time. 18 Because of that, if you have only 30 19 hospitals, for example, that are joining into a trial, 20 many of them have entirely different baseline 21 activities that are ongoing and the best way to handle 22 this of course is large scale randomization, which I</p>	<p style="text-align: right;">Page 228</p> <p>1 is important, but because of the issue related to 2 competing interventions, these types of trials really 3 favor larger, shorter trials. Most clinics and 4 hospitals and ICUs, emergency departments don't like 5 to be locked out from being able to do other things 6 that could improve care. 7 So, this idea of constant quality 8 improvement is a really big activity that pervades 9 through healthcare today. Same thing, often because 10 we're dealing with things that may be minimal risk, so 11 minimal trials often don't need a robust safety 12 assessment. They don't need an interim analysis and 13 that interim analysis would actually in fact prolong 14 trial time. Next slide. 15 Analysis. This is a really key area 16 that's going to be discussed better in the next talks. 17 I'm only going to say a few basic things, is that when 18 you have outcomes that are contagious or non- 19 independent you really do need to involve a 20 statistician who is well trained with expertise in 21 this particular area of clustering. And this ability 22 to handle clustering is not only important to</p>
<p style="text-align: right;">Page 227</p> <p>1 just said it's really difficult. Thirty hospitals is 2 already a huge trial. And the other way is to 3 addresses through a difference-in-differences 4 approach. 5 Another way though that's really 6 important is to really consider what happens during 7 the trial. And so many of the times it's going to be 8 critical for people who are pursuing HAI trials that 9 they actually have to monitor to make sure that new 10 interventions aren't being unleashed every other week 11 during the course of the trial. 12 A good example of this is the REDUCE 13 MRSA trial that we did. This is an ICU trial for 14 decolonization. And during the course of 18 months of 15 that particular trial, there were 69 hospital 16 interventions that were proposed during that time and 17 36 of them directly conflicted with the trial and 18 could not be pursued. So a lot of effort for 19 monitoring, dissuading, and managing dropout is really 20 important. Next slide. 21 Of course, sample size is very, very 22 important. Not only is it important because it always</p>	<p style="text-align: right;">Page 229</p> <p>1 determine the final outcome of the trial, but it's 2 really important when you're estimating sample size 3 and (indiscernible). Next slide. 4 So I'm going to give you two examples, 5 a similar example to the one that I said before. 6 These are two different trials. One, the CLEAR trial, 7 was individual randomized controlled trial of 2000 8 MRSA carriers who were being discharged. They were 9 discharged to either receive education and routine 10 care or they were discharged to receive education and 11 decolonization and that decolonization was repeated 12 for six months and then they were followed for a whole 13 year. So this was to prevent post discharge outcomes 14 of infection and their associated hospitalizations. 15 On the flip side is the REDUCE MRSA 16 trial. This is a cluster randomized trial of 43 17 hospitals and their ICU patients, so that amounted to 18 about 75,000 patients, and this was compared in three 19 groups: routine care, targeted, and universal 20 decolonization in the ICU only. And those outcomes 21 that were evaluated are things that are typically 22 available through the electronic health record and</p>

<p style="text-align: right;">Page 230</p> <p>1 normally being tracked, and that would be hospital 2 onset MRSA culture and bloodstream infections. Next 3 slide.</p> <p>4 So pretty different styles for these 5 two trials. One randomizes individuals and because of 6 that it takes a long time to find them, to identify 7 them, to see who's actually willing to be in a one 8 year trial. So it had a three year intensive 9 recruitment. The REDUCE MRSA trial randomized 10 hospitals in a big health system. It took an eight- 11 week period to recruit them because the system's 12 leaders were reaching out pretty strongly and 13 encouraging people that they knew to actually 14 participate in the trial.</p> <p>15 One required individual consent and 16 compensation. The other one waiver of informed 17 consent and no compensation being conducted usually 18 through the -- through the usual courses and through 19 the usual staffing related to hospital care. One 20 required extensive chart review so that after the 21 trial was finished there was still a two-year period 22 where charts were being garnered, redacted, evaluated</p>	<p style="text-align: right;">Page 232</p> <p>1 change on something that was shown to be very 2 effective against an old control. So knowing what the 3 controls are and having really specific guidelines for 4 them can be really important.</p> <p>5 A second thing that's highly relevant 6 for infection prevention is sometimes you have three 7 different trials and they all are targeting the same 8 exact outcome. They use the same exact set of 9 controls and they all find, let's say, a 20 percent 10 reduction in the outcome of interest. And so one of 11 the other key questions is then, do all of them need 12 to be performed or in fact, are they additive, are 13 they synergistic, or are they replaceable?</p> <p>14 And so there's a lot of questions when 15 we're talking about limited resources and also limited 16 time to train on whether or not these things really 17 are all -- all should be endorsed by upcoming 18 guidelines. Next slide.</p> <p>19 Another key thing related to this 20 entire workshop of course is how do we think about FDA 21 indications. Many times, these types of minimal risk 22 trials, these types of population pragmatic trials are</p>
<p style="text-align: right;">Page 231</p> <p>1 by more than one person, and then adjudicated to get 2 the final answer.</p> <p>3 The other one used data from the 4 electronic data warehouse. That shortened the course 5 of analytic time even though the numbers were much 6 greater. And overall, the price per patient can be 7 much, much lower when you're looking at something 8 that's happening during the usual domain of care. 9 Next slide.</p> <p>10 So a couple more comments about a few 11 things after the trial is done. There's just a few 12 more concerns or considerations that are important, 13 and one is how do you compare trials over time. And 14 this is particularly important for infection 15 prevention guidance. It may be important for 16 indications, but as we all know, gold standards 17 control stay in place for a while, but then they 18 eventually change.</p> <p>19 Whatever is considered gold standard 20 today is unlikely to be the gold standard 10, 15, 21 certainly 20 years from now. And so it raises the 22 question about whether or not we're looking at a</p>	<p style="text-align: right;">Page 233</p> <p>1 actually not being done by the companies that would or 2 would not seek an indication. They're usually done by 3 healthcare systems or infection prevention programs 4 that see a need and therefore pursue this trial.</p> <p>5 For that reason, these pragmatic trials 6 are not structured to achieve FDA indications and in 7 fact it's not common that a indication would actually 8 -- a company would seek to get an indication using 9 somebody else's trial. So it is possible 10 theoretically, but it's not commonly done.</p> <p>11 One thing that's thought provoking is 12 you can imagine that sometimes we say, well it's okay, 13 it's already out on the market. These are usually 14 post-marketing trials, looking for additional usages 15 that are under the domain of medical care but lack of 16 an indication can actually hamper adoption. And why 17 do I say that? Because let's say we just heard that 18 there might be 50, 60 percent of hospitals that are 19 using chlorhexidine bathing, but actually there is no 20 manufacturer indication to do that.</p> <p>21 So let's say another 20 percent of 22 hospitals see the new guidelines and say, we better</p>

<p style="text-align: right;">Page 234</p> <p>1 start to implement this indication which is now -- or 2 this intervention which is now the new gold standard 3 for the field, and now I can't find a manufacturer who 4 will train me because this is not an indicated use. 5 Another thing that could actually 6 happen is that a future trial now looks to have a 7 control group and the control arm is going to use a 8 product that does not carry an FDA indication for it. 9 So there's a number of things that are going to be 10 important when we think about what is the current gold 11 standard, what is actually promulgated in the 12 guidelines, and then what is actually going to be a 13 reasonable way in which you can make comparisons or 14 actually achieve an FDA indication. Next slide. 15 So in summary, there are a wide range 16 of trial designs, trial durations that can be pursued 17 for achieving HAI reduction and evaluating them in the 18 course of a trial. A couple of key issues to consider 19 is whether or not it would be advantageous to use a 20 group level randomization versus an individual 21 randomization, making sure of course, as always that 22 you have sufficient sample size, but this is even more</p>	<p style="text-align: right;">Page 236</p> <p>1 cluster randomized trials or CRTs, using a minimum of 2 mathematical detail. And let me doff my cap to the 3 two good CRT texts listed at the bottom of the slide, 4 both of which provided much of the content in the 5 succeeding slides. Next slide, please. 6 So this is a simple, somewhat idealized 7 CRT sampling and randomization scheme. So we have a 8 large population of clusters typically of different 9 sizes. That is, different numbers of individuals 10 belong to them. So for example, in the context of 11 education research, schools might be clusters. In 12 our present context hospitals or ICUs might be 13 clusters. And there's an associated population of 14 individuals which includes all individuals who belong 15 to a cluster. 16 To implement the trial, we select a 17 random sample of N clusters from the population of 18 clusters and then each of the selected clusters is 19 randomly assigned to treatment one or treatment zero, 20 and then the assigned treatment is administered 21 throughout the cluster. Then for each of the 22 individuals from a selected cluster, we observe their</p>
<p style="text-align: right;">Page 235</p> <p>1 important if you do group randomization to make sure 2 that you have robust ways of balancing confounders in 3 addressing a proper control. 4 You do want to make sure that you count 5 for contagious outcomes in your analysis and in the 6 planning and it's absolutely critical to make sure 7 that during the course of these trials that we 8 actually disclose and assess and record competing 9 interventions and what happens to them as well as 10 ensure data that if a whole group drops out, how do we 11 make sure that we retain the data ongoing so that you 12 can complete an as-randomized analysis. Thanks very 13 much. 14 DR. DAN RUBIN: Thank you very much, 15 Dr. Huang. That was very informative. Our next 16 speaker is Ed Bein. Dr. Bein is a senior statistician 17 at the FDA where he has worked for five years. He has 18 a doctorate in biostatistics from UC Berkeley. Over. 19 DR. ED BEIN: Okay, thank you. Okay, 20 next slide, please. 21 So this presentation is devoted to a 22 review of key statistical and design concepts for</p>	<p style="text-align: right;">Page 237</p> <p>1 endpoint values. And as a running example, let me use 2 the binary endpoint of whether a nosocomial infection 3 was acquired, yes or no. Next slide, please. 4 Okay. Now let's consider the N1 5 clusters that were randomly assigned to treatment one. 6 Typically these clusters -- so let me know if there 7 are a couple of typos in the slide where it states 8 clinical success rates, that should read infection 9 rates. So of the N1 clusters randomly assigned to 10 treatment one, typically these clusters have variable 11 infection rates, and I'll let $\pi(1)(i)$ denote the 12 infection rate for the I-th cluster among the clusters 13 that were assigned to treatment one. 14 This variability in cluster level 15 infection rates is due to differences in cluster level 16 characteristics, so in our context, important 17 differences could include differences in funding 18 levels, degree of understaffing, amount of staff 19 turnover, quality of leadership, and patient 20 characteristics. And these and other important 21 characteristics can account for differences in 22 cluster-specific infection rates, even among clusters</p>

<p style="text-align: right;">Page 238</p> <p>1 that administered the same treatment.</p> <p>2 Going further, we can conceptualize</p> <p>3 these cluster-specific infection rates as belonging to</p> <p>4 a population of such infection rates. That is for</p> <p>5 each cluster in the population, whether or not it</p> <p>6 participates in our trial, we can consider the</p> <p>7 infection rate it would have if it were to administer</p> <p>8 treatment one and then ditto with regard to treatment</p> <p>9 zero. Next slide.</p> <p>10 Okay, now I'm going to talk about the</p> <p>11 intracluster correlation sometimes referred to as the</p> <p>12 intraclass correlation. So if there's positive</p> <p>13 treatment one between cluster variants, then that</p> <p>14 implies that the endpoint values from pairs of</p> <p>15 individuals belonging to the same treatment one</p> <p>16 cluster are positively correlated. This correlation</p> <p>17 is termed the intracluster correlation denoted either</p> <p>18 ICC or using the Greek letter rho.</p> <p>19 On the other hand, endpoint values from</p> <p>20 pairs of individuals from different treatment one</p> <p>21 clusters are independent and are not correlated. So</p> <p>22 the correlation only applies to individuals from the</p>	<p style="text-align: right;">Page 240</p> <p>1 is the same, to estimate the risk difference, the</p> <p>2 treatment one versus treatment zero risk difference.</p> <p>3 And we're going to get -- let $RD(\hat{\theta})$</p> <p>4 be the usual estimator of the risk difference; that</p> <p>5 is, we compute among all of the subjects assigned to</p> <p>6 treatment one. We compute the infection rate. Then</p> <p>7 we focus on all the subjects assigned to treatment</p> <p>8 zero. We compute the infection rate. And the</p> <p>9 difference between those two infection rates is our</p> <p>10 estimate of the true risk difference.</p> <p>11 So in case one we're using an</p> <p>12 individual randomized trial with 100 subjects per arm.</p> <p>13 In case two, we're going to employ a CRT with 50</p> <p>14 clusters per arm and two subjects per cluster, so</p> <p>15 again 100 subjects per arm. And let's suppose that</p> <p>16 the intracluster correlations for both arms is equal</p> <p>17 to .02.</p> <p>18 Then this trial has the same</p> <p>19 statistical power to test the null hypothesis that the</p> <p>20 risk difference equals zero. That would be obtained</p> <p>21 from an individual randomized trial with 98 subjects</p> <p>22 per arm. That is even though the nominal number of</p>
<p style="text-align: right;">Page 239</p> <p>1 same cluster and then ditto for treatment zero and its</p> <p>2 intracluster correlation. Next slide, please.</p> <p>3 So now, let me talk about some of the</p> <p>4 downsides of employing CRTs. So let me start by</p> <p>5 noting that standard statistical methods such as t-</p> <p>6 test or chi square tests assume independent</p> <p>7 observations. However, when the intracluster</p> <p>8 correlations ρ_1 and ρ_0 are positive, this</p> <p>9 assumption is violated because some observations are</p> <p>10 in fact correlated.</p> <p>11 This implies that applying standard</p> <p>12 methods to CRT individual level data will yield overly</p> <p>13 optimistic p values and overly narrow confidence</p> <p>14 intervals. Further, the effective sample size when</p> <p>15 valid nonstandard analysis methods are used is smaller</p> <p>16 than the nominal sample size. And the next slide</p> <p>17 exemplifies what I mean by effective sample size.</p> <p>18 Next slide, please.</p> <p>19 Okay so now we're going to consider</p> <p>20 three different trials, all employing 100 subjects per</p> <p>21 arm, and you can imagine they're being run in three</p> <p>22 parallel universes. And the statistical aim of each</p>	<p style="text-align: right;">Page 241</p> <p>1 subjects per arm in this trial is 100, we say that the</p> <p>2 effective sample size is 98 subjects per arm. And in</p> <p>3 the third case again it's the CRT but now employing 10</p> <p>4 clusters per arm with 10 subjects per cluster. And</p> <p>5 we're assuming the same intracluster correlations.</p> <p>6 Then for this trial it would have the</p> <p>7 same statistical power to test the null hypothesis</p> <p>8 that would be obtained from an individual randomized</p> <p>9 trial with 85 subjects per arm. That is, the</p> <p>10 effective sample size for case three is 85 subjects</p> <p>11 per arm.</p> <p>12 And so the bottom line is that the</p> <p>13 statistical power for testing the null hypothesis is</p> <p>14 greatest in case one, that is the individual</p> <p>15 randomized trial, and smallest in case three, the CRT</p> <p>16 that had the fewest clusters. And so taking a step</p> <p>17 back, CRTs suffer in statistical power relative to</p> <p>18 individual randomized trials with the same number of</p> <p>19 subjects.</p> <p>20 To what extent they suffer will depend</p> <p>21 on the number of subjects per cluster and on the</p> <p>22 magnitude of the intracluster correlation. Next</p>

<p style="text-align: right;">Page 242</p> <p>1 slide, please.</p> <p>2 Okay, but now let's talk about why we</p> <p>3 might want to employ a CRT design, and the most</p> <p>4 compelling reason is that it's the only appropriate</p> <p>5 trial design when we're seeking to evaluate treatments</p> <p>6 that are intended to be administered cluster-wide. So</p> <p>7 this is really an issue of ecological validity that to</p> <p>8 evaluate treatments that are to be administered</p> <p>9 cluster-wide, they should be administered cluster-wide</p> <p>10 in the evaluation study.</p> <p>11 And so there's a related issue that</p> <p>12 CRTs are intended to handle within cluster</p> <p>13 contamination or interference between treatments. And</p> <p>14 this is related to the notion of indirect treatment</p> <p>15 effects that was discussed earlier today. So there's</p> <p>16 interference between treatments when patients'</p> <p>17 clinical outcomes are influenced by both the</p> <p>18 treatments they themselves receive and the treatments</p> <p>19 that others in their cluster receive.</p> <p>20 So imagine I'm living in a household</p> <p>21 with a number of others and I'm a diabetic and there</p> <p>22 are other diabetics in my household. Then my blood</p>	<p style="text-align: right;">Page 244</p> <p>1 So if a regime is intended to be administered cluster-</p> <p>2 wide, it should observe the outcomes resulting from</p> <p>3 cluster-wide administration. Next slide.</p> <p>4 Okay, now let me talk about two</p> <p>5 different broad analysis approaches. In trials that</p> <p>6 randomized individuals, the individuals' endpoint</p> <p>7 values are the outcomes used in efficacy analyses but</p> <p>8 in CRTs, the analyst has a choice between directly</p> <p>9 using individuals' endpoint values as outcomes or</p> <p>10 alternatively using cluster level summaries as</p> <p>11 outcomes.</p> <p>12 So an example of a cluster level</p> <p>13 summary, for each cluster in the trial, compute its</p> <p>14 infection rate and then compare the treatment one and</p> <p>15 treatment zero clusters rates using t-test. An</p> <p>16 example of a subject level endpoint analysis, analyze</p> <p>17 all of the individual binary infection outcomes using</p> <p>18 logistic regression GEE to compare treatments. This</p> <p>19 is a version of logistic regression appropriate for</p> <p>20 hierarchical data where individuals are clustered</p> <p>21 within higher level units. Next slide, please.</p> <p>22 So you may recall that in the second</p>
<p style="text-align: right;">Page 243</p> <p>1 sugar levels will be influenced by the specific</p> <p>2 treatment I'm taking for my diabetes, but my blood</p> <p>3 sugar levels will not be influenced by the treatments</p> <p>4 that may be employed by any of my diabetic housemates.</p> <p>5 So this is an example of no interference between</p> <p>6 treatments.</p> <p>7 However, let's imagine that some</p> <p>8 hideous and highly contagious pathogen rears its ugly</p> <p>9 head and an effective vaccine has been developed for</p> <p>10 it. Then even if I'm vaccinated, my probability of</p> <p>11 becoming infected is lower if all of my housemates are</p> <p>12 also vaccinated than if none of them are vaccinated,</p> <p>13 as if all of my housemates are vaccinated, then my</p> <p>14 level of exposure within my household to this awful</p> <p>15 pathogen will probably be lower. So the treatments</p> <p>16 that are used or not used by my housemates influences</p> <p>17 my probability of becoming infected.</p> <p>18 And so more broadly with regard to</p> <p>19 contagious diseases, my outcome when a specific</p> <p>20 treatment or prevention regime is administered</p> <p>21 throughout my cluster may differ from the outcome I</p> <p>22 would obtain if administration were not cluster-wide.</p>	<p style="text-align: right;">Page 245</p> <p>1 slide, I talked about two populations of interest, the</p> <p>2 population of clusters and the population of</p> <p>3 individuals. And so treatment effects can be defined</p> <p>4 separately with regard to each of these populations.</p> <p>5 So at the cluster level, each cluster can be thought</p> <p>6 of as having its own specific risk difference. This</p> <p>7 is the infection rate the cluster would have if it</p> <p>8 were to administer treatment one minus the infection</p> <p>9 rate the cluster would have if it were instead to</p> <p>10 administer treatment zero.</p> <p>11 And we defined the cluster level risk</p> <p>12 difference as the mean cluster specific risk</p> <p>13 difference over the population of clusters.</p> <p>14 Alternatively, imagine that all individuals in the</p> <p>15 population of individuals receive treatment one call</p> <p>16 the resulting infection rate, rate one. Ditto for</p> <p>17 treatment zero and rate zero. Then we define the</p> <p>18 individual level risk difference as the difference</p> <p>19 between rate one and rate zero. Next slide, please.</p> <p>20 Okay, so buyer beware. In general, the</p> <p>21 individual level risk difference does not equal the</p> <p>22 cluster level risk difference. So now if we could go</p>

<p style="text-align: right;">Page 246</p> <p>1 back to slide nine. So that's two slides back. Thank 2 you. In the example of -- in the t-test example of 3 cluster level infection rates, the null hypothesis is 4 that the cluster level risk difference equals zero. 5 However in the logistic regression GEE example, the 6 null hypothesis being tested is that the individual 7 level risk difference equals zero. So in general, 8 these two null hypotheses differ. Okay, now if we can 9 go forward to Slide 11. 10 So the bottom line is that the method 11 of analysis should target the treatment effect at the 12 level of clinical interest. In practice, this will 13 typically be the individual level risk difference but 14 this is really a substantive issue and not a 15 statistical issue. Next slide, please. 16 Okay, now let me briefly talk about 17 different kinds of CRT designs. So the design -- the 18 simple design that I presented in my second slide was 19 a completely randomized parallel group design. And 20 parallel group design means that each cluster 21 administers a single treatment over the course of the 22 trial. But there are two other kinds of parallel</p>	<p style="text-align: right;">Page 248</p> <p>1 know, dealing with this very briefly. So a major 2 concern is the issue of between-arm imbalance on 3 important cluster-level baseline characteristics. And 4 so this kind of between-arm balance matters for face 5 validity and for statistical power. 6 So regarding face validity, imagine 7 that we're running a CRT with a small number of 8 clusters and by the bad luck of the draw all clusters 9 from rural areas end up in one arm and all clusters 10 from urban areas end up in the other arm. Then 11 whatever the CRT results, readers of these results are 12 likely to be skeptical of generalizing the results to 13 general concerns about how the rival treatments work. 14 Now the concern about between-arm 15 imbalance will be minimal if there are a very large 16 number of clusters included in the trial, but that 17 will be more the exception than the rule, and 18 otherwise pair matching or stratification can improve 19 balance as was discussed in a previous talk. 20 The Hayes & Moulton textbook generally 21 recommends using stratification over pair matching, 22 but this is an area of active research and so there's</p>
<p style="text-align: right;">Page 247</p> <p>1 group designs of note, one is the matched pair design 2 and here, clusters are paired based on similarity on 3 baseline characteristics predictive of outcome. And 4 then one member of each pair is randomized to 5 treatment one and the other pair goes to treatment 6 zero. 7 And another type of parallel group 8 design is a stratified design where clusters are 9 grouped into strata defined in terms of baseline 10 characteristics predictive of outcome, and there are 11 at least two clusters in each stratum that are 12 randomized to each arm. 13 Let me note that there are also designs 14 that are not parallel group designs and examples would 15 be crossover designs and step wedge design. And with 16 these designs, each cluster administers both 17 treatments over the course of the trial but these 18 treatments are administered at different non- 19 overlapping periods of time. Next slide, please. 20 So let me very briefly consider some 21 considerations for choosing the type of CRT design to 22 employ, and this is a complex topic so I'm just, you</p>	<p style="text-align: right;">Page 249</p> <p>1 no final word here. And let me also note that 2 covariate-adjusted statistical analyses can be used to 3 adjust for some degree of between-arm imbalance and 4 thereby increase statistical power. But particularly 5 when the endpoint is binary endpoint, such analyses 6 require a particular amount of care. 7 So that's it for the talk. Thanks very 8 much. 9 DR. DAN RUBIN: Great. Thank you so 10 much, Dr. Bein. Our next talk is Controlling 11 Pathogens in Healthcare: A Way Forward presented by 12 Dr. Robert Weinstein. Dr. Weinstein is C. Anderson 13 Hedberg, MD Professor of Medicine at the Rush Medical 14 College and chairman emeritus, Department of Medicine, 15 Cook County Hospital, Chicago. Dr. Weinstein has been 16 president of the Society for Healthcare Epidemiology 17 of America. He's been chair of CDC's Healthcare 18 Infection Control Practices Advisory Committee, an 19 Infectious Disease Society of America board member and 20 voting member of the President's Advisory Council on 21 Combating Antibiotic-Resistant Bacteria. Dr. 22 Weinstein.</p>

<p style="text-align: right;">Page 250</p> <p>1 DR. ROBERT WEINSTEIN: Thank you. I'm 2 going to be talking today about controlling pathogens 3 in healthcare, what I see is a way forward, and 4 disclosures are this is my personal -- these are my 5 personal views. Next slide. 6 I have what I consider to be three key 7 topics. The first is I'll start with a model of the 8 causal pathway of spread of multidrug-resistant 9 organisms with a focus on potential decolonization 10 interventions. Second, I'll discuss the potential 11 need to deconstruct infection prevention ensembles. 12 And third, I will stress the need to understand the 13 fecal patina, which can be defined as the coating of 14 multidrug-resistant organisms, often on the skin of 15 patients who are in acute and long-term care and the 16 related microbiome interactions. Next slide. 17 The first topic is the causal pathway 18 which is somewhat similar to the slides that John 19 Jernigan showed earlier this morning, and starting in 20 the upper left, the patient comes into a hospital with 21 normal flora or if they're readmitted or a nursing 22 home old patient, they may have pre-existing</p>	<p style="text-align: right;">Page 252</p> <p>1 so we started with the device guidelines and reporting 2 rates and cluster detection as some of our earliest 3 interventions. Device guidelines you've heard about 4 already today related to IV catheters, bladder 5 catheters, endotracheal tubes, and so forth. And 6 these are good sites for decolonization, 7 decontamination interventions. 8 Reporting rates is useful for people to 9 know what's going on -- it turns out if you know that 10 you're worse than your neighbors, you try to do better 11 -- and then cluster detection to try to reduce the 12 risk of further spread of bacteria that are already 13 causing many clusters. Next slide. 14 As you move up the pathway, hand 15 hygiene is applied. Some patients are screened in 16 some interventions. Isolation precautions are 17 applied. And again cluster detection. Hand hygiene 18 is a good site and patient screening are good sites 19 obviously for decolonization interventions. Next 20 slide. 21 Dealing with healthcare worker hand 22 contamination. The obvious intervention is hand</p>
<p style="text-align: right;">Page 251</p> <p>1 antibiotic resistance, and then some reasonable 2 percentage of them -- I've guesstimated 10 to 40 3 percent -- after exposure to antibiotics or due to 4 colonization pressure which is the patients around 5 them who have antibiotic-resistant organisms and maybe 6 other situational factors, will become colonized with 7 drug-resistant bacteria or fungi. 8 Virtually 100 percent of these patients 9 will have this fecal patina, that is skin colonization 10 of these organisms, in addition to GI and respiratory 11 carriage. And then some percentage of these patients 12 will shed these organisms within the environment. 13 They will contaminate healthcare worker hands. The 14 hands will move from patient to patient and lead to 15 patient cross colonization with multidrug-resistant 16 bugs and then some variable percent of patients 17 depending on their procedures, underlying risk 18 factors, exposures, and so forth will develop clinical 19 infections with the bacteria or fungi that are 20 colonizing them. 21 Now historically -- next slide -- we 22 started our interventions at the bottom of this list</p>	<p style="text-align: right;">Page 253</p> <p>1 hygiene, and there's also potential for universal 2 gloving which personally I think is one of the most 3 effective interventions in this, in the interventions 4 I'm going to show in this pathway. Next slide. 5 For the environment, and you've heard 6 that the environment is particularly problematic for 7 some bacteria like vancomycin-resistant enterococci 8 for C. aureus, for C. difficile, also for some 9 acinetobacter strains, for some fungi. It's a problem 10 beyond C. aureus and improved environmental cleaning 11 is obviously an intervention. Next slide. Next 12 slide. 13 I think that the most striking 14 intervention in this whole pathway in my view, and 15 you've already heard about this is chlorhexidine 16 bathing. There have been key demonstrations of the 17 efficacy of decolonization of the skin, sometimes with 18 even greater than expected benefits in terms of 19 preventing bacteremias, for example in ICU patients. 20 Next slide. 21 And then finally the most recent 22 interventions have gone -- have gotten to the very</p>

<p style="text-align: right;">Page 254</p> <p>1 root of the problem which includes antibiotic 2 stewardship, microbiome restoration which you've heard 3 about today, and other potentially situational 4 interventions. 5 This leads me to topic two with all of 6 these -- next slide -- with all of these guidelines 7 and all of the yellow interventions that are on that - 8 - that I put on the pathway which are largely 9 ensembles, what does the heavy lifting? Who is 10 important? And here I show a picture of Seinfeld. 11 You know, is Jerry most important? George? Elaine? 12 Kramer? Or I could have shown a picture of Big Bang 13 Theory which actually I like better. Who does the 14 heavy lifting? Next slide. 15 So I want to give you an example from a 16 guideline. This is from 2002, so two decades ago. 17 This is the first CDC/HICPAC IV Catheter Infection 18 Prevention bundle and you could take all of the 19 recommendations in this guideline and distill them, I 20 think, down, boil them down to the first five 21 interventions: education of personnel about taking 22 care of catheters, checking daily.</p>	<p style="text-align: right;">Page 256</p> <p>1 iteration of guidelines for preventing CLABSIs and 2 what's considered essential. 3 And so you could ask again really, are 4 these all really essential? Which are the most 5 essential? And I think this is an important issue as 6 you start to add decolonization to the bundles or to 7 the ensembles and as already pointed out this morning, 8 it's important to understand what the role of 9 decolonization is in light of all the other 10 interventions. 11 Now, how would you figure that out 12 here? It's difficult. I suppose you could use a 13 network meta analyses or you could do some trials and 14 I can't really tell you how you figure it out exactly, 15 but I can tell you it's an important issue and it will 16 become increasingly important as decolonization 17 strategies are added to ensembles or bundles. I want 18 to give you one other example of an ensemble. Next 19 slide. 20 And this is, you'll see on the next 21 slide the recommendations that are being developed and 22 this is a draft so I superimposed the lists on top of</p>
<p style="text-align: right;">Page 255</p> <p>1 Is the catheter needed? Remove it if 2 it isn't. Avoiding routine catheter replacement is an 3 infection control strategy. Using chlorhexidine skin 4 prep. And then subsequently after this guideline was 5 published, it was shown that bathing patients daily in 6 ICU with chlorhexidine is a major benefit for 7 preventing CLABSIs and then maximum barrier 8 precautions for those inserting lines. That is, they 9 should be wearing masks, gowns, gloves, and so forth. 10 Now there are only five really key 11 interventions in this bundle, and each of them has 12 been shown in a randomized trial to be effective, but 13 we don't know which of these is most important. Does 14 it matter? You might say, so what. There are only 15 five of them. Do them all. And that's a reasonable 16 response. I mean you probably wouldn't want to kick 17 Jerry or George or Elaine or Kramer out of that 18 ensemble. So that's reasonable. So what. 19 But -- next slide -- if you fast 20 forward 20 decades, you can see there is the hackneyed 21 slippery slope and so "essential" -- in air quotes -- 22 now is a very long list. And this is the most recent</p>	<p style="text-align: right;">Page 257</p> <p>1 each other so they're not as easily read, because it 2 is in progress but you can see for hand hygiene there 3 are a lot of "essential" -- in air quotes again -- 4 recommendations. Here though, I think we can be more 5 focused. Next slide. 6 And I think that the guideline as 7 written is an excellent advice for infection control 8 of personnel for hospitals, for nursing departments 9 that are facing a variety of administrative issues. 10 And so we recommended -- I don't know if this is going 11 to be accepted -- but recommended that this hygiene 12 follow the keep it simple principle and start with 13 this declaration. 14 "This is a carefully and thoroughly 15 compiled set of recommendations for use by infection 16 prevention groups that are responsible for developing 17 institutional policies." But "For the individual 18 patient provider, the single message is very simple: 19 hand before and after every patient is essential." 20 So I think some bundles or ensembles 21 can be boiled down to the simplest message, and again, 22 I think this is going to be very important as</p>

<p style="text-align: right;">Page 258</p> <p>1 decolonization strategies are added. 2 And this takes us to the third topic. 3 The next slide. Microbiomes, understanding them at 4 clinical, epidemiologic, and mechanistic levels. This 5 is a translation of an old quote from Goethe that 6 says, "What is the hardest of all? That which seems 7 most simple: to see what is before your eyes." And I 8 want to give you two examples of microbiome 9 interactions and how important it's going to be to 10 understand them. Next slide. 11 This is a picture of an axillary 12 culture of a patient in one of Mary Hayden's long-term 13 care studies, and you can see this is a patient 14 receiving daily chlorhexidine bathing and before the 15 bathing, the patient had -- this wall to wall, 16 multidrug-resistant mucoid <i>Klebsiella pneumoniae</i> in 17 the axilla. Your axilla should not have <i>Klebsiella</i> 18 <i>pneumoniae</i> in it, and you can see afterwards, after 19 the bathing, it's been removed. 20 So this is a good example of the fecal 21 patina. You can find this bug elsewhere, on the neck, 22 in the groin, on the back, on the chest, all over</p>	<p style="text-align: right;">Page 260</p> <p>1 and epidemiologic problems. This does raise the 2 question of the interrelations of the different 3 microbiome compartments. 4 For example, using kind of an older 5 terminology, is this <i>klebsiella</i> on this patient a 6 resident flora that is it permanent flora now in the 7 axilla and on the skin or is only transient? Well, it 8 has to be removed every day which suggests that it may 9 be more resident than transient. 10 The other implication I think is if you 11 focus your intervention on the gut microbiome, what 12 will happen to the skin microbiome? Because if you 13 remove the resistant <i>klebsiella</i> from the gut but it 14 remains on the skin because its resident flora, then 15 your gut intervention may not be very effective. Next 16 slide. 17 Along those lines, I wanted to show you 18 a study that was done by Kyle Popovich looking at MRSA 19 300, which as you heard earlier today is the typical 20 community-acquired methicillin-resistant staph aureus. 21 And this is looking at genomic clusters; that is, the 22 relatedness of MRSA among women who are detainees at</p>
<p style="text-align: right;">Page 259</p> <p>1 these patients. This is just one site that's 2 colonized, and I think it makes the point that the 3 fecal patina is a very interesting, important, and 4 dynamic concept. Next slide. 5 You can see removing the fecal patina 6 made the patient happy or at least in this picture 7 made the agar plate happy. And chlorhexidine bathing 8 has an effect on resistant gram-negatives, on 9 resistant gram-positives like MRSA and VRE and the 10 benefits for the patient clinically are very marked 11 with decreased risk of infection with the bugs that 12 are on -- the that are removed from the fecal patina, 13 and the benefits to the hospital and the nursing home 14 epidemiologically as John Jernigan showed this morning 15 with a slide about VRE in an ICU that with 16 chlorhexidine bathing daily, there's lessened 17 likelihood of spread of MDROs. 18 It's important to realize that these 19 patients may still have GI or respiratory tract 20 colonization with this pathogen. The only thing 21 that's been removed is the fecal patina, and yet there 22 is a major benefit in terms of both clinical outcomes</p>	<p style="text-align: right;">Page 261</p> <p>1 the Cook County Jail and genomic clusters are defined 2 genetically by looking at the number of variants 3 between MRSA isolates. 4 And you can see in the top line of this 5 table that if you have nares colonization, your chance 6 of being in a cluster, that is having your staph 7 aureus similar to other detainees, was much less than 8 if -- than not being in a cluster. So women who had 9 nasal colonization were much more likely to have 10 unique strains of MRSA not related at all to the other 11 strains of other individuals. 12 And you can see bullet one, an 13 interpretation was nares colonization was negatively 14 associated with being in a genomic cluster and could 15 represent mostly endogenous colonization. 16 Now if you look at the bottom line of 17 that table, this looks at those detainees who have 18 what's called exclusive extranasal colonization. That 19 is, they were carrying staph aureus, MRSA, 20 methicillin-resistant staph aureus, USA-300, community 21 acquired strains, but they had it at sites other than 22 the nose. So their noses had no MRSA, but their</p>

<p style="text-align: right;">Page 262</p> <p>1 groins or backs or axilla or other side on their body, 2 perianal sites had MRSA. And you can see in bullet 3 two under the interpretation that exclusive extranasal 4 colonization was associated with being in a genomic 5 cluster. 6 So those with only extranasal 7 colonization, 80 percent of them were in a cluster, 8 meaning their strains were similar to other patients 9 suggesting that this colonization pattern predisposes 10 to exogenous MRSA acquisition. And in the last bullet 11 underlined, "the findings suggest that nasal 12 colonization may serve a controller role in limiting 13 exogenous acquisition." 14 So it's important I think to understand 15 the interrelations of various components of the 16 microbiome in various compartments. Next slide. 17 So in conclusion, a model of the causal 18 pathway of spread of antimicrobial-resistant 19 organisms, I believe, can help focus implementation of 20 strategies for pathogen reduction and the role of 21 colonization and decolonization. 22 Second, infection control guidelines</p>	<p style="text-align: right;">Page 264</p> <p>1 also touch on an opportunity to bring innovative 2 products to the market. Next slide, please. 3 As already noted, the American Cleaning 4 Institute is a trade association for the cleaning 5 products industry, including suppliers, formulators, 6 and packaging companies. ACI is also the trade 7 association representing the topical antiseptics 8 industry and is currently supporting the safety and 9 efficacy research for five of the six over-the-counter 10 antiseptic active ingredients that were deferred from 11 final regulation by FDA several years ago. Slide, 12 please. 13 This is brief slide to show you who are 14 the ACI members that are producing topical skin 15 antiseptic ingredients and products, and these are the 16 companies that are actively supporting the extensive 17 FDA data requirements for generally recognized as safe 18 and effective determination. This collaboration 19 really has been ongoing since 1994, when FDA 20 promulgated the tentative final monographs regulating 21 healthcare and consumer antiseptics. 22 The topical antiseptics have been used</p>
<p style="text-align: right;">Page 263</p> <p>1 and bundles are not parsimonious as currently 2 formulated, and the relative importance of the 3 individual components should be evaluated. And I 4 think this is going to take on increased importance as 5 new components may be added to target colonization. 6 And the third point is that studies the 7 microbiome should assess mechanisms behind the 8 creation of the fecal patina, how does it get there, 9 how does it persist, and explore the interrelations of 10 different components and compartments of the 11 microbiome. Thank you very much. 12 DR. DAN RUBIN: Thank you very much, 13 Dr. Weinstein. Our next speaker is James Kim. Dr. 14 Kim is the vice president of Science and Regulatory 15 Affairs and leads the scientific team at the American 16 Cleaning Institute, the trade association for 17 manufacturers of soaps, hand sanitizers, cleaning 18 products, and their chemistries. Over. 19 DR. JAMES KIM: Afternoon. Thank you 20 for having me today to discuss the American Cleaning 21 Institute's ongoing research to support the safety and 22 efficacy of over-the-counter topical antiseptics and</p>	<p style="text-align: right;">Page 265</p> <p>1 safely for many decades in both professional and 2 consumer settings, and as illustrated by Dr. Weinstein 3 on the previous presentation, there is a role for 4 effective hand hygiene practices and these antiseptic 5 products in preventing hospital associated infections. 6 Just to backtrack with a little 7 history, ethyl alcohol started being used in the 1880s 8 in Germany for presurgical hand disinfection. And in 9 fact, professor Philip Price from the Johns Hopkins 10 University published a paper in the Archives of 11 Surgery in 1939 titled "Ethyl Alcohol as a Germicide." 12 Alcohol-based hand sanitizers have been recommended 13 over soap and water by the CDC in their healthcare 14 hand hygiene guidelines since 2002, and also by the 15 World Health Organization in 2009. 16 And we also saw that alcohol-based hand 17 sanitizers were a critical tool during the COVID 18 pandemic, as evidenced by the FDA allowing emergency 19 production of hand sanitizers. OTC topical 20 antiseptics are regulated by FDA's OTC monographs and 21 recently monograph reform. And while new drug 22 approvals can be pursued for these products, this</p>

<p style="text-align: right;">Page 266</p> <p>1 regulatory pathway is long, costly, and commercially 2 risky.</p> <p>3 It is also important to note that OTC 4 monographs provide the criteria for antibacterial 5 efficacy claims, but these monographs do not include 6 antiviral or decolonization claims and this constrains 7 development and use of products for reducing 8 infections due to skin colonization. Slide.</p> <p>9 Okay, this table shows the five active 10 ingredients on the left side that ACI is supporting 11 for safety and efficacy research, and these are cross 12 reference with the consumer and healthcare indications 13 promulgated by FDA in the final monographs. The 14 healthcare indications are patient preoperative skin 15 preparation as well as preinjection skin preparations, 16 personal hand washes, personal hand rubs, surgical 17 hand scrubs, and surgical hand rubs. All five 18 ingredients that ACI is supporting are eligible for 19 the patient preoperative and preinjection skin uses. 20 Slide.</p> <p>21 This table summarizes FDA's assessment 22 of the safety data gaps for over-the-counter topical</p>	<p style="text-align: right;">Page 268</p> <p>1 active work streams to ensure that progress towards 2 meeting FDA's data requirements were generally 3 recognized and safe and effective determinations 4 continues. Programs on topical antiseptics have been 5 searching for infection prevention study designs that 6 are reasonable and manageable and so special thanks to 7 Dr. Theresa Michele for providing an overview of the 8 rule makings governing these products a few talks 9 earlier.</p> <p>10 For consumer antiseptics, FDA requires 11 a clinical outcome study that demonstrates a direct 12 clinical benefit such as reduction in infection. This 13 is in contrast to the requirements for healthcare 14 antiseptics that used surrogate endpoints such as 15 bacteria log reductions to demonstrate effectiveness.</p> <p>16 The studies that were pursuing for the 17 consumer clinical efficacy study, FDA provided 18 feedback to us several years ago on using an enriched 19 population to manage confounding variables as well as 20 to increase the power of the study. We are currently 21 pursuing a study design using U.S. Marine Corps 22 recruits as an enriched population with different</p>
<p style="text-align: right;">Page 267</p> <p>1 antiseptic ingredients. As you can see, ethyl alcohol 2 safety is well proven and understood, but filling the 3 remaining safety gaps for all of the active 4 ingredients will be costly. Ethyl alcohol and 5 povidone iodine are the two ingredients that have 6 nearly complete safety information for a GRAS 7 determination and also have shown no resistance 8 potential.</p> <p>9 ACI has also completed a literature 10 review on resistance potential for the three other 11 active ingredients that we are working on, including 12 benzalkonium chloride, benzethonium chloride, and PCMX 13 or chloroxylenol, and this literature review was 14 submitted to FDA last year, in 2021.</p> <p>15 This slide shows the current status of 16 ACI research. I'm not going to go into too much 17 detail on this slide except to say that the topical 18 antiseptics program has been actively working on the 19 maximum usage trials to fill the safety data gaps and 20 is also working on several healthcare efficacy 21 studies.</p> <p>22 In total, we are managing over 20</p>	<p style="text-align: right;">Page 269</p> <p>1 barracks serving as control and treatment groups. 2 Skin infections are always a challenge for our 3 military, particularly in situations like basic 4 training and in situations of close quarters like on 5 ships, and these infections can result in significant 6 loss of active time.</p> <p>7 The plan is to propose to FDA to use 8 skin colonization as one of the clinical endpoints in 9 the study and we will have to provide evidence to FDA 10 that correlates colonization with other outcomes 11 including infection rates. So I am very appreciative 12 of the earlier talks today by CBC that provided an 13 excellent overview of these issues.</p> <p>14 And finally, just a brief summary of 15 some of the topics I discussed today. The current 16 regulatory structure can be a significant barrier to 17 the development of innovative topical skin 18 antiseptics. While the new drug approval process for 19 new skin antiseptics exists, it is a long, costly, and 20 challenged with uncertainty type of process.</p> <p>21 Monograph reform is a potential 22 mechanism to facilitate new skin antiseptic products</p>

<p style="text-align: right;">Page 270</p> <p>1 and technologies to reduce infections and pathogen 2 transmission, but for either regulatory pathway 3 establishment of skin decolonization and pathogen 4 reduction as a determinant of clinical outcomes would 5 greatly facilitate new antiseptic development. 6 So we look forward to working with FDA 7 to clarify these requirements for new products and 8 continue to enable innovation to benefit public 9 health. 10 So finally, I'd like to thank you for 11 your time and turn it over to my colleague Nicholas 12 Georges who will talk about surface disinfectants in 13 healthcare settings. 14 DR. JOHN JERNIGAN: Thank you, Dr. Kim. 15 Let me -- this is Dr. Jernigan. Let me introduce Dr. 16 Georges who will talk about Development of Efficacious 17 Cleaning and Disinfecting Products in Healthcare 18 Settings. Mr. Georges is the senior vice president, 19 Scientific and International Affairs for the Household 20 and Commercial Products Association. HCPA represents 21 member companies that manufacture and sell products 22 used for cleaning, protecting, maintaining, and</p>	<p style="text-align: right;">Page 272</p> <p>1 comes to these products. 2 All right. Products used to kill 3 viruses and bacteria on surfaces are registered as 4 antimicrobial pesticides. I'll be discussing 5 sterilants, disinfectants, and sanitizers today and I 6 should note that when I say sanitizer, I'm referring 7 to products used on inanimate objects and not on the 8 human body. I will not be talking about antiseptic 9 rubs, which James Kim just covered. 10 For the most part, the products that I 11 will be talking about are regulated by the Environment 12 Protection Agency under the Federal Insecticide, 13 Fungicide, and Rodenticide Act, also known as FIFRA. 14 FIFRA is the federal law that sets up the basic U.S. 15 system of pesticide regulation to protect humans and 16 the environment. To kick things off, I'm going to 17 first be discussing disinfectant sanitizers. 18 Disinfectants are subject to more rigorous EPA testing 19 requirements and need to meet a higher bar for FDA 20 than sanitizers. 21 For both product types, either the 22 product meets the efficacy requirements or they do</p>
<p style="text-align: right;">Page 271</p> <p>1 disinfecting homes, commercial, and institutional 2 environments. Mr. Georges. 3 NICHOLAS GEORGES: Thank you. My name 4 is Nicholas Georges and I'm the -- with the Household 5 and Commercial Products Association, a trade 6 association representing the interests of member 7 companies which are involved in the manufacturing, 8 supply, and marketing of trusted and familiar products 9 used for cleaning, protecting, maintaining, and 10 disinfecting home and commercial environments 11 including healthcare settings, as just was said. 12 HCPA is comprised of seven products 13 divisions including a dedicated product division for 14 antimicrobial products such as disinfectants and 15 sanitizers and a product division dedicated to 16 cleaning products which we'll be getting into here 17 shortly. 18 Before working for HCPA, I came from 19 industry where I held roles in which I was responsible 20 for formulating these types of products as well as 21 ensuring their compliance with applicable laws and 22 regulations, so I have hands on experience when it</p>	<p style="text-align: right;">Page 273</p> <p>1 not. Once they meet the efficacy requirements, 2 industry is not allowed to compare them against 3 another. For instance, for products that meet the 4 efficacy requirements, I cannot say an aerosol 5 products is a better delivery form than a trigger 6 spray or compare those to a wipe product. This is a 7 requirement under FIFRA and EPA takes it very 8 seriously. 9 Sterilants get a bit more complicated, 10 as they are regulated by FDA when they're used on 11 medical devices. Whereas they're regulated by EPA for 12 all of their applications. Registrants are not 13 allowed to have products, you know, mix their claims, 14 that is both have medical device and other 15 applications, and as such because companies cannot 16 have one product that is one label for multiple 17 applications that cover both, it makes it easier to 18 distinguish who has authority over regulating the 19 product. This approach stems from the 1993 memorandum 20 of understanding between FDA and EPA. 21 Then cleaning products don't undergo 22 the same rigor that disinfectants and sanitizers do as</p>

<p style="text-align: right;">Page 274</p> <p>1 they do not make any biocide claims to control 2 microbial pests. Cleaning products are either 3 regulated by the Consumer Product Safety Commission or 4 the Occupational Safety and Health Administration, 5 depending on where the product is being used. 6 If a cleaning product were to make a 7 biocidal claim, the product would need to be 8 registered with the EPA as a disinfectant 9 (indiscernible) sanitizer, otherwise the company may - 10 - would be making a claim in violation of FIFRA. Next 11 slide, please. 12 EPA, through the Office of Prevention, 13 Pesticides, and Toxic Substances has developed a 14 series of test guidelines for the use and the testing 15 of pesticides, including disinfectants, sanitizers, 16 and sterilants. Group B within Series 810 offers 17 antimicrobial efficacy test guidelines which are 18 intended to meet testing requirements under FIFRA. 19 The term product performance refers to 20 all aspects of a product's effectiveness and 21 usefulness conducted in light of expressed and implied 22 labeling claims or recommendations concerning pests,</p>	<p style="text-align: right;">Page 276</p> <p>1 and businesses identify effective green cleaning 2 products utilizes both ASTM and our HCPA performance 3 test methods and guidelines for their certification. 4 Next slide, please. 5 So how should healthcare institutions 6 go about selecting the right product? There are a few 7 things to ask oneself before selecting your product. 8 What is it that you are looking the product to do? 9 Are you looking to clean a surface or disinfect and 10 sanitize it? If clean, what type of surface or 11 surfaces and is the chemistry of the cleaning product 12 compatible? 13 If you're looking to disinfect or 14 sanitize, are you looking for a general disinfectant 15 or sanitizer or is there a specific bacteria or virus 16 you are concerned with? If it is the latter, ensure 17 the organism is listed on the label. And in all 18 cases, it is critical to read and understand the 19 label. Next slide, please. 20 So in closing, choosing the correct 21 product for the specific task can help reduce the 22 chance of infection. So with that I would like to</p>
<p style="text-align: right;">Page 275</p> <p>1 sites, methods of application, application equipment, 2 dosage rates, timing and number of applications, new 3 situations, nature and level of pest control, duration 4 of pest control, compatibility with other chemicals, 5 benefits and or adverse effects of product use, 6 compatibility of common practices associated with the 7 sites, active ingredient status of chemicals and 8 formulation and equipment. 9 FDA as part of their guidance for 10 industry and FDA reviewers also has guidance as part 11 of the premarket notification submission of 12 sterilants. This guidance facilitates the assembly of 13 the necessary data to support the introduction of a 14 sterilant for medical devices into the market. 15 Cleaning products don't have this level of detail in 16 terms of guidance from federal agencies. However, 17 there are industry standards that help companies 18 determine the effectiveness of their products and 19 those standards can be referenced by government 20 programs. 21 For instance, EPA's Safer Choice 22 program, a government program which helps consumers</p>	<p style="text-align: right;">Page 277</p> <p>1 thank you for your time today. 2 DR. DAN RUBIN: Thank you very much for 3 that presentation. Our next speaker is Erin Duffy. 4 Dr. Duffy is the chief of research and development at 5 CARB-X. CARB-X is a global biopharmaceutical 6 accelerator for the discovery and early development of 7 products to prevent, diagnose, and treat bacterial 8 infections. Most of her professional growth was with 9 Melinta Therapeutics founded as Rib-X Pharmaceuticals 10 where over 17 years she became executive vice 11 president, chief scientific officer, R&D site head. 12 Over. 13 DR. ERIN DUFFY: Thanks very much, Dan 14 and the organizers for the invitation to participate 15 in this workshop. It's been terrific so far. I hope 16 I don't mess that up. Next slide, please. 17 So for those of you who aren't familiar 18 with CARB-X, as you just heard, we are a 19 biopharmaceutical accelerator funded by three 20 international governments and two foundations for the 21 purpose of supporting the discovery and early clinical 22 development of products to diagnose, treat, and</p>

<p style="text-align: right;">Page 278</p> <p>1 prevent bacterial infections.</p> <p>2 You can see the numbers here. We have</p> <p>3 about now \$800 to \$900 million to deploy in these</p> <p>4 endeavors. Some stats in the bottom here. We've</p> <p>5 funded just about 10 percent of all of the</p> <p>6 applications that we've received since 2016, and I</p> <p>7 should say these are all through active funding calls.</p> <p>8 Today, there are 45 active projects and</p> <p>9 we've had a lot of maturation in the program in terms</p> <p>10 of movement into clinical stage programs and into</p> <p>11 advanced clinical development. And this is going to</p> <p>12 frame a lot of what I'm going to talk to you about,</p> <p>13 especially where our non-traditional portfolio is</p> <p>14 concerned. Next slide, please.</p> <p>15 So just to give you a sense of the</p> <p>16 types of products that we invest in the non-</p> <p>17 traditional space, I should say our heritage certainly</p> <p>18 was direct acting small molecule therapeutics but we</p> <p>19 recognize, like many have said today, the need for</p> <p>20 many different ways to target antimicrobial</p> <p>21 resistance. And so on the left, you see the</p> <p>22 distribution of the types of modalities that we</p>	<p style="text-align: right;">Page 280</p> <p>1 And so to that end, we are commencing a</p> <p>2 series of discussions on decolonization, both to</p> <p>3 educate ourselves and then hopefully to give some</p> <p>4 quality advice to our product developers. And so this</p> <p>5 is a workshop that we convened in early July. It</p> <p>6 followed on a series of discussions that we had at</p> <p>7 ECCMID this year in a small session with surgeons</p> <p>8 titled, "How do I treat my transplantation patients?"</p> <p>9 And so this is the group that we</p> <p>10 assembled. The first, his name is Maxime Mallet. He</p> <p>11 is a surgeon, a French surgeon who's focused on liver</p> <p>12 transplantation. Eugene Katchman from Israel is a</p> <p>13 transplant ID consult. Miriam Furst-Wilmes is part of</p> <p>14 our accelerator network at (indiscernible) and so she</p> <p>15 participated to give the view of (indiscernible) on</p> <p>16 decolonization.</p> <p>17 Many of you will know Mark Goldberger,</p> <p>18 former medical director of Emerging and Pandemic</p> <p>19 Threat Preparedness, and also director of Office of</p> <p>20 Antimicrobial Products. And then finally, David Cook,</p> <p>21 who is an advisor of our, formerly the chief scientist</p> <p>22 of Seres and now with Forma Therapeutics. Next slide,</p>
<p style="text-align: right;">Page 279</p> <p>1 support, non-traditional modalities for treatment that</p> <p>2 includes programs in anti-virulent antibody-based</p> <p>3 programs, immune-directing programs, and bacteriophage</p> <p>4 programs and other modalities as you can see.</p> <p>5 On the right is a representation of our</p> <p>6 prevention portfolio, and certainly while half of that</p> <p>7 is vaccine directed, we do embrace other modalities as</p> <p>8 well. The two that I'm calling out here are our live</p> <p>9 biotherapeutic portfolio and our engineered</p> <p>10 bacteriophage portfolio, and these are programs that</p> <p>11 are focused on decolonization in different -- of</p> <p>12 different pathogens in different populations.</p> <p>13 So I should say these programs are</p> <p>14 maturing towards a clinical stage and one of the</p> <p>15 things that we want to do, even though it is true we</p> <p>16 only fund to the end of first in human, we feel it's</p> <p>17 important to prepare these programs for success so</p> <p>18 that there is a next best advanced development partner</p> <p>19 and so that the work and the money that we've spent to</p> <p>20 bring these programs forward doesn't die on the vine</p> <p>21 but rather delivers a meaningful product for patients.</p> <p>22 Next slide, please.</p>	<p style="text-align: right;">Page 281</p> <p>1 please.</p> <p>2 So we raised a number of questions or</p> <p>3 poised a number of questions to the participants, and</p> <p>4 I'm not going to read all of these for you, but it was</p> <p>5 really to set the stage for the discussion. And I</p> <p>6 want to highlight two key questions where we spent</p> <p>7 most of the discussion, and the first is -- we've</p> <p>8 heard a lot about this today -- what patient</p> <p>9 populations or populations are best suited to obtain</p> <p>10 early proof of concept, and then what endpoints in a</p> <p>11 clinical setting do you feel are meaningful to show a</p> <p>12 benefit for decolonization product. And relatedly,</p> <p>13 what is the time frame where you would consider a</p> <p>14 patient sufficiently de-risked from an infection</p> <p>15 perspective. Next slide, please.</p> <p>16 So here are some key themes that</p> <p>17 emerged from the discussion. In terms of our surgeon</p> <p>18 and surgeon consult, decolonization was not routinely</p> <p>19 employed in their practices, but they feel that they</p> <p>20 need something beyond antibiotics. They're not using</p> <p>21 antibiotic prophylaxis now because of the extreme</p> <p>22 prevalence of colonization with ESBL, CRE, and</p>

<p style="text-align: right;">Page 282</p> <p>1 fluoroquinolone-resistant organisms, in some cases 2 greater than 80 percent. 3 And so the discussion sort of ended 4 saying, well, what if we worked back from a label that 5 might begin with, "For the reduction of colonization 6 in a closed population..." And so the closed 7 population is meant to say that there was a lot of 8 feeling that we really needed a homogeneous group or 9 as homogeneous as you can get in order to reduce the 10 signal to noise and perhaps have meaningful outcomes. 11 So in terms of proof of concept, we 12 agreed that a quantitative microbiology endpoint is 13 good but what is a sufficient measure of success? So 14 for instance, what if, you know, there's 10 to the 15 11th colony forming units at the outset and you reduce 16 that to 10 to the 8th; is that meaningful? You're 17 still leaving a lot of bacteria on the table. 18 So how do we think about this and what 19 are the bounds that we should put on that? The second 20 point of course is that for pivotal studies the 21 quantitative microbiological endpoint will not be 22 enough. There needs to be a link to clinical benefit.</p>	<p style="text-align: right;">Page 284</p> <p>1 post transplantation and indeed they are most fragile 2 in days following surgery. And it's important to note 3 that it was not felt that infection would be gained in 4 the ICU. 5 So thoughts about a study could involve 6 decolonization at some time point prior to 7 transplantation and then with early and late readouts. 8 Now of course, we would need an understanding of the 9 time course with respect to transplant for the 10 development of infection. It's likely that this would 11 be placebo controlled unless, of course, standard care 12 requires preventative antibiotic therapy where it 13 would be on top of. And then we would need an 14 understanding of how this impacts those on the 15 transplant list. Next slide, please. 16 The second population that we discussed 17 was cirrhosis patients who are hospitalized with 18 ascites and this is because they are reported to have 19 about a 10 to 30 percent likelihood of developing a 20 spontaneous bacterial peritonitis. And indeed in a 21 study in 2016 published in the World Journal of 22 Hepatology, it appears that There's a 40 percent</p>
<p style="text-align: right;">Page 283</p> <p>1 And of course this might vary with the closed 2 population, so can we in fact translate results to 3 other populations. 4 We certainly discussed biomarker 5 strategies and felt that while they're interesting, 6 the question is what is relevant and what is the 7 signal to noise where we can harvest interesting and 8 usable information, again a big question about 9 translatability from one population to the other, and 10 then finally a need to understand the effects of 11 decolonization, how they manifest over time, and what 12 external variables might influence them. Next slide, 13 please. 14 So I'm going to give you four examples 15 of populations that we felt were perhaps reasonable to 16 consider in the conduct of clinical trials, and the 17 first was patients awaiting liver transplantation and 18 here are the reasons. They often present with 19 recurrent ascites. Greater than 30 percent are 20 carriers of CRE, ESBL, and fluoroquinolone-resistant 21 organisms, and again, this varies by country and by 22 hospital. They're at risk for developing infection</p>	<p style="text-align: right;">Page 285</p> <p>1 chance after six months and a 70 percent chance after 2 12 months of recurrence following antibiotic use. 3 And so a thought was that the study 4 could be a small pilot to understand durability of the 5 antibiotic effect, treat at some point after 6 discontinuation of the antibiotic, and then follow up. 7 Of course some patients are eligible for preventative 8 use of antibiotics. Do we add decolonization on top? 9 Do we compare decolonization to the use of 10 antibiotics? Do we consider studying lower risk 11 patients versus placebo? 12 Third population -- next slide -- that 13 we discussed with patients awaiting induction 14 chemotherapy? The reasons is that there are many of 15 them. They're often less complicated and fragile. 16 Many are neutropenic and need antibiotic therapy. And 17 so a thought here was that a study would be on top of 18 standard of care antibiotic versus antibiotic alone, 19 and likely we would need to demonstrate a benefit in 20 mortality. 21 And then finally, a population on the 22 next slide that we discussed was something that's been</p>

<p style="text-align: right;">Page 286</p> <p>1 discussed here today, which is decolonization of 2 residents in nursing homes. Certainly as we learned 3 here today, high rate of multidrug-resistant organism 4 colonization and the worries about that with potential 5 transfer to the hospital for higher level care. 6 Now thoughts where we could randomize 7 by facility but we had some questions. Need to have 8 similar demographics across those facilities. We 9 would need decontamination of significant reservoirs. 10 There's the issue of testing of staff as well as all 11 new residents that come in. Decolonization product 12 would need to be broad spectrum unless you want to 13 start slicing and dicing within that community. And 14 that this is, in our estimation, best considered after 15 proof of concept has been shown in one of the other 16 populations that I just shared. 17 So in summary, on the final slide I 18 just want to emphasize that we are committed to 19 bringing solutions from nontraditional approaches 20 forward because we feel they're going to be important 21 in the overall approach to antimicrobial resistance. 22 We see both several challenges and opportunities in</p>	<p style="text-align: right;">Page 288</p> <p>1 innovative products to tackle antimicrobial 2 resistance. Ms. Sejourne. 3 FLORENCE SEJOURNE: Thank you very 4 much, FDA and CDC, to have invited me as the 5 representative of De Volterra as well as the BEAM A 6 Alliance. I'm glad to present to the virtual audience 7 today the status of development of a novel microbiota 8 protective therapy named DAV132 and highlight 9 challenges faced and lessons learned. Next slide. 10 Everyone in the audience is very 11 familiar now after a few hours of workshop with the 12 well-described impact of antibiotics on the intestinal 13 microbiota which leads to a decreased diversity called 14 dysbiosis triggering a series of deleterious 15 consequences as human. This has actually been very 16 well covered earlier today by the colleagues from CDC. 17 Next slide. 18 Da Volterra has been actually 19 developing for the last 15 years gut microbiota 20 protective therapies to be co-administered with any 21 antibiotic in order to prevent such deleterious 22 consequences and maintain the function of a healthy</p>
<p style="text-align: right;">Page 287</p> <p>1 decolonization strategies, but we emphasize that a 2 closed population is critical and the need for both 3 microbiological and clinical endpoints is clear. 4 And then finally, and I think the 5 purpose of a meeting like this is to emphasize that a 6 coordinated approach among many of the stakeholders 7 will be beneficial to the ecosystem. Thank you very 8 much. 9 DR. JOHN JERNIGAN: Thanks very much, 10 Dr. Duffy. It's great to hear that CARB-X has been 11 thinking about this and has been having discussions to 12 advance this field along. 13 Our next talk is entitled Challenges 14 and Lessons Learned Developing DAV132, a Novel Therapy 15 Protecting the Gut Microbiota from Antibiotic-Induced 16 Dysbiosis. It will be given by Ms. Florence Sejourne. 17 Ms. Sejourne is the CEO of Da Volterra, a biotech 18 company that develops innovative products such as 19 antibiotics targeting medical needs, including 20 prevention of infections. She's also the founding 21 board member of the BEAM Alliance, which represents 22 European biotech companies involved in developing</p>	<p style="text-align: right;">Page 289</p> <p>1 and diverse microbiota. Several benefits are expected 2 for such novel drug: prevention of <i>C. difficile</i> 3 infections, reduction of colonization by resistant 4 strains, and more recently maintenance of the immune 5 system enabling, for example, immune oncology drugs 6 like ENTPD1 to remain efficient in cancer patients who 7 have infections and need to be treated by antibiotics. 8 Next slide. 9 DAV132 is the most advanced product 10 developed by Da Volterra. It is composed of a 11 powerful absorbent and selected coating that capture 12 and inactivate antibiotics only in the colon. The 13 full and only delivery of the absorbent in the colon 14 enables the antibiotic block peaking levels to remain 15 intact while protecting the microbiota. Next slide. 16 So a lot of data has been generated on 17 DAV132 those last years, most of which being 18 published. I have a list of publication here at the 19 end of the slide set. We have first validated 20 DAV132's capacity to prevent CDI in a series of 21 preclinical experiments with multiple antibiotics 22 using the hamster reference model. More recently, we</p>

<p style="text-align: right;">Page 290</p> <p>1 have demonstrated in a proof of concept study in mice 2 the capacity of DAV132 to actually maintain the ENTPD1 3 one efficacy which was impaired by only five days of 4 antibiotic exposure using fecal samples or clinical 5 studies, and that will be presented very shortly at 6 SMO in Paris.</p> <p>7 I will comment in the next four slides 8 some of the clinical and microbiological data obtained 9 in a series of seven clinical studies where DAV132 was 10 shown to have an efficient and reproducible mode of 11 action in humans with a good safety profile enabling 12 us to move to Phase 3, and the CMC package of the 13 product was validated for Phase 3 as well. Next 14 slide.</p> <p>15 So first set of data there. You can 16 see DAV132 can, on the left, inactivate most 17 antibiotics in vitro and ex vivo. Then we moved to 18 clinics and we've shown that DAV132 was efficiently 19 capturing antibiotics in the colon, both 20 fluoroquinolones as well as beta-lactams, whatever 21 oral and IV, without impacting the plasma 22 concentration that is here presented on the right.</p>	<p style="text-align: right;">Page 292</p> <p>1 looked as well at VRE counts within our clinical Phase 2 2 trial and here you see that at the end of the 3 antibiotic treatment DAV132 group had a significantly 4 reduced VRE count. So overall, all we manage in those 5 series of clinical studies to have a solid Phase 1, 6 Phase 2 clinical package in order to move forward to 7 Phase 3 study which was designed to demonstrate the 8 prevention of <i>C. difficile</i> infections in patients at 9 risks. Next slide.</p> <p>10 So we decided to select the AML patient 11 population as an enriched patient population at risk 12 of CDI, as they were described actually to have more 13 than 12 percent risk of <i>C. diff</i> infection four months 14 after the start of their induction chemo.</p> <p>15 Furthermore, in those patients protection of the 16 microbiota from antibiotic dysbiosis is expected to 17 lead to additional clinical benefits such as reduction 18 of resistance colonization, infections, and even 19 prevention of GvHD for those who have to undergo 20 (indiscernible).</p> <p>21 The protocol was designed as a 22 multicenter randomized placebo controlled parallel arm</p>
<p style="text-align: right;">Page 291</p> <p>1 Next slide.</p> <p>2 Such decrease of antibiotic exposure in 3 the colon has led to a nice protection of the 4 microbiome diversity, once again both demonstrated 5 with fluoroquinolones and beta-lactams. This was 6 evaluated both from diversity indexes as well as 7 microbiome composition heat map as you see here with 8 16S and shotgun technologies. Next slide.</p> <p>9 So in order to associate such 10 biological demonstration of microbiome protection to 11 actual biological functions, we have conducted 12 additional analysis. The first analysis was done here 13 was done in ex-vivo study conducted with fecal samples 14 from our clinical trials showing that in patients 15 receiving our product DAV132 together with either 16 fluoroquinolones or beta-lactam, fecal samples when 17 exposed to <i>C. difficile</i> spores were protected from 18 proliferation. This really meant to us that DAV132 19 maintained the gut barrier effect and allows the 20 resistance to colonization function by <i>C. diff</i> to be 21 protected.</p> <p>22 In addition to this -- next slide -- we</p>	<p style="text-align: right;">Page 293</p> <p>1 clinical trial and the study was designed and launched 2 in a public private partnership with European 3 academics via the COMBACTE-NET consortium, co-funded 4 by IHI in 2021 and 2022. Next slide.</p> <p>5 An interesting point I wanted to 6 highlight today was the discussion we've had with the 7 FDA division on the primary analysis in such severe 8 at-risk patient population. We actually selected CDI 9 occurrence as an event of interest and death as a 10 competing risk with cause specific hazard ratio as a 11 statistical outcome.</p> <p>12 It's -- we don't really have time to go 13 through in details through that today, but this 14 analysis proposed was really innovative and was 15 actually worked out through collaboration with experts 16 from STAT-NET Group in Europe, now part of the e-cred 17 network.</p> <p>18 So we managed to launch that clinical 19 trial in 13 countries in Europe, but unfortunately we 20 had to stop it this summer for operational futility 21 because of too low recruitment rates in the hemato- 22 oncology settings to conduct the study in reasonable</p>

<p style="text-align: right;">Page 294</p> <p>1 timelines. So unfortunately at this stage, DAV132 2 development towards prevention of CDI is unfortunately 3 in standby status even though it has shown as a very 4 solid safety and biological efficacy profile in 500 5 individuals. And of course this raises a few 6 questions for the development of such protective 7 therapy. Next slide. 8 So there has been quite a lot of data 9 presented earlier today, so I'm going to go really 10 fast through those slides, especially by the CDC team. 11 But here are a few examples of papers in the 12 literature showing for example here the association 13 correlation between low diversity microbiota and 14 occurrence of CDI clinically and in -- pre-clinically. 15 Next slide. 16 Those, you know, references been have 17 been as well pointed out early on. It shows the 18 association between low diversity gut microbiota and 19 antibiotic use to colonization by MDROs, which is well 20 described in literature. 21 And finally, next slide, we have a list 22 of papers correlating colonization bacteria -- by</p>	<p style="text-align: right;">Page 296</p> <p>1 threat infections and AMR dissemination. 2 Similarly, some colleagues of the BEAM 3 Alliance developed pathogen-specific antibacterials 4 that have microbiota sparing properties expected to 5 lead to reduced risk of selection of resistance and 6 minimizing the overall burden of resistance. So we 7 all realize that it represents an important 8 competitive advantage in Phase 3 efficacy study to 9 show such an asset as well as in a higher economic 10 valuation. 11 The question is, you know, how could we 12 imagine including new achievable biomarkers such as 13 colonization with bacterial species in the gut 14 associated with mortality and morbidity risk which 15 could then be described and included in the clinical 16 section of a label for a such an antibiotic. 17 And we talked right before with Erin 18 about decolonization strategy and the need for new 19 endpoints as well to be considered there. Otherwise, 20 it's true that those studies are really big. So the 21 next and final take home message that are on my final 22 slide here.</p>
<p style="text-align: right;">Page 295</p> <p>1 resistant bacteria such as ESBL and VRE to increase 2 risk of HAI, especially in severe patients with cancer 3 in ICU or in dialysis. So I've seen a few of those 4 earlier today, so the data behind dysbiosis induced by 5 antibiotics and the cause of those secondary 6 infections is quite there in the literature and 7 recognized with CDC. Next slide. 8 So I would like to end this 9 intervention by sharing a few thoughts after having 10 faced the challenges around DAV132 development path in 11 the prevention of infection, especially putting a few 12 questions on the table for regulators to consider new 13 endpoints. So I'm taking kind of my two hats here, Da 14 Volterra and the BEAM Alliance. 15 Obviously, with DAV132, clearly co- 16 admins prevention approaches reducing dysbiosis and 17 colonization by bacteria and yeast caused by 18 antibiotics make clear medical sense and today's 19 session is extremely clear indeed about that. So the 20 question is how could we envision to facilitate their 21 access to market considering rather microbiological 22 markers as surrogate endpoints to combat those urgent</p>	<p style="text-align: right;">Page 297</p> <p>1 You know, there has been brainstorm 2 together with Da Volterra scientific founder Antione 3 Andremont, microbiologists in Paris, who dreamt of 4 protecting the microbiome while giving antibiotics and 5 obviously today after many, many years and efforts 6 behind, sparing the microbiota from antibiotic 7 dysbiosis and colonization is technically possible. 8 We've done it. We have very solid and 9 nice data but however it's really not yet 10 operationally financially feasible because we are 11 asked to show reduction of secondary infections which 12 necessitates really too large and expensive studies, 13 especially as you know, most of the research is done 14 by SMEs in that field and definitely our belief is 15 that new regulation which could -- which would accept 16 an accelerated path prevention of colonization as 17 endpoints for clinical development would be a really, 18 nearly a necessity to be able to develop that strategy 19 later on for the benefits of individual patients as 20 well as the global control of AMR. 21 So I thank you very much for your 22 attention and happy to exchange later on and these are</p>

<p style="text-align: right;">Page 298</p> <p>1 the publications for interest.</p> <p>2 DR. DAN RUBIN: Thank you very much for</p> <p>3 that presentation. Our next speaker is Vince Wacher.</p> <p>4 Dr. Wacher is currently the head of corporate and</p> <p>5 product development at Synthetic Biologics. He has</p> <p>6 nearly 30 years of experience leading corporate</p> <p>7 strategy, partnering research, clinical development</p> <p>8 and intellectual property programs for startups, small</p> <p>9 companies, and new business units within large</p> <p>10 companies. Over.</p> <p>11 DR. VINCE WACHER: Thank you very much.</p> <p>12 The -- today I'm going to talk about our product SYN-</p> <p>13 004 as a potential point of care preventative for</p> <p>14 healthcare-acquired Clostridioides difficile</p> <p>15 infection. Today I want to concentrate on the lessons</p> <p>16 we learned. All of our information is being published</p> <p>17 and I refer everybody to the publications, but you</p> <p>18 will hear a little bit of reiteration of the previous</p> <p>19 talk and some of the challenges that we meet as we try</p> <p>20 to develop these products. Next slide, please.</p> <p>21 Synthetic Biologics is a publicly</p> <p>22 traded company, so our aspirations and our</p>	<p style="text-align: right;">Page 300</p> <p>1 versus host disease with this product. Next slide,</p> <p>2 please.</p> <p>3 The concept for SYN-004 is very simple.</p> <p>4 Once the person is admitted to hospital, they get an</p> <p>5 IV beta-lactam antibiotic. Some of that is excreted</p> <p>6 into the bile. That moves down and damages the</p> <p>7 microbiome. SYN-004 is an orally administered beta-</p> <p>8 lactamase enzyme that is given that is enteric</p> <p>9 protected. The patient takes that during the time</p> <p>10 that they're being given this antibiotic. The product</p> <p>11 passes through the stomach and releases the enzyme</p> <p>12 into the upper GI tract and it's there waiting to</p> <p>13 degrade the excess antibiotic that gets into the colon</p> <p>14 -- sorry, into the GI tract and then breaks it down</p> <p>15 before it gets the colon.</p> <p>16 And that way we preserve this</p> <p>17 microbiome. Again this is a preventative. We want to</p> <p>18 make sure that the microbiome is preserved to prevent</p> <p>19 these diseases. And as you can see, this is something</p> <p>20 that's done at the time of the antibiotic</p> <p>21 administration, so a point of care preventative is the</p> <p>22 way we view this product. We go on to the next slide,</p>
<p style="text-align: right;">Page 299</p> <p>1 expectations are all subject to SEC disclosure</p> <p>2 requirements and our forward-looking statement</p> <p>3 description is on -- in our presentation, but also in</p> <p>4 all of our literature that we filed and made public.</p> <p>5 Next slide, please.</p> <p>6 So SYN-004 itself is a pretty simple</p> <p>7 concept. The microbiome is complex. We know that for</p> <p>8 sure. We also know that the microbiome protects us</p> <p>9 from different kinds of diseases, and when we damage</p> <p>10 the microbiome we are subject to all kinds of</p> <p>11 potential different diseases and one of the worst</p> <p>12 offenders in this particular instance is beta-lactam</p> <p>13 antibiotics.</p> <p>14 So we are looking to prevent the</p> <p>15 effects of beta-lactam antibiotics on the microbiome</p> <p>16 and by doing that let the microbiome do the heavy</p> <p>17 healthcare lifting. Let the microbiome protect us and</p> <p>18 prevent the diseases. We have in fact advanced, you</p> <p>19 know, forward to the end of a Phase 2b study looking</p> <p>20 at Clostridioides difficile infection but also looking</p> <p>21 at vancomycin-resistant enterococci decolonization and</p> <p>22 now we're in a Phase 1b2a study looking at acute graft</p>	<p style="text-align: right;">Page 301</p> <p>1 please.</p> <p>2 So in looking at the life cycle and</p> <p>3 where we intervene with this product, this is a very</p> <p>4 simplified model but I hope it helps people understand</p> <p>5 the kinds of things that enter into the thought</p> <p>6 process around the development of these point of care</p> <p>7 preventative. So a patient comes into the hospital</p> <p>8 with what's called their index infection, their index</p> <p>9 admission, the reason they come there, and in our</p> <p>10 Phase 2 study, it was lower respiratory tract</p> <p>11 infections.</p> <p>12 They are treated with an antibiotic.</p> <p>13 In this case, it was intravenous ceftriaxone. The</p> <p>14 antibiotic, as we saw, can be excreted into the GI</p> <p>15 tract and cause dysbiosis and then that can cause</p> <p>16 damage to the microbiome that ends up leading to</p> <p>17 Clostridioides difficile infection.</p> <p>18 And there's a lot on this slide, but I</p> <p>19 want to point out that red arrow, that red there where</p> <p>20 it says C. difficile colonization bloom and</p> <p>21 toxigenesis. This is a challenge. Twenty percent of</p> <p>22 us are sitting around here today and we have</p>

<p style="text-align: right;">Page 302</p> <p>1 asymptomatic Clostridioides difficile infection --</p> <p>2 colonization in our gut. Most of us will never end up</p> <p>3 getting an infection, and that is true, too, for the</p> <p>4 hospital population.</p> <p>5 In our study, when we treated the</p> <p>6 patients with IV ceftriaxone, about 3.4 percent of the</p> <p>7 patients got CDI. None of them were pre-colonized.</p> <p>8 Anybody that was colonized when they walked in the</p> <p>9 door of the hospital, they did not get CDI. Everybody</p> <p>10 picked up new colonization. About half of them got</p> <p>11 CDI in hospital and half of them when they left the</p> <p>12 hospital. So that's a challenge. Just having that</p> <p>13 that bacteria in my gut doesn't predispose me</p> <p>14 necessarily to getting the disease.</p> <p>15 Once the person gets CDI, obviously</p> <p>16 there's treatment and management involved and there's</p> <p>17 different medicines for that, different processes, and</p> <p>18 then the number one challenge or significant</p> <p>19 challenges is this recurrence. Once you've had CDI,</p> <p>20 you're -- you have a dramatic increase in your chances</p> <p>21 of getting it again. And in fact, getting recurrent</p> <p>22 CDI, the number one risk factor for getting CDI is</p>	<p style="text-align: right;">Page 304</p> <p>1 That's paid for by insurers by what's called the</p> <p>2 diagnosis-related group, a lump sum payment that</p> <p>3 covers that payment.</p> <p>4 As we go through, if the patients get</p> <p>5 CDI, there's obviously an added cost and the added</p> <p>6 cost can be significant and so here we're saying about</p> <p>7 \$500,000 additional per 1,000 patients. And then</p> <p>8 there's recurrence and the cost of that is even</p> <p>9 higher, so another \$300,000 on top of that. And this</p> <p>10 is before we consider mortality, before we consider</p> <p>11 the patient burden, before we consider potential</p> <p>12 penalties. Just as a simple baseline, let's look</p> <p>13 at the \$810,000 worth of increased cost per 1,000</p> <p>14 patients.</p> <p>15 If we go to the next slide, point of</p> <p>16 care prevention has the opportunity to really knock</p> <p>17 that down. That's a 70 percent decrease in the total</p> <p>18 cost, just in this very simple model. That doesn't,</p> <p>19 again, include the death. It doesn't include the</p> <p>20 patient burden. It doesn't include the liabilities.</p> <p>21 But the challenge here is how much is</p> <p>22 this intervention worth? Is it something that you</p>
<p style="text-align: right;">Page 303</p> <p>1 having previously had CDI. That doesn't really help</p> <p>2 us when we were trying to prevent primary CDI.</p> <p>3 So there's two things that we should be</p> <p>4 thinking about now before we get onto even the bigger</p> <p>5 challenges. One is having the bug doesn't equal</p> <p>6 getting the disease. And second of all, the risk</p> <p>7 factors involved require that you either were</p> <p>8 previously in hospital or previously have had disease.</p> <p>9 Underneath, some numbers. And this is</p> <p>10 just an example because one of our challenges here is</p> <p>11 how do we define the value of this intervention?</p> <p>12 Medically unquestioned. Patients don't want to get</p> <p>13 it. Doctors don't want patients to get CDI. There's</p> <p>14 about 46,000 deaths a year from CDI. Clearly,</p> <p>15 preventing CDI is a medical imperative but there is a</p> <p>16 challenge. And the challenge is these clinical trials</p> <p>17 don't happen for free.</p> <p>18 So let's have a quick look underneath</p> <p>19 there at the way this potentially works, a very</p> <p>20 simplified model. So the absolute numbers are not</p> <p>21 important. But for say 1,000 patients come to the</p> <p>22 hospital and they're treated with the antibiotic.</p>	<p style="text-align: right;">Page 305</p> <p>1 have to break even or is it something that has a more</p> <p>2 expansive value because once we start including the</p> <p>3 mortality, the patient burden, and all these other</p> <p>4 issues.</p> <p>5 So that's been one of the underlying</p> <p>6 challenges of development in this space is defining</p> <p>7 the value, and I don't mean the therapeutic value. I</p> <p>8 mean for someone who's going to pay to develop this</p> <p>9 product, what is the value that enables them to come</p> <p>10 forward and actually to develop this program? Next</p> <p>11 slide, please.</p> <p>12 So I want to give you three of our four</p> <p>13 key lessons on this slide and the first, based on our</p> <p>14 experience with Clostridioides difficile infection, is</p> <p>15 that the trials are large and costly. And part of the</p> <p>16 reason is that you have to treat everybody that comes</p> <p>17 in, because as I said before, just having that CDI --</p> <p>18 the Clostridioides difficile in your gut really</p> <p>19 doesn't help you pick the patient population because</p> <p>20 it doesn't necessarily mean that patient is going to</p> <p>21 get the infection, which is the actual disease, the</p> <p>22 actual disease outcome.</p>

<p style="text-align: right;">Page 306</p> <p>1 The other, as we know these are 2 patients in hospital. So there are adverse events and 3 there are deaths and balancing out the incidence of 4 the disease with the incidence of the adverse events 5 and deaths again requires a large number of patients 6 to try and tease those apart so you can get a proper 7 therapeutic outcome from your clinical trial. And so 8 when we looked at this for our Phase 3 study, that's 9 about 4,000 patients and then we're up to about \$100 10 million. That is a very, very large amount of 11 clinical trial funding required and gets back to this 12 concept of how do we convince people to -- this is 13 something that should be paid for? 14 The second lesson in all of this was 15 really that clinical trial recruitment is difficult. 16 As you can see, if our incidence is about 3 percent in 17 our population, there is no immediate benefit to 97 18 percent of the patients that come in. None. Ninety- 19 seven percent of the patients won't get anything from 20 this. So that's a philosophical challenge to get 21 patients into the study. 22 The other is, and we found this out</p>	<p style="text-align: right;">Page 308</p> <p>1 you're not familiar with this, if you're in the lowest 2 25 percent of hospitals that are -- based on your 3 healthcare-acquired infectious scores, you're 4 penalized 1 percent of all of your Medicare 5 reimbursements per year, and then your name -- naughty 6 list. There's a public list of hospitals that are in 7 that lower 25 percent, so nobody wants that. 8 So on top of that, there's a potential 9 liability from patients and patient advocates and the 10 lost revenue to the hospital of having to deal with 11 this. So the hospitals are extremely keen to use the 12 product, but they don't pay for the development of the 13 product. And then the next slide please. 14 The lesson that that absolutely stopped 15 us in our tracks when we first heard it -- I mean, it 16 hasn't stopped us moving the product forward but this 17 was an absolute jaw dropper. We were looking around 18 for partners for this program and got this specific 19 feedback and -- to our face. Incidence is low. Drugs 20 are cheap. Just treat the CDI. 21 That's a problem. That's a value 22 perception problem because if I have to find 4,000</p>
<p style="text-align: right;">Page 307</p> <p>1 very quickly, is when you start talking about CDI, 2 doors start closing because hospitals and healthcare 3 facilities are working extremely hard to not have CDI 4 or any other of the potential hospital-acquired 5 infectious organisms in their institutions. So it's 6 quite difficult to actually get these trials up and 7 running. 8 And then the third thing we learned in 9 in the market outreach study was that hospitals are 10 the primary customer, and I mean this from a from a 11 financial point of view, not necessarily from a 12 therapeutic point of view. Hospitals are the ones 13 that bear the burden because the insurers, they look 14 at it and go well if this person has had an adverse 15 outcome, a hospital-acquired infection from your index 16 admission, you should just pay for it out of what we 17 gave you for the original infection. So the payers 18 aren't really thinking about it that way. So that 19 means there's a shortfall in the overall payment to 20 the Hospital. 21 There are also healthcare acquired 22 condition reduction programs from Medicare, and if</p>	<p style="text-align: right;">Page 309</p> <p>1 patients and \$80 to \$100 million, I need people to 2 understand the value. So this is a significant 3 challenge in the development of preventatives for 4 these kinds of infections, because again we know 5 medically, we know therapeutically it's valuable. How 6 do you make this value proposition to people that will 7 pay for the drug development. So if we go to the next 8 slide, please. 9 So some of the things, and I'm just 10 going to reiterate, echo what I think we've heard a 11 lot today. We need to find some risk factors and some 12 biomarkers that help us with patient pre-selection and 13 things that we can follow in a meaningful timeframe 14 and an affordable timeframe to actually be able to say 15 this product is something we can develop. We can take 16 it to the market and patients will use it to protect 17 patients from these kinds of diseases. 18 The other thing that -- this is 19 something that we're pursuing now and as was said in 20 the previous talk, can we conduct trials in patient 21 populations with higher incidences of the endpoint and 22 bone marrow transplant patients is one and we're</p>

<p style="text-align: right;">Page 310</p> <p>1 moving forward with a study in the bone marrow 2 transplant patient population. And just one more 3 slide.</p> <p>4 Because I've talked a lot about money, 5 but let's face it at the end of the day this is 6 feedback from a chief medical officer of a hospital 7 that's very encouraging. We want to heal people. We 8 want to do it the right way. I think that within 9 these hospitals if the products are available, they 10 will be willing to pay for it for therapeutic reasons, 11 but also for the to protect themselves.</p> <p>12 So I think the value is there. The 13 opportunity is that if we can overcome that energy of 14 activation, that financial challenge and be able to do 15 trials that get us to the market. And with that, 16 thanks very much for listening and thank you for the 17 invitation.</p> <p>18 DR. JOHN JERNIGAN: Thank you very 19 much, Dr. Wachter. Our next talk is Defined Bacterial 20 Consortia, a Novel Approach to Tackle Healthcare- 21 Associated Infections given by Dr. Silvia Caballero. 22 Dr. Caballero is director of infectious diseases at</p>	<p style="text-align: right;">Page 312</p> <p>1 developed our lead drug product, VE303 to reestablish 2 organization resistance against C. difficile and 3 restore a protective gut environment. Next slide.</p> <p>4 VE303 is a defined bacterial consortium 5 consisting of eight well characterized strains 6 isolated from healthy human donors, which makes VE303 7 a safer alternative to FMT, given that there is no 8 donor material and therefore the likelihood of 9 pathogen transfer distinction is essentially zero.</p> <p>10 We selected this consortium based on 11 its ability to prevent C. difficile infection and 12 restore beneficial metabolites in preclinical models.</p> <p>13 Each strain is grown from clonal cell banks under GMP 14 conditions, enabling a pure and consistent drug 15 product with the same quality attributes from batch to 16 batch.</p> <p>17 Also, the manufactured drug is stable, 18 which enables flexible storage conditions and dosing, 19 and in the next few slides, I'm going to show you that 20 VE303 is able to colonize human subjects and prevent 21 C. diff (indiscernible). Next slide.</p> <p>22 VE303 was given to healthy volunteers</p>
<p style="text-align: right;">Page 311</p> <p>1 Vedanta Biosciences in Cambridge, Massachusetts. She 2 is also the head of Vedanta's multidrug resistance 3 program aimed at reducing risk of MDRO infections by 4 promoting reduction of intestinal carriage with 5 defined bacterial consortia. Dr. Caballero.</p> <p>6 DR. SILVIA CABALLERO: Thanks, John, 7 for the introduction and thanks to the organizers for 8 the invitation.</p> <p>9 Today, I'm going to be sharing with you 10 some of our learnings from recent clinical as well as 11 pre-clinical studies using microbiome therapeutics 12 based on bacterial consortia specifically in the 13 context of CDI and MDR decolonization. Next slide.</p> <p>14 As we've heard from multiple speakers 15 today, one of the major risk factors for C. difficile 16 infection and expansion of MRDOs is treatment with 17 broad spectrum antibiotics. This causes a disruption 18 of the microbial ecosystem in the intestine and 19 reduces the pool of beneficial metabolites such as 20 secondary bile acids and short-chain fatty acids which 21 have been shown to be important for preventing CDI. 22 And with this in mind, we at Vedanta</p>	<p style="text-align: right;">Page 313</p> <p>1 in a Phase 1 study where the goal was to evaluate 2 safety and tolerability of the drug adding from the 3 dose for our Phase 2 study in (indiscernible) 4 patients. We had multiple culprits that were given 5 differing doses of VE303 on a single day or multiple 6 days after every course of vancomycin.</p> <p>7 Pharmacokinetics for us in the 8 microbiome field refers to detection of the drug 9 components in the host, which is what this one is 10 showing. So on the Y axis, there is a number of VE303 11 strains detected in these patient cohort and on the X 12 axis is time from the start of dosing out to one year.</p> <p>13 And what we observed was that the 14 multiday culprits that received the highest VE303 dose 15 showed the most robust and persistent colonization 16 where we were able to detect 100 percent of the VE303 17 strains. Another takeaway from the study was that in 18 the absence of vancomycin, our strains (indiscernible) 19 on the scan, and that's the panel that I'm showing on 20 the right.</p> <p>21 Pretreatment with an antibiotic, as we 22 know, reduces microbial density which in our case</p>

<p style="text-align: right;">Page 314</p> <p>1 helps create a niche for our strains so that they can 2 colonize. So this is an important consideration for 3 microbiome-based therapeutics to ensure that the drug 4 product is able to get in. And in the case of CDI 5 patients, they are already getting antibiotics as part 6 of their standard of care, so no additional 7 antibiotics are necessary.</p> <p>8 Lastly, I'm not showing this data, but 9 we also saw recovery of the indigenous microbiota and 10 beneficial metabolites which refers to the 11 pharmacodynamics of the drug. And as far as safety is 12 concerned, there were no severe adverse events 13 associated with VE303. Next slide.</p> <p>14 So that was our Phase 1 study. Then we 15 moved to a Phase 2 studying in CDI patients to assess 16 efficacy of VE303. So here I'm going to show you some 17 of our key findings. This plot, and I apologize it's 18 so small, shows the probability of being recurrent 19 free. So the larger the number, the better. Once 20 again, we found that dose levels do matter. We had 21 two groups of patients, one that received a low dose 22 of VE303 which is shown in red and a second one that</p>	<p style="text-align: right;">Page 316</p> <p>1 didn't refer had a higher level of colonization of the 2 majority of VE303 strains, so that's the blue line, 3 again suggesting that colonization of our drug is a 4 strong predictor of cure. Next slide.</p> <p>5 And last but not least, microbiota 6 recovery is also important for clinical success. We 7 saw that responders, here shown in blue, had a more 8 diverse microbiome than non-responders, and this 9 increase in diversity was much more pronounced in the 10 high dose group. Next slide.</p> <p>11 So switching gears a bit, we also have 12 a program where the focus is on gram-negative bacilli. 13 This is our VE707 program, currently in a preclinical 14 stage where the goal is to educe defined bacterial 15 consortia to prevent infection in the hospital setting 16 by reducing carriage of these organisms in intestine. 17 And we're specifically looking carbapenem-resistant 18 Enterobacteriaceae producing E. coli and Klebsiella 19 pneumoniae.</p> <p>20 As others have mentioned, the clinical 21 evidence that decolonization translates to less 22 infections is very strong. This has been demonstrated</p>
<p style="text-align: right;">Page 315</p> <p>1 received a high dose, which is indicated by the blue 2 line, and this is the dose that we selected based on 3 the Phase 1 data.</p> <p>4 As you can see, there was no difference 5 in outcomes between the low dose and placebo, which is 6 shown in gray, and only the high dose met our primary 7 efficacy endpoint where we saw an 85 percent sustained 8 cure rate, which is comparable to what has been seen 9 with FMT.</p> <p>10 Interestingly, most of the action seems 11 to happen -- seems to be happening within these 14-day 12 window which is the area highlighted in blue where we 13 observed the most recurrences in all groups, but once 14 the treatment course was completed, difference in 15 efficacy became very clear. Next slide.</p> <p>16 And what we know is that around this 17 timeframe, the prevalence of VE303 strains is much 18 higher in the high dose group shown in red compared to 19 the low dose group, and that's the panel that I'm 20 showing in the upper right corner. And if we stratify 21 these patients based on clinical response -- that's 22 the panel below -- you can see that the patients that</p>	<p style="text-align: right;">Page 317</p> <p>1 with selective digestive decontamination and fecal 2 microbiota transplantation, but there are caveats 3 associated with these modalities, as we know.</p> <p>4 I the case of SDD, antibiotics can 5 foster the development of resistance and also the 6 ecological dysbiosis which is the main culprit for 7 colonization and infection is not addressed, which is 8 why recurrence rates tend to be a bit high with SDD. 9 And for FMT, as we know, the main issue is donor and 10 batch-to-batch variability which we know can impact 11 the efficacy of the FMT material. Next slide.</p> <p>12 There are several patient populations 13 where the risk of MDRO infection goes up 14 significantly, if they happen to be colonized and one 15 of them is the bone marrow transplant population. 16 This is just an example of the microbiota changes that 17 these patients go through during the course of the 18 transplant. They start out with a very diverse 19 microbiota. These are indicated by the brown and gray 20 colors. And once antibiotics are administered, 21 pathogens like E. coli, shown in red, emerge and 22 increase in abundance days before it is detected in</p>

<p style="text-align: right;">Page 318</p> <p>1 the bloodstream, in the case of this one patient. 2 This particular infection was readily 3 treated with antibiotics and you can see E. coli going 4 away, but we then see a massive expansion of another 5 pathogen, vancomycin-resistant enterococcus, which now 6 puts the patient at risk for VRE infection. 7 So having a surveillance system in 8 place where patients are routinely monitored for 9 colonization can be extremely helpful to identify a 10 timeframe where we can intervene and minimize the risk 11 of conversion from colonization to infection. Next 12 slide. 13 And something that's important that we 14 need to remember is that complete MRDO elimination is 15 not required for infection prevention. FMT studies 16 like the one that I'm referencing here have shown that 17 the risk of MDRO infection can be significantly 18 reduced despite modest decolonization. And that's 19 because in addition to reducing carriage to low enough 20 levels which is important, there the other functions 21 that microbiota exert on the host, like the production 22 metabolized that produce -- that promote health and</p>	<p style="text-align: right;">Page 320</p> <p>1 by doing so we also hope to be able to reduce 2 antibiotic use in the clinic. Thanks very much. 3 DR. DAN RUBIN: Thank you very much, 4 Dr. Caballero. Our final speaker of this session is 5 Matt Henn. Dr. Henn is executive vice president and 6 chief scientific officer at Seres Therapeutics. He 7 has been involved in the discovery and development of 8 multiple microbiome therapeutics across infectious, 9 inflammatory, and oncology indications. Over. 10 DR. MATTHEW HENN: Good afternoon. Let 11 me start by thanking the organizers of this timely and 12 important workshop for the opportunity to speak today 13 about Seres microbiome therapeutic technologies and 14 our progress on deploying our novel drug technologies 15 to combat bacterial infections and AMR. Next slide, 16 please. 17 In the next ten minutes, I'll provide a 18 quick snapshot on how we are advancing novel 19 microbiome therapeutics that are consortia of multiple 20 species of bacteria. Briefly, our drugs are designed 21 to have the bacteria engraft into the gut, meaning 22 they germinate and vegetatively grow in patients' GI.</p>
<p style="text-align: right;">Page 319</p> <p>1 reestablishment of the gut epithelial barrier which 2 together limits the ability of these pathogens to 3 become invasive. Next slide. 4 So going back to VE707, we tested 5 around 60 defined bacterial consortia in mouse models 6 of colonization and VE707 was the most potent 7 (indiscernible) where we saw at least 1,000-fold 8 reduction in klebsiella and E. coli carriage over 9 time. 10 Now, we think this degree of 11 decolonization could be clinically meaningful based on 12 evidence from (indiscernible) and others where it is 13 more common to see high infection rates in patients 14 who are dominated or have high titers of an MDRO. 15 Next slide. 16 Okay, so in closing, we understand that 17 there are many challenges but we believe that we can 18 make a difference in the lives of these patients, 19 especially those that are high risk, by modulating the 20 microbiome. In the case of CDI, we have shown that it 21 is possible to do this and the same idea applies for 22 decolonization and an MDRO infection prevention where</p>	<p style="text-align: right;">Page 321</p> <p>1 Engraftment is a measure of the drug's 2 pharmacogenetics. 3 Next, the engraftment of bacteria from 4 our investigational drugs leads to broader 5 restructuring of the microbiome and modulation of the 6 metabolic landscape of the gut. These are measures of 7 the drug candidate's pharmacodynamics. These are -- 8 importantly with our technology we're engrafting 9 several species at the same time with a single 10 investigational drug. This allows us to attempt to 11 modulate multiple disease relevant pathways at the 12 same time with one treatment. Next slide, please. 13 As heard throughout today, the 14 increasing emergence of AMR is a significant public 15 health threat. It is a slow pandemic. Recently in a 16 review of the global impact of AMR in The Lancet, 17 bloodstream infections tied to AMR were identified as 18 a major cause of death. As those involved in this 19 workshop know well, there has been limited innovation 20 in new antimicrobials despite the growing impact of 21 AMR and as we've heard multiple times today, 22 beneficial microbes in our gut are an important piece</p>

<p style="text-align: right;">Page 322</p> <p>1 of the puzzle in combating infection and AMR.</p> <p>2 Microbiome therapeutics provide a novel</p> <p>3 approach to manage AMR and their mechanisms of action</p> <p>4 are potentially less susceptible to the emergence of</p> <p>5 resistance. Moving a slide forward, please.</p> <p>6 Data from our ECOSPOR III study of SER-</p> <p>7 109 shows that this novel therapeutic modality can</p> <p>8 work successfully in the clinic. As published earlier</p> <p>9 this year in The New England Journal of Medicine, SER-</p> <p>10 109 achieved superiority compared to placebo at eight</p> <p>11 weeks of follow up. Only 12.4 percent of subjects in</p> <p>12 the SER-109 arm recurred in the <i>C. difficile</i> patients,</p> <p>13 whereas 39.8 percent of subjects in the placebo arm</p> <p>14 recurred.</p> <p>15 This translates to a sustained clinical</p> <p>16 response of 88 percent. The relative risk at eight</p> <p>17 weeks, which was the primary endpoint, was highly</p> <p>18 significant at 0.32 but the upper bound of the 95</p> <p>19 percent confidence interval is well below the</p> <p>20 threshold predefined for the trial to be a single</p> <p>21 pivotal trial.</p> <p>22 While not shown here, results from our</p>	<p style="text-align: right;">Page 324</p> <p>1 I'm showing data here that supports</p> <p>2 some of the mechanisms of action of SER-109 in</p> <p>3 establishing colonization resistance to <i>C. difficile</i>.</p> <p>4 As shown in the left panel, we observed significant</p> <p>5 engraftment of bacteria in our drug as compared to</p> <p>6 placebo patients. Here we are reporting the total</p> <p>7 number of drug species observed. Engraftment is rapid</p> <p>8 and durable with significant signatures observed</p> <p>9 rapidly and as early as one week, which is important</p> <p>10 in the context of treating an infectious disease.</p> <p>11 Engraftment leads to restructuring of</p> <p>12 the disrupted disease state microbiome and modulation</p> <p>13 of the metabolic landscape in the gastrointestinal</p> <p>14 tract. As example shown on the right in the log scale</p> <p>15 plot, this includes a significant increase as compared</p> <p>16 to placebo patients in secondary bile acids that</p> <p>17 inhibit <i>C. difficile</i> vegetative growth and not shown</p> <p>18 on the graph a reciprocal depletion of primary bile</p> <p>19 acids that stimulate <i>C. difficile</i> spore germination.</p> <p>20 Next slide, please.</p> <p>21 I'll now switch gears to focus on</p> <p>22 observations that SER-109 can reduce additional</p>
<p style="text-align: right;">Page 323</p> <p>1 ECOSPOR IV open label safety study were confirmatory</p> <p>2 of these results and demonstrated comparable sustained</p> <p>3 clinical response rates in both multiple and first</p> <p>4 recurrent patients. In both ECOSPOR III and IV, SER-</p> <p>5 109 was well tolerated with most adverse events being</p> <p>6 GI related. As stated publicly previously, we are in</p> <p>7 the final stages of a BLA submission for SER-109.</p> <p>8 Next slide, please.</p> <p>9 SER-109 was designed to restructure the</p> <p>10 gastrointestinal microbiome and modulate the metabolic</p> <p>11 landscape in the GI to establish colonization</p> <p>12 resistance to <i>C. difficile</i>. Pathogenesis of <i>C.</i></p> <p>13 <i>difficile</i> infection is a two-hit process. The first</p> <p>14 hit is the use of broad spectrum antibiotics that lead</p> <p>15 to loss of beneficial bacteria and their associated</p> <p>16 functions which play a dominant role in host defense,</p> <p>17 leaving the patient with a disrupted microbiome that</p> <p>18 is vulnerable to potential pathogens.</p> <p>19 The second hit is patient exposure to</p> <p>20 <i>C. difficile</i> spores. These pathogenic spores</p> <p>21 germinate into the toxin producing bacteria that lead</p> <p>22 to diarrhea and colitis. Next slide, please.</p>	<p style="text-align: right;">Page 325</p> <p>1 pathogens that harbor antimicrobial resistance.</p> <p>2 Treatment with SER-109 rapidly and significantly</p> <p>3 reduced the abundance of proteobacteria in patients'</p> <p>4 guts. These are the bacteria that harbor antibiotic</p> <p>5 resistance genes. As shown in the plot on the left,</p> <p>6 the proteobacteria in the Enterobacterales and</p> <p>7 Enterobacteriaceae that were most significantly</p> <p>8 reduced are also those significantly associated with</p> <p>9 more frequent carriage of genes that confer</p> <p>10 antimicrobial resistance.</p> <p>11 The Y axis shows statistical</p> <p>12 significance in terms of negative log P values. As</p> <p>13 has shown on the right side, SER-109 treatment leads</p> <p>14 to significant reduction in the total abundance of</p> <p>15 antimicrobial resistant genes in the gastrointestinal</p> <p>16 tract of patients as compared to placebo. Our SER-109</p> <p>17 program provides strong in-human proof of concept that</p> <p>18 a microbiome therapeutic has the potential to be a</p> <p>19 novel technology to address AMR and decolonize</p> <p>20 potential pathogens. Next slide, please.</p> <p>21 Seres microbiome therapeutics provide a</p> <p>22 novel potentially transformative technology for the</p>

<p style="text-align: right;">Page 326</p> <p>1 protection from the treatment of infections, AMR, and 2 bacteremia. As noted earlier, a disrupted 3 gastrointestinal microbiome can lead to domination in 4 the gut by undesirable microbes and we've heard about 5 that multiple times today. It can also lead to the 6 breakdown of the mucosa and epithelium that can lead 7 to bloodstream infections resulting from bacterial 8 translocation.</p> <p>9 Seres consortia are designed to restore 10 colonization resistance to pathogens, bacteria, and 11 our drugs can out compete pathogens and inhibit their 12 growth through nutrient competition and other 13 mechanisms. This can decrease pathogen abundance in 14 the gut which both potentially reduces the likelihood 15 of patient-to-patient transmission and of bacterial 16 translocation to the bloodstream.</p> <p>17 Our drug candidates are specifically 18 designed to also reduce translocation through 19 enhancing epithelial barrier integrity. And lastly, 20 our drug candidates are designed to modulate immune 21 responses. Next slide, please.</p> <p>22 I will now transition to our SER-109 --</p>	<p style="text-align: right;">Page 328</p> <p>1 respectively where mice are first infected and heavily 2 colonized with VRE or CRE, the red lines, subsequent 3 therapeutic oral administration of SER-155, the blue 4 lines, led to significant 2 to 3 log reductions in VRE 5 and CRE titers in the gut compared to untreated mice.</p> <p>6 Notably, these reductions in VRE and 7 CRE occur rapidly after SER-155 dosing. SER-155 also 8 includes bacteria that produce metabolites that have 9 the potential to prevent bacterial translocation and 10 reduce graft versus host disease. Next slide, please.</p> <p>11 As I noted earlier, SER-155 is 12 specifically designed to also improve epithelial 13 barrier integrity and is effective in doing so in our 14 in vitro primary colonic membrane assay. In this 15 screening model, an intact epithelial barrier is 16 established and as shown in the left panel treatment 17 with interferon gamma alone will lead to epithelial 18 damage and permeability.</p> <p>19 In this model, we include consortia 20 that are designed to not produce the metabolites that 21 we have optimized SER-155 to produce. As you can see, 22 these negative consortia are not protective of the</p>
<p style="text-align: right;">Page 327</p> <p>1 sorry, SER-155 program specifically. Building on the 2 data and the mechanisms I just spoke about, we have 3 designed SER-155 using our reverse translational MVTX 4 discovery platform. Briefly, SER-155 is an 5 investigational consortium of a unique human commensal 6 bacterial strains that are cultivated from master cell 7 banks and encapsulated for oral delivery. SER-155 is 8 currently in a Phase 1b study that targets assessment 9 of drug safety and drug pharmacology in hematic stem 10 cell transplant patients that are highly 11 immunocompromised and susceptible to VRE and CRE 12 colonization and bloodstream infections. Next slide, 13 please.</p> <p>14 In the case of SER-155, we optimized 15 the consortia to have a powerful effect in directly 16 decolonizing CRE and VRE. These bacterial species are 17 frequent pathogens in people receiving stem cell 18 transplants as well as in a broad spectrum of 19 antimicrobial resistant infections in various hospital 20 settings that we heard about a couple of times today.</p> <p>21 As shown here in mouse models of VRE 22 and CRE colonization shown on the left and right</p>	<p style="text-align: right;">Page 329</p> <p>1 epithelium. In contrast, SER-155 is protective and 2 achieved significant greater barrier protection than 3 both experimental controls.</p> <p>4 This pharmacological property of SER- 5 155 enhances its potential ability to protect patients 6 from infections, not only by targeting the pathogens 7 directly to decolonize them, but also by reducing the 8 ability of the pathogens to translocate from the GI 9 tract to the bloodstream.</p> <p>10 As shown on the right, SER-155 also is 11 designed to modulate immune responses that are of 12 relevance to graft versus host disease.</p> <p>13 Unfortunately, I don't have time to cover that data 14 today, but those can review the slides after which are 15 publicly available. Next slide, please.</p> <p>16 So Seres is committed to advancing 17 microbiome therapeutics as a novel technology to 18 combat infections and AMR. In addition to SER-109 and 19 SER-155, we have active programs in multiple high risk 20 populations including cancer, neutropenia, cirrhosis, 21 and several others of the populations discussed 22 earlier today.</p>

<p style="text-align: right;">Page 330</p> <p>1 Our preclinical and clinical data 2 support that our investigational products can 3 directly decolonize various GI pathogens and that they 4 have the potential to prevent infections, 5 translocation, and bacteremia. I've touched today on 6 some of the novel mechanisms of Seres' drug 7 technologies and I'll close by providing a few 8 considerations based on our experience over the past 9 ten-plus years in developing these drugs that are 10 important as we broaden the arsenal of microbiome 11 therapeutics.</p> <p>12 These include continuing to improve the 13 translatability of our preclinical screens and models 14 for lead optimization; continue to enhance methods to 15 evaluate drug PK, PD, and dosing strategies; refining 16 our understanding of patient subpopulations on disease 17 pathogenesis and drug pharmacology; developing drug 18 formulation strategies that optimize patient access 19 and can capture the broad breath of microbial biology 20 we have accessible to us; and lastly scaling GMP 21 manufacturing capabilities to be able to leverage 22 those and manufacture those.</p>	<p style="text-align: right;">Page 332</p> <p>1 everybody. This is Michael Craig, the director of 2 Antimicrobial Resistance at CDC and I'm joined by my 3 colleague Peter Kim. Peter, do you want to introduce 4 yourself?</p> <p>5 DR. PETER KIM: Yes. Thank you, 6 Michael. My name is Peter Kim. I'm the director of 7 the Division of Anti-Infective in the Office of 8 Infectious Diseases in the Center for Drugs at FDA. 9 Thank you for joining us today.</p> <p>10 MICHAEL CRAIG: And Peter --</p> <p>11 DR. PETER KIM: -- back over to you, 12 Michael.</p> <p>13 MICHAEL CRAIG: Thank, Peter. Peter 14 and I are going to be moderating the last session here 15 for today's meeting, and I wanted to note to everybody 16 that what we're going to be doing here is actually 17 having a Q&A session, a question and answer session 18 with the panelists that you heard throughout the day 19 today. So as you can see on the screen there, there's 20 a list of panelists from FDA, CDC, as well as the 21 external panelists that we had, and there are three 22 questions that Peter and I are going to be asking the</p>
<p style="text-align: right;">Page 331</p> <p>1 So I'll go to the last slide, please 2 and just like to close by thanking really many folks 3 who helped make this work possible and our 4 collaborators to advance and most importantly, I'd 5 really like to take a minute to specifically 6 acknowledge the patients and the clinical 7 investigators that participate in our trials and 8 really make the ability to advance these programs 9 possible. Thank you.</p> <p>10 DR. JOHN JERNIGAN: All right. Thank 11 you, Dr. Henn, for a fascinating presentation and 12 thanks to all the speakers for what really I think was 13 a great stimulating and encouraging and hopeful 14 session. So thank you all for the work you put into 15 those.</p> <p>16 We'll take a brief break now and 17 reconvene at 3:50. So that brings us to an end of 18 this section. Again, we'll see you again at 50 -- 19 that's five, oh -- minutes after the hour, 3:50 20 eastern time. Thank you. Bye bye.</p> <p>21 (Break)</p> <p>22 MICHAEL CRAIG: Welcome back,</p>	<p style="text-align: right;">Page 333</p> <p>1 panelists and we're going to be having time allotted 2 for each of these.</p> <p>3 So we have roughly half an hour 4 allotted for each of the three questions and we're 5 going to have the panelists -- we're going to start 6 with specific panelists and then have the panelists 7 raise their hand in the Zoom function and then we're 8 going to call on them and hear from them about their 9 thoughts on each of these questions.</p> <p>10 So it's sort of an open conversation 11 and I think a great opportunity for us to hear more 12 about some of the specific issues that we've heard 13 today and areas that we think are maybe greatest need 14 or areas of potential challenge that that we'd all 15 like to overcome. So with that, why don't we get 16 started. And as you can see there, question one is 17 please discuss the greatest needs for drug product 18 development for the prevention of healthcare 19 associated infections. And I think we were -- we've 20 been talking about including it within that 21 antimicrobial resistant bacteria. And you heard a lot 22 from that in the morning session.</p>

<p style="text-align: right;">Page 334</p> <p>1 So we're actually going to kick this 2 off with Dr. Bob Weinstein and hear from him on his 3 thoughts on question one. Dr. Weinstein, why don't 4 you turn on your camera and unmute yourself. 5 DR. ROBERT WEINSTEIN: I'm unmuted. 6 When I go to turn on my camera, it says, you cannot 7 start your video because the host has stopped it. 8 MICHAEL CRAIG: Okay. 9 DR. ROBERT WEINSTEIN: So host, unstop 10 it. So while we're waiting for that I'll go ahead. I 11 think as demonstrated by today's great symposium, the 12 great need is brainstorming. And although I commented 13 that infection control bundles might be parsimonious, 14 I think research has to be broad based. So I want to 15 comment on four general areas of need for product 16 development, some of which have already been 17 highlighted today by outstanding talks, and I will try 18 to highlight what I see is one of them which I see as 19 the greatest need. 20 So the first of the four is the role of 21 topical agents, antimicrobials and antiseptics 22 considered broadly to include topical decolonization</p>	<p style="text-align: right;">Page 336</p> <p>1 and anti-infective coated devices which really didn't 2 discuss much today, seems like a good idea but has 3 never yet made a major splash and maybe that could be 4 reconsidered. 5 A second area is product development 6 for GI tracts which has been discussed extensively 7 today and I'm not going to go over any more of that. 8 A third area is for treatment of 9 infections and I want to add to today's discussion two 10 things that I didn't hear and that's development of 11 antibiotics that delay or defeat or resist bacterial 12 resistance, especially for those pathogens such as 13 Pseudomonas aeruginosa that can spin off resistant 14 progeny with great proficiency. Something like 15 15 percent of Pseudomonas aeruginosa become resistant 16 during the course of therapy, so we need antibiotics 17 that can overcome that. 18 And also we should consider whether 19 advanced molecular diagnostics can be used to alert 20 prescribers to the presence of even low levels of pre- 21 existing resistant elements, for example in the 22 patient's stool (indiscernible) mucosa that might help</p>
<p style="text-align: right;">Page 335</p> <p>1 of the fecal patina which has been a highly successful 2 approach and patients need to be bathed anyway, so in 3 my view, I see this as the potential for the greatest 4 need which could include bringing this approach to 5 additional venues, assess additional agents besides 6 chlorhexidine in the event that resistance develops or 7 more because of some agents like clostridium difficile 8 may have very high MICs for chlorhexidine, and so 9 assess topicals that might get into deeper layers of 10 the dermis. 11 We saw in one of the slides this 12 morning about hair follicles having MDROs in them and 13 there may be some agents that may get better into hair 14 follicles. 15 I think also as systemic antibiotics 16 are developed they could be assessed for the 17 possibility of excreting antibiotic into the sweat 18 perspiration so that axillary glands might have 19 antibiotics in them which might control or prevent 20 development of MDRO fecal patina. All of these have 21 pros and cons as everything does today. 22 In the category of topicals, you know,</p>	<p style="text-align: right;">Page 337</p> <p>1 when the prescriber has to choose between different 2 classes of antibiotics. So that might be directed in 3 part by knowing what resistance pre-exists there. 4 And the final, the fourth areas to 5 develop products that attack bacterial mechanisms 6 facilitate infection. I didn't hear a discussion 7 today -- I may have missed it -- about products to 8 block quorum sensing so that bacteria cannot 9 communicate with each other. There's no 10 communication, no infection, there'll be no 11 resistance. We've already heard about compounds that 12 destroy or inhibit biofilms. We talked about 13 monoclonal antibodies and there's a lot of the 14 literature about compounds that attack virulence, that 15 is, make MRSA less virulent. 16 But of all these again for product 17 development, as I said at the outset, my personal view 18 is the approach to control the fecal patina which I 19 believe plays a pivotal role in the epidemiology of 20 many MDROs and control of the fecal patina has had an 21 impressive impact on the risk of spread and infection 22 with a variety of resistant strains, bacteria and</p>

<p style="text-align: right;">Page 338</p> <p>1 potentially fungi. And I think we should capitalize 2 and improve on these successes. That's my view. 3 MICHAEL CRAIG: Thank you, Dr. 4 Weinstein. Other speakers, other panelists, who would 5 like to share their thoughts on this question? What 6 are some of the areas of greatest need from your 7 perspective and point of view, and please use the 8 raise hand features so that we can get -- identify 9 folks and get them in order. The raise hand feature 10 is at the bottom of the screen. Lilian Abbo. 11 DR. LILIAN ABBO: Hi. I agree with 12 everything Dr. Weinstein mentioned. I think another 13 area where we have great need is more effective 14 antimicrobials to decolonize against Candida auris and 15 more effective therapies. We have a very limited 16 armamentarium and so far nothing has worked for 17 decolonization other than repopulating the gut, and as 18 we saw many of these, you know, gut microbiota 19 products that are being developed are targeting 20 bacterial pathogens, but we also need to think of 21 fungal pathogens that are emerging with increased 22 resistance and very rapid horizontal transmission.</p>	<p style="text-align: right;">Page 340</p> <p>1 well as general health of patients as well, and so I 2 think as we think about that as a target that's 3 important for us to keep that in mind. 4 MICHAEL CRAIG: Thank you. Other 5 panelists. I am not going to be shy about calling on 6 folks if you don't raise your hand. There was great 7 conversation today and many engaging talks. There's 8 Dr. McDonald. Cliff. 9 DR. CLIFFORD MCDONALD: Yeah, thank 10 you, Michael. I would maybe add and maybe this is for 11 FDA to comment on, is what would be the studies that 12 could be done that would perhaps lift the entire field 13 around establishing surrogates and what do they see 14 maybe as most important? Maybe it is -- could be a 15 couple of these larger studies. I think we've heard 16 several in industry talking about the prohibitive size 17 of studies and what would those need to be to help 18 establish surrogates that then could smooth a pathway, 19 building the better mousetrap to achieve reaching 20 surrogates. 21 MICHAEL CRAIG: Thank you, Cliff. And 22 I think some of that response, I think touched on some</p>
<p style="text-align: right;">Page 339</p> <p>1 And then if there is any topical 2 antimicrobial that can substitute and improve hand 3 hygiene and make it even easier than alcohol and water 4 and soap, I think that would be a Nobel prize winner 5 because we would stop a lot of the problems as well. 6 Thank you. 7 MICHAEL CRAIG: Thank you, Dr. Abbo. 8 And Matthew Henn. 9 DR. MATTHEW HENN: Sure. Thanks, 10 Michael. You know, I think the thing I'll emphasize 11 as well, we heard about it quite a few times today 12 throughout multiple different talks, is really 13 thinking about what the proximal cause of disease is 14 in some of these settings, and so there I really think 15 about that need to really think about the 16 gastrointestinal microbiome and the important role 17 that it plays in the pathogenesis of multiple of these 18 different diseases that we talked about and how we 19 think about restructuring that microbiome, protecting 20 that microbiome, because I think we know that that has 21 pretty substantial implications both in terms of the 22 ability to establish colonization resistance but as</p>	<p style="text-align: right;">Page 341</p> <p>1 of our questions two and three that we're going to get 2 to momentarily, but thanks for teeing those up for us. 3 Want to still focus on, you know, what are the areas 4 of greatest need. I'm going to take the moderator's 5 prerogative here and actually call on Susan Huang. 6 She's worked in this field very extensively and had a 7 great presentation earlier today. Dr. Huang, what do 8 you see as some of the areas of greatest need for 9 product development? 10 DR. SUSAN HUANG: I think that there's 11 a lot of good questions out there. I think we're 12 going to need to move faster and be able to do 13 pragmatic trials. I think one way in order to do that 14 is to actually continue to enable the trials that are 15 done while you're in a learning health system to 16 actually matter for FDA indications. So I think 17 there's a real use case to talk about, what does it 18 take to do that when they're created to be real 19 pragmatic trials and influence what happens today. 20 So that's one of the things that I 21 think there's great questions, but we need more trials 22 and they can't cost the amount that they're costing</p>

<p style="text-align: right;">Page 342</p> <p>1 now, and so availing ourselves of a lot of people who 2 are interested in the operational need can be one 3 great way to be able to move something forward. 4 I want to just echo the other thing 5 that was stated earlier, I think by Dr. Weinstein, 6 about deconvoluting some of the bundles that are out 7 there. I think that that's true in two different 8 ways. One, when you have completely disparate things 9 that go into the bundle, sometimes it's a device plus 10 an antiseptic plus something else, those types of head 11 of bed, you know, all those things are kind of pretty 12 different, but I actually want to talk about also the 13 fact that when you do something like decolonization, 14 you can attack different body sites. 15 So what is that relative proportion of 16 value and can we actually measure that, so that we 17 understand when you have to have the budget in a 18 certain amount, you're going to always go after the 19 most effective things first. So I thought that was a 20 really thoughtful approach as well. 21 MICHAEL CRAIG: Great. Thank you, Dr. 22 Huang. And it looks like we have Theresa Michele from</p>	<p style="text-align: right;">Page 344</p> <p>1 them won't receive benefit. 2 MICHAEL CRAIG: Thank you. Very good 3 point and I think that's a strong consideration for 4 how do we address these preventative agents where 5 we're talking about benefit to both the individual and 6 the group and the application of those. Dr. Jernigan. 7 DR. JOHN JERNIGAN: Thanks. And I 8 agree with Dr. Michele totally that the safety issues 9 are first and foremost. First do no harm. I did want 10 to comment on your very last thing about the number 11 needed to treat, and again bringing this argument of 12 the indirect benefit. 13 When you consider the indirect benefit 14 of infections -- colonizations and subsequently 15 infections prevented through transmission, the number 16 needed to treat comes way, way down and one of the 17 problems with the number needed to treat for diseases 18 like this is it doesn't consider the indirect benefit. 19 I think, tried to show some of the modeling data -- 20 again, they're only models -- but they're 21 parameterized based on real world good observational 22 data -- suggest the number needed to treat for, for</p>
<p style="text-align: right;">Page 343</p> <p>1 FDA. Theresa. 2 DR. THERESA MICHELE: Thank you. So 3 one thing that I just wanted to note as we're 4 considering these things, another point to consider is 5 that we also have to think about the safety of the 6 regimens that we're prescribing and that we are, you 7 know, considering which was part of the point of the 8 limitations in the data that we have for some of these 9 agents. And certainly as we develop new agents you 10 have to think about that as well. 11 Some of the basic science behind it, 12 the toxicology studies, making sure that these things 13 aren't carcinogenic if you're using them over and over 14 and over again or you're exposing, you know, large 15 body surfaces. And I thought Dr. Wachter really 16 presented this very beautifully when he talked about 17 the number needed to treat that you are potentially 18 exposing 100 patients to an intervention to prevent 19 three infections with C. diff. 20 So we have to remember that when we are 21 thinking about these preventative therapies safety is 22 very paramount because a lot of patients who receive</p>	<p style="text-align: right;">Page 345</p> <p>1 example, CRE decolonization to prevent infection, when 2 you consider the indirect benefit is really much, much 3 lower than that. 4 So I just wanted to make that point to 5 not forget about indirect benefit when we think about 6 these things. I acknowledge that there -- it's 7 challenging to measure and quantify indirect benefit. 8 But I think that's one of the things we need to 9 grapple with because I think the promise of these 10 agents is going to be most of the harm that's going to 11 be prevented I believe will be through indirect 12 benefit more than the direct benefit. Over. 13 MICHAEL CRAIG: Thank you, Dr. 14 Jernigan. I'm going to call on a couple other folks 15 here because I think they had some very interesting 16 and engaging talks that I think this question is 17 particularly important for hearing from them. Dr. 18 Brown with the CF Foundation, what do you think are 19 some of the areas of greatest prioritization and -- in 20 terms of product development here? 21 DR. A. WHITNEY BROWN: Thank you. For 22 our patient population, I think I highlighted that the</p>

<p style="text-align: right;">Page 346</p> <p>1 multidrug resistance, the inherent nature through a 2 lifetime of infections and healthcare exposures, so 3 really I think the development of new novel 4 antibiotics to address MDR and how to entice companies 5 when the financial benefit may, you know, may not be 6 there because we're not talking about volumes and 7 volumes of patients, but to keep our armamentarium 8 growing and to do that in a responsible way. 9 Of course, we want to reduce our 10 antibiotic use as well and I think we've been very 11 lucky in our population that that has happened over 12 the last couple of years for a confluence of reasons, 13 as I said, but being good antibiotic stewards but also 14 having the right powerful, appropriate antibiotics 15 available for the most vulnerable MDR infections and 16 to include looking at bacteriophage therapy as an 17 option as well. 18 MICHAEL CRAIG: Thank you. And Jim 19 Kim, you had a very interesting talk and wanted to see 20 what your thoughts are on potential product 21 development. 22 DR. JAMES KIM: Yeah, thank you. So</p>	<p style="text-align: right;">Page 348</p> <p>1 like we have a hand. Dr. Walker. 2 DR. VINCE WACHER: Thanks very much. I 3 just wanted to maybe follow up on the indirect benefit 4 question or comment, because it's terrific that if we 5 can measure the indirect benefit, the number of 6 patients in my study goes down. But even if I have to 7 cut that number to 2,000 or 1,000, I still have to 8 follow them into the community and maybe for a year or 9 maybe even two years and then I have to follow who 10 they're connected to and who they're connected to 11 until I can determine, have I spread antimicrobial 12 resistance? Have I spread CDI? 13 So it doesn't necessarily change the 14 challenge of my study even if the number of people are 15 smaller. But I mean clearly the indirect benefit 16 getting out in the community, spreading it around, 17 going back into hospitals. We had a group from Mexico 18 that had to close an entire wing of a hospital forever 19 because they could not get it under control, the CDI. 20 So you know, the indirect benefit is a 21 tremendous potential outcome therapeutically for the 22 community. But again, just incorporating that into my</p>
<p style="text-align: right;">Page 347</p> <p>1 from my vantage point, you know, one of the things 2 that we're working on, a lot of the healthcare 3 efficacy studies for the products that we're working 4 on our ASTM methods, so they're validated methods 5 using those surrogate endpoints. What I talked about 6 today were some of the challenges facing our consumer 7 antiseptics and I thought it was just an opportune 8 time to review a surrogate endpoint, like 9 decolonization. 10 This is something that I think will 11 take some data to convince FDA that this could be a 12 useful end point for the development of products, but 13 certainly I think I was very excited to see this 14 workshop. I thought that a lot of our work pertains 15 to what's going on in this field, and so for me it was 16 a great learning experience to see the other talks 17 today. 18 But I think that's sort of one of the 19 areas and I think OTC reform gives us, I think, an 20 avenue to talk about what FDA's data requirements are, 21 so sort of what I'm looking forward to. 22 MICHAEL CRAIG: Thank you. It looks</p>	<p style="text-align: right;">Page 349</p> <p>1 study design gives me another one or two years to 2 follow patients in pretty difficult circumstances. 3 MICHAEL CRAIG: Thank you. And I think 4 Dr. Jernigan is back to discuss the same topic. 5 DR. JOHN JERNIGAN: Well, I just want 6 to agree with you that one of the challenges we have 7 here is that the adverse effect of acquiring 8 colonization is sometimes very, very far removed in 9 time from the actual acquisition, as you point out, 10 maybe years later. So how do we study that? That's 11 tough. 12 One sort of plug, and this may get into 13 study designs and study populations which I know is 14 the second topic, Michael, but I want to point out, 15 you know, healthcare settings where the lengths of 16 stays are very long and where prevalence and 17 transmission of some of these pathogens is very high. 18 This may not help C. diff much, but I'm thinking of 19 CRE, Dr. Henn, et cetera. I mean, you may have 20 considered LTACH populations or other long-term care 21 populations, again, that have pretty high prevalence, 22 pretty high incidence of transmission, pretty high</p>

<p style="text-align: right;">Page 350</p> <p>1 incidence of infection, long length of stay where you 2 might be able to enrich capture of those indirect 3 benefits. Something to consider. Over. 4 MICHAEL CRAIG: Thank you, Dr. 5 Jernigan. And Matthew Henn. 6 DR. MATTHEW HENN: Yeah, so I'll just 7 quickly respond there. I mean, I think it's an 8 important point. I think we'll probably get into this 9 a little bit in the next question, but it really does 10 also important to aging populations and 11 (indiscernible) targeting and where you can see the 12 outcomes, you need to see (indiscernible) most 13 rapidly. 14 So you know, at Seres, we focused our 15 infection portfolio on immunocompromised patient 16 populations and that's where we are focused. That's 17 very intentional because we feel we can design trials 18 in that setting and get to meaningful potential 19 readouts rapidly. 20 At the same time, I think there needs 21 to, as was brought up earlier today by multiple of our 22 CDC colleagues, to really think about other readouts</p>	<p style="text-align: right;">Page 352</p> <p>1 this. 2 I think there was a Dutch study showing 3 that your risk of having fluoroquinolone resistance in 4 your gut was greatest if you lived in a community 5 where there's a lot of fluoroquinolone use, not you 6 necessarily but other people in the community. 7 So I think we have to look in the 8 community and when we looked at MRSA in some of the 9 zip codes in Chicago, we've seen that having been in 10 the jail was a risk factor for MRSA in the community. 11 So I think we have to look at the extension of some of 12 these interventions into communities very specifically 13 and focus on the epidemiology in the community to 14 understand the spread there. It's not always the 15 hospital or the nursing homes. 16 MICHAEL CRAIG: Yeah, a very good point 17 that when we're talking about transmission here, the 18 transmission is certainly not limited to the 19 healthcare setting and can go beyond that. Silvia. 20 DR. SILVIA CABALLERO: Yeah, something 21 that I would add is that having a good understanding 22 of the mechanism of action is something that I think</p>
<p style="text-align: right;">Page 351</p> <p>1 that can be more rapid such as decolonization readouts 2 or things of that nature because I think those are 3 certainly needed. 4 And I think we need -- I can tell you 5 as a drug developer we need increased guidance and 6 would benefit from increased guidance from the agency 7 on how to best think about a decolonization surrogate 8 endpoint, particularly for Phase 1 or Phase 2 trials. 9 MICHAEL CRAIG: Thank you, Matthew. 10 Well, I think we can close out question one but I just 11 want to see if there's any other hands and panelists 12 who want to talk about our greatest need for product 13 development. Bob Weinstein. 14 DR. ROBERT WEINSTEIN: Yeah, I think we 15 haven't really discussed the community very much, so 16 Latania Logan at Rush Children's, when she looked at 17 kids coming in the hospital, in a bunch of hospitals 18 in Chicago, I think every children's hospital in 19 Chicago with resistant organisms, resistant 20 Enterobacteriaceae, those were kids from the 21 community. They had not been in the hospital ever 22 before. So somewhere in the community they acquired</p>	<p style="text-align: right;">Page 353</p> <p>1 we should also think about. So regardless of the 2 product in question, right, whether it is antibiotics 3 or (indiscernible), I think that knowing how the 4 products work will help rationalize failures and 5 successes in the clinic, and we need human data for 6 that. Preclinical models, mouse models, in vitro 7 models, they're great, but we need human data. 8 And the other thing that I would add is 9 that something else that that would help with is the 10 identification biomarkers that will help us select 11 patients that would benefit the most (indiscernible) 12 products and I don't know if this was mentioned 13 already, but also thinking about the microbes that 14 we're targeting. 15 Some of these organisms may be very 16 difficult to decolonize. Even strains within the same 17 species, you know, can be difficult to target, so you 18 know, spending, you know, more time sort of looking 19 into how active these products are preclinically can 20 also help us to, you know, develop better products in 21 the future. 22 MICHAEL CRAIG: And Dr. Elkins from</p>

<p style="text-align: right;">Page 354</p> <p>1 CDC.</p> <p>2 DR. CHRISTOPHER ELKINS: Well, thanks,</p> <p>3 Michael. One thing I wanted to bring up and it does</p> <p>4 develop off of what Silvia's last comment was, but</p> <p>5 something that Dr. Weinstein brought up which was</p> <p>6 quorum sensing and I think it's an interesting piece</p> <p>7 with mechanism of action. So how do we look at it</p> <p>8 from the microbes perspective?</p> <p>9 And I think it hearkens back to a</p> <p>10 lecture that I attended with Dr. Stuart Levy at one</p> <p>11 point and you know it straddles both antimicrobial</p> <p>12 drug development but also how you can apply it in a</p> <p>13 decolonization sense, so targeting the organism in a</p> <p>14 much more subtle way. So it does get to the mechanism</p> <p>15 piece and I think taking that into account with</p> <p>16 product development is very, very important.</p> <p>17 In other words you're not really</p> <p>18 killing the microbe, you're just inhibiting or, you</p> <p>19 know, at least with quorum sensing you are able to in</p> <p>20 effect reduce its ability to colonize and to</p> <p>21 communicate properly without killing it. So you do</p> <p>22 have some aspects there on the downstream as far as</p>	<p style="text-align: right;">Page 356</p> <p>1 Abbo.</p> <p>2 DR. LILIAN ABBO: Hi again. One of the</p> <p>3 other areas I think it's important to consider in</p> <p>4 addition to the community is also the global impact of</p> <p>5 all of this. We're in Miami and we don't live in an</p> <p>6 isolated bubble in the United States, and we saw that</p> <p>7 in COVID, we're seeing it with monkeypox. So I think</p> <p>8 as we're trying to develop cost effective solutions</p> <p>9 they need to be scalable to the rest of the world and</p> <p>10 having effective therapeutics and effective point of</p> <p>11 care diagnostics would be very helpful.</p> <p>12 For example, we saw the difference that</p> <p>13 maybe not 100 percent of the antigen testings work,</p> <p>14 but if we could have a point of care flow, you know,</p> <p>15 analytics like a pregnancy test to determine</p> <p>16 colonization with MDROs, it might be very helpful upon</p> <p>17 admission because the cost of all of this is adding to</p> <p>18 our (indiscernible). It's not just the cost of</p> <p>19 preventing and the cost of treating this multidrug-</p> <p>20 resistant infections, adds to everything. So anything</p> <p>21 we can do to prevent and early detection will stop the</p> <p>22 chain of transmission.</p>
<p style="text-align: right;">Page 355</p> <p>1 developing resistance, but I think those are keys I</p> <p>2 think in in developing that and appreciate his</p> <p>3 comments along those lines as Silvia's as well.</p> <p>4 MICHAEL CRAIG: Thank you, Chris. More</p> <p>5 hands up is great. Erin Duffy, CARB-X.</p> <p>6 DR. ERIN DUFFY: Yeah, thanks. I just</p> <p>7 wanted to build on also something Silvia said which is</p> <p>8 we didn't emphasize much the things that remain not</p> <p>9 understood in the translation from preclinical to</p> <p>10 clinical work and this is particularly when a lot of</p> <p>11 these products are going on top of standard of care.</p> <p>12 There's a lot of shenanigans. I don't</p> <p>13 mean that in a negative sense. I think that's a</p> <p>14 negative word, but there's a lot of stuff that's done</p> <p>15 to demonstrate, you know, efficacy preclinically</p> <p>16 including like fractions of a dose of the antibiotic</p> <p>17 to try to demonstrate an effect that we really have no</p> <p>18 sense of how that translates clinically.</p> <p>19 And so I think some dedicated work to</p> <p>20 understand what's enough to feel confidently moving</p> <p>21 into patients is really important.</p> <p>22 MICHAEL CRAIG: Thank you. And Dr.</p>	<p style="text-align: right;">Page 357</p> <p>1 Other things that I think are important</p> <p>2 for -- especially with cystic fibrosis and other</p> <p>3 multidrug-resistant gram-negatives is really looking</p> <p>4 at more effective ways of combining therapeutics,</p> <p>5 right, whether it's synergy testing through TREK</p> <p>6 panels and deciding, hey, combination therapy in this</p> <p>7 situation short course may be more effective than --</p> <p>8 rather than you know burning each one antibiotic</p> <p>9 individually.</p> <p>10 We need more studies looking at that.</p> <p>11 What are the effective combinations and what's the</p> <p>12 right duration when we use combination therapy</p> <p>13 especially for these extreme drug-resistant organisms</p> <p>14 that are very challenging and in particularly</p> <p>15 immunocompromised populations which we deal with</p> <p>16 transplant and oncology in which sometimes it's very</p> <p>17 hard to restore the immune system and eradicate the</p> <p>18 colonization or the infection. So that's an area</p> <p>19 where we need more therapeutics.</p> <p>20 MICHAEL CRAIG: Absolutely. Thank you.</p> <p>21 And I think that is actually the time we have allotted</p> <p>22 for question one, so I'm going to turn it back over to</p>

<p style="text-align: right;">Page 358</p> <p>1 Peter Kim of FDA who's going to take questions two. 2 DR. PETER KIM: Thanks, Michael, and 3 thanks everyone on the panel for the excellent 4 responses. 5 Okay, so question two, please discuss 6 ideas for study designs that could provide evidence of 7 the contribution of a new therapeutic for prevention 8 of healthcare-associated infection on the background 9 of existing infection prevention measures including 10 but not limited to the pros and cons of cluster 11 randomized study designs as well as enrichment 12 strategies for populations at greatest risk. 13 And we would like to call on Dr. Susan 14 Huang to kick off the response to this question. 15 DR. SUSAN HUANG: Thank you, Peter. 16 So, I'm going to answer in a way that actually I think 17 bridges questions one and two a little bit more in a 18 provocative way. I'll just generally say that there 19 are a large number of options for study designs that 20 could really complement standard randomized controlled 21 trials and I'm just going to name three specific ones 22 that can be really, really helpful when you're trying</p>	<p style="text-align: right;">Page 360</p> <p>1 I'm going to now switch my comment to 2 hopefully something that's a little more provocative. 3 I'm really interested in how people will respond, but 4 when we think about these designs, I think of two 5 different things about the products we've been talking 6 about. There's the post market indications that don't 7 exist and there's the premarket approvals or 8 indications. 9 And one of the things that's really 10 interesting about, for example, each of us, FDA, CDC, 11 the manufacturers, and then those of us in academia or 12 those of us who actually, you know, run hospitals and 13 hospital infection programs, is we all have really, 14 really important but critically different vantage 15 points. 16 And I will just highlight what Teresa 17 Michele said about, you know, safety. So is there a 18 way to actually, as the next step, take a case 19 example, really do a case study and I'll throw out the 20 example of using chlorhexidine in ICUs for routine 21 bathing. There is no indication for that. There have 22 been many trials on children and adults. It's been</p>
<p style="text-align: right;">Page 359</p> <p>1 to account for contagious outcomes. 2 So the group designs, which are less 3 commonly discussed, would be the standard cluster 4 randomized design that I talked about, but also to 5 just remember that there are other ways that you can 6 do randomized crossover design. You don't have as 7 many hospitals. As I mentioned, even 20 is a really 8 large trial. You could assign someone to be both a 9 control and a participant in the intervention. They 10 just can't choose when. So that's a randomized 11 process. 12 There's also randomized stepped wedge 13 design. That is, it's really hard to roll out 14 something in a hospital, it takes a lot of phase-in 15 time and so maybe you can only roll it out to ten, 16 which is a lot at one moment, so you have a 40, you 17 know, trial, 40 group trial and so you're going to 18 roll ten at a time, but they can't when. 19 So there's So there's many different 20 ways that you can try to use group designs that can be 21 really, really powerful and still allow for the proper 22 roll-out of these types of designs.</p>	<p style="text-align: right;">Page 361</p> <p>1 used daily. It is now guidance. 2 So yes, we have no safety that's been 3 submitted to the FDA that's really specific to this, 4 but it's been done in millions of patients every 5 couple of months, millions. And so can we sit down 6 and have the right people at the table to talk about 7 these really complex vantage points because if you're 8 an agency and you're authorizing a safety, you're -- 9 you've got a lot of responsibility, you know, compared 10 to a doctor that's saying, you know what, I'm going to 11 try this off label. 12 So I don't want to dismiss anybody's 13 valued perspective, but getting us all at the table to 14 talk about one explicit example can really, really 15 help, and dig into the trials that have been done in 16 hundreds of thousands of patients might be really 17 illustrative and open up the mind of someone like 18 myself when we do the trials about what else can we 19 collect, because that would be really meaningful, but 20 maybe also open up the idea that there are ways in 21 which we can think about stuff that's already 22 happening and try to garner that so we don't have to</p>

<p style="text-align: right;">Page 362</p> <p>1 start from square one.</p> <p>2 And similarly for premarket approval, I</p> <p>3 was just thinking about the same thing. There's lots</p> <p>4 of things that are not here in the United States. For</p> <p>5 example, there are antiseptics that have been commonly</p> <p>6 used in other European countries for years. So do we</p> <p>7 have to start the safety discussion at zero?</p> <p>8 Is there a way to create some two-</p> <p>9 tiered structure that would be understandable and</p> <p>10 amenable for everybody to say, you know what, small</p> <p>11 consent studies for safety and then large waived</p> <p>12 consent studies for population outcome or some small</p> <p>13 studies really hard to do that show the connection</p> <p>14 between carriage and infection, and then once that's</p> <p>15 been shown in a way that's definitive enough, now we</p> <p>16 can use a surrogate endpoint.</p> <p>17 And I think we've got to really put --</p> <p>18 we've got to get down to real details to talk about</p> <p>19 what it really would take to get us to that point. So</p> <p>20 more questions than I think an answer.</p> <p>21 DR. PETER KIM: Thank you, Dr. Huang.</p> <p>22 I thought I saw a hand up for a moment. Perhaps, Dr.</p>	<p style="text-align: right;">Page 364</p> <p>1 cost.</p> <p>2 And I know I'm sounding very mercenary,</p> <p>3 but honestly this is what's stopping things going</p> <p>4 forward right now. We've got to find ways that this</p> <p>5 can be done because otherwise it's not going to get</p> <p>6 done and it's very sad to hear about Phase 3 trials,</p> <p>7 Phase 2 trials that cannot go ahead because of the</p> <p>8 cost.</p> <p>9 DR. PETER KIM: Thank you, Dr. Wachter.</p> <p>10 Dr. Weinstein.</p> <p>11 DR. ROBERT WEINSTEIN: Yes. To expand</p> <p>12 on one of Susan Huang's points, I think that the COVID</p> <p>13 pandemic really made it clear that we need to have a</p> <p>14 mechanism for using global data. So studies done in</p> <p>15 other countries of products that we might use here,</p> <p>16 how do we use that without having to have the full</p> <p>17 registration data, in a pandemic at least.</p> <p>18 The other aspect I think is that if</p> <p>19 we're going to understand, we're going to develop</p> <p>20 interventions for communities, we have to understand</p> <p>21 the epidemiology communities which we don't yet and I</p> <p>22 think this requires citizen science and enrolling, for</p>
<p style="text-align: right;">Page 363</p> <p>1 Duffy?</p> <p>2 DR. ERIN DUFFY: That was a mistake.</p> <p>3 DR. PETER KIM: Okay. Dr. Wachter.</p> <p>4 DR. VINCE WACHER: So -- yeah, Wachter.</p> <p>5 Perfect, thank you. So the trial design -- and</p> <p>6 thanks, Dr. Huang, for bringing up sort of premarket</p> <p>7 and post-market and things like that and to go</p> <p>8 completely out there, completely out there right now,</p> <p>9 how would we be able to get our point of care</p> <p>10 preventative evaluated effectively. And that is if we</p> <p>11 could be approved to put it on formularies based on</p> <p>12 safety, and then let the hospitals evaluate this and</p> <p>13 collect the data over time.</p> <p>14 So maybe the product is safe enough to</p> <p>15 be on the formulary. I know that the infection</p> <p>16 control people will prescribe it. I know physicians</p> <p>17 will prescribe it if they think it will benefit the</p> <p>18 patient, but rather than having dedicated efficacy</p> <p>19 data, maybe we have some signal that encourages</p> <p>20 efficacy but definitive safety and then we can put it</p> <p>21 in multiple hospitals and that way get a massive trial</p> <p>22 that funds itself, even if we were to charge this at</p>	<p style="text-align: right;">Page 365</p> <p>1 example, parents to see where their kids may be</p> <p>2 picking up resist and bugs. You know, are they</p> <p>3 picking up on the playgrounds, where are they getting</p> <p>4 it.</p> <p>5 And so I think we need to think of ways</p> <p>6 that we can enroll community members to study problems</p> <p>7 in the community more efficiently than we're doing</p> <p>8 now. Otherwise we'll never be able to craft community</p> <p>9 interventions.</p> <p>10 DR. PETER KIM: Very innovative</p> <p>11 thoughts. I see a hand up and I'm sorry, I'm going to</p> <p>12 mispronounce --</p> <p>13 FLORENCE SEJOURNE: Florence --</p> <p>14 DR. PETER KIM: -- your last name.</p> <p>15 FLORENCE SEJOURNE: Florence, it's</p> <p>16 okay.</p> <p>17 DR. PETER KIM: Florence, please.</p> <p>18 FLORENCE SEJOURNE: You can say my</p> <p>19 first name. Yes, I mean I'm coming back to, you know,</p> <p>20 following the two last comment, three last comment</p> <p>21 from Robert and Vince. I'm coming back to Cliff</p> <p>22 McDonald's question because at the end, I think this</p>

<p style="text-align: right;">Page 366</p> <p>1 is it. I mean, what would -- I mean based on today's 2 workshop where we have heard for the morning sessions 3 CDC showing us how much colonization makes sense and 4 is associated to risk of infections, and as companies 5 developing products where we have trouble showing 6 directly the prevention of infection but we could 7 definitely show prevention of some biological markers 8 and I've shown a few that we have developed at Da 9 Volterra.</p> <p>10 So what would be required today to move 11 to the next steps in terms of endpoint demonstration 12 in association, of course, with safety database.</p> <p>13 DR. PETER KIM: Yeah. I mean, this is 14 truly the question of the hour and that's part of -- 15 I'm sorry go ahead. Go ahead, John.</p> <p>16 DR. JOHN JERNIGAN: So Dan, did you 17 want to start or do you want me to make some comments, 18 or Peter?</p> <p>19 DR. PETER KIM: I think so --</p> <p>20 DR. JOHN JERNIGAN: I wasn't sure if 21 you were going to talk about this one. Okay. So 22 here's what I learned today, and I've learned a lot</p>	<p style="text-align: right;">Page 368</p> <p>1 I can tell you that most of the 2 experience of using either new endpoints or new 3 justifications for noninferiority margins largely gets 4 driven by development programs and that tends to be 5 more efficient than a global qualification process.</p> <p>6 But the first thing to do is be -- is 7 someone being willing to put the data together and 8 actually have that discussion. That's step one.</p> <p>9 I think there are a fair number of pros 10 and cons of considering that as a trial endpoint, and 11 I think a lot of that came up in the CARB-X focus 12 group that that Erin talked about that, that you could 13 see. And none of them actually -- we ended up in the 14 scenarios they were discussing talking about other 15 than a clinical endpoint. There is the need, unless 16 it's a very robust surrogate that can be kind of 17 defined as a validated surrogate, going to be the need 18 to confirm the clinical benefit, you know, perhaps by 19 continuing the trial.</p> <p>20 And I think there's another stakeholder 21 at the table these days, which is very important, 22 which is payers in terms of what you've demonstrated</p>
<p style="text-align: right;">Page 367</p> <p>1 actually from this process because I feel like I've 2 been living in COVID-land for two-and-a-half years, as 3 do most of you probably.</p> <p>4 So I think that the population and the 5 pathogen is important and each situation is going to 6 be different in terms of whether use of a surrogate in 7 a clinical trial is scientifically supported or 8 actually makes sense to a sponsor, you know, in terms 9 of feasibility.</p> <p>10 So I think that first of all, you don't 11 need necessarily clinical trial data to support the 12 clinical benefit of a surrogate, but you do need high 13 quality prospective observational data and preferably 14 more than one source for folks to talk about, and 15 there are a number of processes to come in and begin 16 to have those discussions.</p> <p>17 We can do that more globally with 18 Cliff's team at CDC. We are happy to do that with 19 sponsors under a pre-IND focused on a particular 20 product, a particular population, a particular 21 pathogen, and talk about, you know, how strong is the 22 data.</p>	<p style="text-align: right;">Page 369</p> <p>1 in your trial and whether or not that product's going 2 to be supported either by a formulary committee or by 3 payers at that level. So those are just some general 4 observations and I would invite others to add.</p> <p>5 DR. PETER KIM: And just to add on to 6 what John was saying, we are open to ideas and 7 considerations. That's part of why we partnered with 8 CDC on this workshop and this is probably the first of 9 several conversations. But once again, as John had 10 noted, we need someone to come in with a consolidation 11 of the evidence for us to evaluate.</p> <p>12 I'll let Dan speak. He has his hand 13 up.</p> <p>14 DR. DAN RUBIN: Sure. I had actually 15 raised my hand before the surrogate question came up, 16 so I don't want to derail us, but just to add a few 17 points to this. I mean, I agree with John that 18 whether a surrogate is reasonably likely to predict 19 clinical benefit can certainly depend on the pathogen, 20 the disease, and the intervention. And there are 21 definitely hierarchies to the levels of evidence that 22 at one level you would need a strong mechanistic</p>

<p style="text-align: right;">Page 370</p> <p>1 rationale.</p> <p>2 Then I guess the next level of endpoint</p> <p>3 would be a correlate where you've shown that the</p> <p>4 surrogate you're trying to reduce is correlated at the</p> <p>5 individual level with the clinical outcome and then</p> <p>6 really the highest form of evidence would be kind of</p> <p>7 large outcome trials showing that your treatment</p> <p>8 effect on the surrogate at the trial level was</p> <p>9 associated with the treatment effect on the clinical</p> <p>10 benefit, but how those different forms of evidence are</p> <p>11 weighed in different settings is obviously complex and</p> <p>12 it may be hard to get to today.</p> <p>13 So I guess the more minor point I</p> <p>14 wanted to raise was just listening to Dr. Huang's</p> <p>15 presentation one idea I had when she was talking about</p> <p>16 kind of the competing interventions in the background</p> <p>17 of that trial, that some of the settings we've talked</p> <p>18 about today could be good settings potentially for</p> <p>19 platform trial. I think they've shown their worth in</p> <p>20 in COVID-19.</p> <p>21 These are trials where different</p> <p>22 sponsors work together and interventions can come, you</p>	<p style="text-align: right;">Page 372</p> <p>1 up that kind of dollars to actually get that read by</p> <p>2 FDA?</p> <p>3 DR. JOHN JERNIGAN: I can make some</p> <p>4 comments if you want me to start. So I think we do</p> <p>5 have examples where noncommercial sponsors, you know,</p> <p>6 have actually taken drugs through the process. The TV</p> <p>7 consortium is one example.</p> <p>8 One of the important points about the</p> <p>9 United States is that we the government can't take the</p> <p>10 intellectual property of another. And so whoever is</p> <p>11 sponsoring needs a right of reference to the data that</p> <p>12 might be important. And that may be the product</p> <p>13 quality data, the nonclinical data for the particular</p> <p>14 molecule in question. And that sometimes is an issue.</p> <p>15 Just something to keep in mind, but there's nothing</p> <p>16 barring a consortium from taking, for example,</p> <p>17 something that's well off patent in for a regulatory</p> <p>18 action, Susan, and we'd absolutely be delighted to</p> <p>19 work with you, of course.</p> <p>20 DR. PETER KIM: And I would --</p> <p>21 DR. SUSAN HUANG: Likewise.</p> <p>22 DR. PETER KIM: I'm sorry go ahead.</p>
<p style="text-align: right;">Page 371</p> <p>1 know, into the trial in different arms as the study's</p> <p>2 ongoing or if there aren't competing mechanisms,</p> <p>3 potentially certain types of sectorial randomization</p> <p>4 can be used, but just kind of thinking about the</p> <p>5 different interventions and the bundles. This could</p> <p>6 be a potential setting for platform trials. Thank</p> <p>7 you.</p> <p>8 DR. PETER KIM: Thanks, Dan. Susan, I</p> <p>9 see your hand up.</p> <p>10 DR. SUSAN HUANG: Yes. I wanted to</p> <p>11 just ask, there was a -- someone had mentioned that</p> <p>12 sometimes the sponsor to FDA of raising to get an</p> <p>13 indication is not the manufacturer, and I wanted to</p> <p>14 better understand.</p> <p>15 Let's say that there was a value for</p> <p>16 infection prevention. Can an infection prevention</p> <p>17 society or can CDC come and raise the ability to have</p> <p>18 something be accepted as an appropriate indication and</p> <p>19 barring the fact that that might take billions of</p> <p>20 dollars -- I actually have no idea what that cost is -</p> <p>21 - but someone raised the fact that it's not always the</p> <p>22 manufacturer. So who else would be a sponsor and put</p>	<p style="text-align: right;">Page 373</p> <p>1 DR. SUSAN HUANG: No just saying</p> <p>2 likewise.</p> <p>3 DR. PETER KIM: I would just add the --</p> <p>4 that probably the best mechanism to facilitate the</p> <p>5 beginning of the discussion would be a pre-</p> <p>6 investigational new drug application, a pre-IND. That</p> <p>7 way, we can begin the conversation. We can look at</p> <p>8 submitted data and whatnot and provide some</p> <p>9 consultative advice.</p> <p>10 DR. JOHN JERNIGAN: And for those of</p> <p>11 you unfamiliar, a pre-IND is our way of making sure we</p> <p>12 don't -- we have access and file the stuff properly</p> <p>13 that you've submitted and we actually have a process</p> <p>14 for offering you a meeting. There is no cost for</p> <p>15 receiving advice through that that program, but then</p> <p>16 you have a dossier that we're keeping through the</p> <p>17 development program and eventually if you're ready to</p> <p>18 move to human trial and need an IND, we can then rely</p> <p>19 upon that file and it simply becomes an IND file.</p> <p>20 DR. PETER KIM: Absolutely. I see Dr.</p> <p>21 Sharon Wright has her hand up.</p> <p>22 DR. SHARON WRIGHT: Thank you. I just</p>

<p style="text-align: right;">Page 374</p> <p>1 wanted to pivot us back just for a minute to the 2 question that came up about population, particularly 3 what Drs. Huang and Weinstein were mentioning. You 4 know, I think the distinction between community and 5 the healthcare setting is becoming increasingly 6 blurred.</p> <p>7 And this may be that my newer view 8 looking from the health system but as we start moving 9 things, particularly complex surgeries into the 10 ambulatory setting and then patients going directly 11 home afterwards, of things that, you know, some 12 patients might have even wound up in a community ICU 13 afterwards to recover, and as we look into medical 14 home and giving full medical care in patients homes, I 15 think thinking about how we design these studies and 16 for maybe larger systems that have combined electronic 17 health records may be a way to look at that data and 18 follow patients through all settings, including things 19 we often don't think about like freestanding 20 psychiatric facilities where things pass very quickly, 21 like summer camp when they are all sharing kitchen 22 space and activities together or, you know,</p>	<p style="text-align: right;">Page 376</p> <p>1 Dmitri. Dr. Kim, would you like to comment? 2 DR. JAMES KIM: Yeah, thank you. I 3 guess to build off of Dr. Huang's statements about 4 looking at things from all the different vantage 5 points, I think that discussion here on new drug 6 applications is very interesting and timely subject. 7 I also want to sort of, you know, think 8 about the way that Dr. Weinstein spoke about the 9 different places where you can have interventions. 10 And you know, thinking about hand hygiene and the 11 importance of hand hygiene, I think Dr. Weinstein 12 specified several places where I think proper hand 13 hygiene could have a real positive impact on 14 decreasing transmission of hospital-associated 15 infections. 16 So just want to sort of put that on the 17 table that, you know, we do have a toolkit here. The 18 OTC active ingredients that we use in antiseptics that 19 I think could be, you know, expanded in the way that 20 they're used or used more effectively. And I think 21 that, you know, is something that we should have some 22 discussion about also with FDA, thinking about the</p>
<p style="text-align: right;">Page 375</p> <p>1 immunocompromised units. 2 So just taking those things in mind 3 when we think about some of the study design and the 4 populations that are at risk who bring those things 5 then back into our tertiary and quaternary care 6 setting. 7 DR. PETER KIM: Thank you, Dr. Wright. 8 I see Dr. Dmitri Iarikov. Would you like to comment? 9 Dr. DMITRI IARIKOV: I thank everyone. 10 A great discussion. Just a few points to add to what 11 John and Peter was saying to Dr. Huang's point. 12 Please keep in mind that approval of 13 the IND, it's not the end of the process. There 14 should be an entity responsible for maintaining the 15 product, right, so there should be someone to keep 16 manufacturing in order, providing stability data, 17 providing reports, paying fees. 18 So it's not just that -- not, it's 19 just. It's not only a collection of the data and 20 submitting it to the agency. It's just the beginning 21 of the process. Over. 22 DR. PETER KIM: Very good point,</p>	<p style="text-align: right;">Page 377</p> <p>1 ultimate goal of improving. 2 DR. PETER KIM: Thank you. Thank you, 3 Jim, for your comment. I'll just ask if Dr. Michele 4 would like to comment. 5 DR. THERESA MICHELE: Nothing further. 6 Thanks. 7 DR. PETER KIM: Thank you. Any other 8 thoughts or questions before we move on to the next 9 question? I think we are close to time. Dr. Jjingo, 10 would you like to go? Would you like to speak? 11 DR. CAROLINE JJINGO: Yes. I just 12 wanted to say in terms of Dr. Wachser's presentation, I 13 think you brought up a lot of important at least I 14 think logistical and operational issues which at least 15 from the regulatory standpoint, I think it's good for 16 us to consider, like -- and also many of speakers in 17 terms of the expense of these trials and really I 18 think there needs to be probably and I don't know how 19 to think of this, but in terms of like funding 20 frameworks. 21 I don't know -- I mean, I know Dr. 22 Farley talked about some consortiums but I don't know</p>

<p style="text-align: right;">Page 378</p> <p>1 if maybe down the line we might need to think of, I 2 don't know, government strategies to try and fund what 3 might ultimately be really expensive studies, you 4 know, to get the information that we need, especially 5 because I think culturally when we look at how our 6 healthcare systems, it's usually less proactive in 7 terms -- and more reactive. So in terms of when we're 8 thinking about things in terms of like prevention, 9 where do we get the buy-in to even fund what will 10 ultimately seem like it's going to be expensive 11 studies? 12 And on top of that, the point that you 13 said in terms of like with stakeholder buy-ins, if we 14 think about hospitals and how I guess several of them 15 I guess, you know, based on, you know, being dinged 16 for, like, healthcare acquired infections, so how, if 17 we're going to think about cluster randomized trials, 18 do we get those -- where we're looking at health care 19 institutions, be they hospitals or long-term care 20 facilities in order to even try and volunteer yourself 21 to be a part of a study? 22 I mean, somehow it seems like there</p>	<p style="text-align: right;">Page 380</p> <p>1 logistic was actually not a problem really of money. 2 At the end we -- it was a problem of, you know, we 3 managed to get regulatory authorization. We managed 4 to get some level of funding. 5 The thing is the study would last nine 6 years. We don't have that time. So why? Because we 7 have selected the right patient population which is an 8 enrich patient population. I think that's part of the 9 question of the designs. However, those are hemato- 10 oncology patients and hemato-oncology patient, as we 11 well know they take a lot of antibiotics and therefore 12 have a very high risk of secondary infection, C. diff 13 as well as resistant bacteria and sepsis. 14 But guys, when they do clinical 15 studies, what they're concentrated in in getting 16 treated, their cancer. So the competition in those 17 patient population, enrich patient population of 18 infectious disease are very difficult to recruit for 19 very good reasons which is their own -- their 20 physician own priority to get treated, to treat their 21 cancer. 22 And even though we understand</p>
<p style="text-align: right;">Page 379</p> <p>1 might be some tension between the fact that you don't 2 want to actually have -- you don't want to have 3 healthcare-acquired infections, but yet we would need 4 their buy-in in order to conduct these studies. So I 5 think there are several conundrums, be they funding 6 mechanisms and also getting necessary stakeholders to 7 even be able to conduct the science that we need to 8 answer then these regulatory questions and to fulfill 9 the public health and at the individual level patient 10 level need that we need to even do this. 11 So it's not necessarily the science but 12 I think it's the operational logistics that are 13 important. So I thank you guys for bringing those up, 14 but -- and I don't know the answer. 15 DR. PETER KIM: Thank you, Caroline. 16 Florence, would you like -- 17 FLORENCE SEJOURNE: Yes. 18 DR. PETER KIM: -- to go? 19 FLORENCE SEJOURNE: Yes, I wanted to 20 just rapidly reply to Caroline. We had the chance in 21 our program to have a co-funding from Europe, from the 22 European Commission through IHI. So this issue of</p>	<p style="text-align: right;">Page 381</p> <p>1 microbiome protection is not only about infection but 2 as well as immune system towards GvHD, et cetera, et 3 cetera. This is still a little bit science fiction 4 for physicians so that it's difficult to recruit big 5 population in those severe oncology patients because 6 we just have as well competition with cures for 7 cancer. 8 DR. PETER KIM: Thank you, Florence. 9 Okay, we'll take Vince as our last comment for this 10 question. 11 DR. VINCE WACHER: Thanks very much. 12 And so first of all, everything Florence said, 13 absolutely agree. It took us a year to just get to 14 our patients. So it is a tough even in an enriched 15 population with a high incidence endpoint like the 16 bone marrow transplant population. But I did have an 17 idea about how we can force this along. Maybe we 18 could talk to CMS and talk to -- about the HSCRP 19 program, and you have a choice. 20 We will take 1 percent of all your 21 Medicare reimbursement or you will have let us do 22 clinical trials in your institutions. And that way</p>

<p style="text-align: right;">Page 382</p> <p>1 they have a way out of their thing and we have an 2 opportunity to get to some patients. 3 DR. PETER KIM: Thank you, Vince. And 4 thank you all for this -- for the responses to the 5 question. It's been really helpful to hear your 6 thoughts. 7 Okay, now the third question. Please 8 discuss clinical endpoints effects on how a patient 9 feels, functions, survives that would be most relevant 10 for evaluating the efficacy of a new therapeutic for 11 the prevention of healthcare-associated infections 12 including but not limited to possible differences and 13 endpoints used in trials randomized at the unit level 14 versus the patient level, defining endpoints for 15 pathogen specific versus broader spectrum therapeutics 16 and handling of dust during the study in endpoint 17 analysis. 18 And we'd like to ask Dr. Vance Fowler 19 to start off with a response to this question. Vance. 20 DR. VANCE FOWLER: Sure. Thanks Peter. 21 I appreciate the opportunity to participate and 22 learned a great deal from the previous speakers. So</p>	<p style="text-align: right;">Page 384</p> <p>1 you've got at-risk patients who are not infected at 2 the time of enrollment and you want to see which arm 3 of your trial is best able to keep them that way. 4 This fundamentally differs from your 5 traditional anti-infective trials in which all of the 6 patients at the beginning have got an infection and 7 the goal is simply to compare the efficacy of two 8 different comparator anti-infective agents and that's 9 going to drive how these trials are designed. It's 10 going to drive how they're interpreted. 11 So given that, the second thing, I 12 think the primary endpoint in these prevention trials 13 needs to -- wherever possible, needs to be a micro 14 biologically confirmed and blindly adjudicated event. 15 So you know, interventions that target specific 16 pathogens -- and I'm going to largely focus my 17 comments on staph aureus just because it's far and 18 away the most interesting pathogen -- is you know, 19 really should be assessed on its ability to reduce 20 infections that are caused by the pathogen of 21 interest. 22 I think that in terms of how resistance</p>
<p style="text-align: right;">Page 383</p> <p>1 yeah, it's a tricky issue, this endpoint thing, 2 because in many ways it's governed in part by the 3 audience to whom you're ultimately designing your 4 trial. 5 And I mean, two sort of broad buckets 6 are strategy trials and registrational trials and 7 unavoidably, because they have fundamentally different 8 goals that are both critical, the audiences of these 9 trials are different. You know, strategy trials are 10 fundamentally about how do we best use the product 11 that we have in our hands. Registration trial is 12 about getting that product into the hands of 13 clinicians at the end of the day. 14 I'm going to focus my comments on 15 registrational trials because that's ultimately why 16 we're all here. Four sort of thoughts on endpoints 17 that can hopefully get things going. You know, the 18 interesting thing about these prevention trials is 19 that the end point in this situation is the event that 20 you don't see and that really permeates the way the 21 trial is interpreted, the way it's designed, and you 22 know, because ultimately you've got a study in which</p>	<p style="text-align: right;">Page 385</p> <p>1 infuses into that scenario, you know, really in the 2 absence of biological basis, microbiological endpoints 3 should be calculated by including both antibiotic 4 susceptible and antibiotic resistant bacteria. In 5 other words, in this sense, the example, methicillin- 6 susceptible and methicillin-resistant staph aureus, 7 again, unless there's some sort of biological or 8 mechanistic reason to the contrary. 9 Interventions that don't target 10 specific organisms should also be evaluated by micro 11 biologically confirmed events whenever you can. But 12 the problem is in some clinical syndromes, in fact, 13 some big clinical syndromes we have to deal with like 14 hospital-acquired pneumonia, you're almost never going 15 to get a microbiological endpoint, just because of the 16 nature of the disease and I think in that instance, 17 the least bad scenario that we can come up with is 18 going to be a blinded clinical adjudication committee 19 using pre-established guidelines. 20 So that's probably how I would think 21 about tackling that in the particular settings where 22 you're targeting specific pathogen, you're targeting a</p>

<p style="text-align: right;">Page 386</p> <p>1 syndrome, and you're targeting a syndrome without any 2 organism. 3 Quality of life and economic impact, I 4 think, should be captured both as secondary endpoints 5 but for different reasons. Quality of life, I think, 6 should -- would fundamentally fit into the overarching 7 mission of you know, evaluating how patients feel, 8 function, and survive for obvious reasons. It's 9 tricky because you're almost certainly going to need a 10 validated syndrome specific quality of life 11 instrument. 12 I mean, if you look at the OVIVA trial 13 published in 2019 in New England Journal, looked at 14 oral antibiotics for osteomyelitis, when they looked 15 at oral versus IV antibiotics and asked the question, 16 does oral antibiotics improve the quality of life of 17 patients as compared to IV antibiotics, the answer was 18 no. And if you -- you know, I think all of us would 19 fundamentally say that's probably not right. And a 20 lot of it has to do with the tool instrument in which 21 they use to try to answer the question. So you're 22 going to have to get specific. They use a thing</p>	<p style="text-align: right;">Page 388</p> <p>1 research. 2 I see that as something that's 3 ultimately going to fall on the shoulders of 4 government, of federal funding, and I think that we 5 can try to stimulate appropriate trials looking at 6 surrogates through RFAs, targeted RFAs. 7 You know, you think about Mike Saag's 8 science paper that demonstrated the, you know, the 9 role of HIV quantitative viral load as a valid 10 surrogate for the use of HIV -- in HIV clinical trials 11 and, you know, how do you translate that to the 12 scenario of C. diff where, you know, you can colonize 13 and not only could you colonize, but then you have to 14 express the toxin for it to go -- you know, so it's 15 going to be tricky. 16 How do you do it? Well, I think that 17 for example, you could start, do your RFAs with 18 targeting the top five to ten top syndromes that a 19 group of experts like Susan Huang and, you know, a 20 bunch of others on this call could come up with. Say 21 these are the ones we really need to crack. We need 22 some sort of system by which to establish, you know,</p>
<p style="text-align: right;">Page 387</p> <p>1 called the EuroQol-5, which was not really a specific 2 to that syndrome. 3 Economics are obviously critical, less 4 so from the perspective of regulatory but absolutely 5 vital for the purposes of, you know, of dealing with 6 the third party payers as our other speakers have 7 raised. 8 And the final point I guess I'd make 9 would be, you know, endpoints for interventions that 10 reduce rates of infection by reducing bacterial 11 colonization, that's tough. We've already heard 12 several examples here on this call. You know, I think 13 that they're almost certainly going to require hard 14 endpoints such as infection until we've got a 15 validated surrogate endpoint. 16 And we've heard several examples of why 17 that's the case, the struggles with it. You know, 18 there's staph aureus carriage versus post-operative 19 infection. There's the C. difficile scenario. I 20 don't see that as being a realistic expectation from 21 industry, personally, because I think the cost and the 22 time are far beyond the scope of sponsor driven</p>	<p style="text-align: right;">Page 389</p> <p>1 what if, what would -- you know, how are we going to 2 trust a surrogate. 3 And then, you know, in terms of 4 funding, some of the options include, well you know, 5 the ORISE fellowship. I can tell you, you know, we're 6 doing that right now with some of the members of this 7 call using a collaboration between ARLG and the FDA to 8 focus on the possible exploration of door endpoints 9 for the four most common anti-infective indications, 10 and it's just been fabulous. So you know, there's 11 precedent in which some of these scenarios such as an 12 ORISE fellowship for one, the CTTI, Clinical Trials 13 Transformation Initiative that, you know, Dr. Farley 14 and I had the opportunity to work on years ago with 15 hospital acquired pneumonia is another, and things of 16 that nature. 17 So maybe I'll stop there and appreciate 18 the opportunity. Thank you. 19 DR. PETER KIM: Thanks, Vance. Thank 20 you for your thoughts. Very provoking. I'm looking 21 for hands. Any takers before I start asking -- we 22 have about roughly ten minutes. Dr. Huang, could you</p>

<p style="text-align: right;">Page 390</p> <p>1 like to comment on any aspect of this question?</p> <p>2 DR. SUSAN HUANG: You know, I think</p> <p>3 that my first thought when I see this question is just</p> <p>4 the plethora of studies that you could do because each</p> <p>5 of those things are incredibly important. Of course,</p> <p>6 patient reported outcomes are important. The things</p> <p>7 that drive hospital systems to want to adopt something</p> <p>8 and quality improvement is incredibly important. The</p> <p>9 ability to hone in the microbiome as we understand it</p> <p>10 and influence it to prevent disease is critically</p> <p>11 important.</p> <p>12 So I really I think that the answer all</p> <p>13 of us, our first reaction is going to be yes all of</p> <p>14 that matters deeply and how can we -- however how can</p> <p>15 we translate something like a patient reported outcome</p> <p>16 much like the ecological outcomes of an ICU into</p> <p>17 something that can move into an FDA indication.</p> <p>18 And I do think that there is a divide,</p> <p>19 maybe it's a chasm but it was there for a good reason,</p> <p>20 you know, safety really, you know, really defined</p> <p>21 endpoints. There's a reason why the system exists the</p> <p>22 way that we have it. But given the gray spaces that</p>	<p style="text-align: right;">Page 392</p> <p>1 to public health here. So I think it's a great</p> <p>2 conversation. I hope it's the first of many more.</p> <p>3 DR. PETER KIM: Thank you. Thank you,</p> <p>4 Dr. Huang. Anyone else? Dr. Jjingo, I see your hand</p> <p>5 is up.</p> <p>6 DR. CAROLINE JJINGO: Yeah, hi. I just</p> <p>7 wanted to ask Dr. Fowler or any of our panelists, but</p> <p>8 since Dr. Fowler mentioned about quality of life</p> <p>9 measures or -- like, how would you approach? I mean,</p> <p>10 how would you approach that? Would it be like, I</p> <p>11 mean, what kind of, like, instrument would you -- or</p> <p>12 are there any existing ones or how would you go about</p> <p>13 that and at what point it seems like it might be --</p> <p>14 have to address something that's longitudinal or some</p> <p>15 sustained or early on or -- yeah, I just wanted to</p> <p>16 hear your thoughts or anyone's thoughts about how it</p> <p>17 would capture quality of life measures from a patient</p> <p>18 perspective,</p> <p>19 DR. VANCE FOWLER: Would someone else</p> <p>20 like to respond first? Okay, I can comment then. So,</p> <p>21 you know, as you will -- you doubtless know, they're</p> <p>22 sort of quality of light -- quality of life that these</p>
<p style="text-align: right;">Page 391</p> <p>1 exist with the microbiome and a lot more attention on</p> <p>2 patient desires and interests, this idea of population</p> <p>3 health, which you know, how do you get an indication</p> <p>4 for a population, right, and who governs that</p> <p>5 population and who owns consent for that population?</p> <p>6 Is it public health? Is it the health</p> <p>7 system? Is it -- who is it? I think that if we can</p> <p>8 all agree that there is a new world of conversations</p> <p>9 that needs to be furthered and how we get there and</p> <p>10 how it might change what we have held fast to as the</p> <p>11 dogma of how we conduct studies or approved products</p> <p>12 or, you know, I think that what we're saying through</p> <p>13 all of this is that these things need to shift in some</p> <p>14 way, none of us are certain exactly how, but we need</p> <p>15 to come closer together because there's a lot of</p> <p>16 people who need us and they need these products and</p> <p>17 they need them in a way that can't be decades in the</p> <p>18 making and we don't -- we can't afford it because the</p> <p>19 resistance is growing because of the way we Americans</p> <p>20 use antibiotics.</p> <p>21 And you know, these are, you know,</p> <p>22 first world problems, but they're very, very germane</p>	<p style="text-align: right;">Page 393</p> <p>1 instruments that haven't been fully validated by the</p> <p>2 FDA takes years and years and it's onerous.</p> <p>3 In no way am I proposing them. There</p> <p>4 is sort of a middle ground which is being developed</p> <p>5 and in fact there's a Duke faculty person working, I</p> <p>6 think the majority of his time at the FDA on quality</p> <p>7 of life instruments that can be developed in that</p> <p>8 regard.</p> <p>9 ARLG is also working on quality of life</p> <p>10 instruments amongst the, you know, the four anti --</p> <p>11 primary indications for anti-infectives. And that can</p> <p>12 be, you know, it's sort of essentially internally</p> <p>13 validated, largely using -- I know I'm going to get</p> <p>14 the wording wrong because I -- usually we have to have</p> <p>15 a responsible adult with these quality of life guys</p> <p>16 which -- when we start these trials, but they have</p> <p>17 essentially validated pods or sections of previous</p> <p>18 quality of life studies that they can then build in</p> <p>19 and integrate into a syndrome specific indication.</p> <p>20 For example, we're doing it with</p> <p>21 complicated urinary tract infection. As a matter of</p> <p>22 fact, we're also as a second trial with the ARLG,</p>

<p style="text-align: right;">Page 394</p> <p>1 we're asking kind of interesting response to that and 2 that is, evaluating how well physicians estimate the 3 quality of life of their patients. So you're asking 4 the quality of life of the patient and then 5 simultaneously of those same providers that are 6 providing care to them asking the same -- asking their 7 expectation and their interpretation of it. 8 I can't wait to see what that one is 9 going to be, because my guess is we probably don't get 10 it quite as well as we think we do. But I think it's 11 going to have to as the OVIVA example sort of 12 illustrates, I think it's going to have to have some 13 specificity of a particular syndrome in place and, you 14 know, that can be done with a reasonable price, you 15 know, and a reasonable timeline using some of these 16 sort of pre-existing validated components. I'll stop 17 there. 18 DR. PETER KIM: Thanks, Vance. Any 19 last minute thoughts? Florence, would you like to 20 take the floor? 21 FLORENCE SEJOURNE: Sorry -- 22 DR. PETER KIM: Florence, you're on</p>	<p style="text-align: right;">Page 396</p> <p>1 Dr. Weinstein. 2 DR. ROBERT WEINSTEIN: Yeah, I think 3 the issue of patient reported outcomes is fascinating 4 and comparing it to what we think and what the patient 5 thinks. I think the other aspect is the nursing 6 staff. I don't think we get enough input from the 7 nursing staff for interventions and what they think of 8 them. And if you've had patients in the -- relatives 9 in the hospital recently, you value the nurses more 10 than the doctors. No question about it in my mind. 11 You certainly see them a lot more. And 12 I think understanding what they think of some of the 13 interventions and how they affect their day-to-day 14 work, I think would be very useful to incorporate into 15 some of the studies we do. 16 DR. PETER KIM: Thank you, Dr. 17 Weinstein. So, we're at time for this panel 18 discussion. What we'll now do is Michael and I will 19 split the summary of today's session. So, Michael, I 20 turn the floor over to you. 21 MICHAEL CRAIG: Thank you, Peter. And 22 I want to thank all of our panelists and everyone for</p>
<p style="text-align: right;">Page 395</p> <p>1 mute. 2 FLORENCE SEJOURNE: -- muting. Yeah. 3 I'm sorry to give a very brief private company 4 reaction to the discussions. It's very good that CDC, 5 FDA gathered together to put this on the table and 6 that we share the info. It's going to be too late for 7 some of us, maybe not all, but to bring those products 8 to market now. The example of DAV132 is \$18 million 9 for 15 years already spent. Five hundred, you know, 10 volunteer patients treated with safety, good safety 11 database. This takes time. This takes a lot of 12 money. 13 As you well know, pharma is not really 14 interested in that and biotech have trouble 15 fundraising. So there is some kind of emergency if we 16 want actually the products already kind of available 17 and developed today to go to market -- similarly to 18 new antibiotics where we know this is an issue and 19 CARB-X knows that more than anyone else. Sorry for 20 the negative comment in terms of timelines, but that's 21 the reality we're into. 22 DR. PETER KIM: Thank you, Florence.</p>	<p style="text-align: right;">Page 397</p> <p>1 today. And I think for all of our participants, we 2 had, I think at times over 1,000 folks participating 3 in the day, so really appreciate everyone's engagement 4 and interest in the topic. 5 I just want to note from the CDC 6 perspective, as I noted at the outset, we're 7 incredibly grateful to our colleagues at FDA, John 8 Farley and his team for bringing this meeting together 9 with us. This is an area of intense interest from 10 CDC, as you heard this morning from my presentation as 11 well as that of my colleagues, and I think what we 12 wanted to highlight was just the challenge that we see 13 in public health that I think is growing. And it's 14 one that we really do think that there are enormous 15 opportunities here for collaboration and I think it's 16 collaboration between the public health side, the FDA 17 regulatory side, as well as the private sector. 18 And I think what you heard this morning 19 is, you know, the challenge that we see is the 20 transmission of these dangerous pathogens, many of 21 them antimicrobial resistant is growing. And how do 22 we address that? And the issues of resistance are</p>

<p style="text-align: right;">Page 398</p> <p>1 only increasing.</p> <p>2 You heard from Dr. Jernigan talking</p> <p>3 about that the power of the indirect effect on</p> <p>4 prevention and what that could potentially hold and</p> <p>5 some of the modeling that we have seen and that we</p> <p>6 think is important. You heard from Dr. McDonald</p> <p>7 talking about agents that are currently available that</p> <p>8 are being used for some of these purposes already and</p> <p>9 the positive benefit that we're seeing from many of</p> <p>10 those and the potential that there could be more,</p> <p>11 especially as we, you know, potentially could have</p> <p>12 pathways for some of these products being brought to</p> <p>13 market.</p> <p>14 And then you heard from a series of CDC</p> <p>15 experts, fantastic presentations that delve deeply</p> <p>16 into the specific pathogen areas. And I'm not going</p> <p>17 to go over all of them, but I just want to commend all</p> <p>18 of them for very fantastic, in-depth perspectives that</p> <p>19 really show the expertise and the data that we have in</p> <p>20 many of those areas and the potential for what</p> <p>21 prevention could mean for all of the people who are</p> <p>22 affected, both in terms of colonization and infection</p>	<p style="text-align: right;">Page 400</p> <p>1 relationship with you, CDC, Michael, and also with</p> <p>2 academia and we will continue to work with industry as</p> <p>3 well.</p> <p>4 All right, so I'm going to go through a</p> <p>5 whirlwind of session two. All right. So Heidi Smith</p> <p>6 discussed Regulatory Considerations for the</p> <p>7 Registration of Products for the Prevention or</p> <p>8 Reduction in the Incidence of Healthcare-Associated</p> <p>9 Infections. She discussed FDA's standards for</p> <p>10 approval of new products, the characteristics of</p> <p>11 adequate and well-controlled trials. She provided</p> <p>12 illustrative examples of possible development programs</p> <p>13 such as drugs for the prevention of surgical site</p> <p>14 infections, and also drugs to reduce the incidence of</p> <p>15 catheter-related bloodstream infections and she</p> <p>16 discussed safety database considerations.</p> <p>17 Next, Dr. Theresa Michele's talk was</p> <p>18 Regulation of Healthcare Antiseptics, and Dr. Michele</p> <p>19 discussed the categories of over-the-counter</p> <p>20 antiseptics such as healthcare antiseptics including</p> <p>21 but not limited to patient preoperative skin</p> <p>22 preparation. She compared and contrasted pathways for</p>
<p style="text-align: right;">Page 399</p> <p>1 of those pathogens as well as those who are</p> <p>2 potentially at risk of those pathogens.</p> <p>3 And then I would also just really like</p> <p>4 to highlight and thank our panelists who followed the</p> <p>5 CDC presenters, both our public commenters as well as</p> <p>6 those who from -- that shared the patient perspective.</p> <p>7 I think, you know, we had tremendous presentations</p> <p>8 about cystic fibrosis and the impacts of a MRSA</p> <p>9 infection on patients and the ongoing challenges that</p> <p>10 patients face because of those infections. And I</p> <p>11 think that they highlighted really, what we all need</p> <p>12 to remember is what is the patient experience, how can</p> <p>13 we bring prevention to bear on patients and how can we</p> <p>14 protect patients ultimately from risk of infection and</p> <p>15 the risk of transmission.</p> <p>16 So that's I think where I would note it</p> <p>17 and I again want to thank everybody for their</p> <p>18 participation and Peter, I'll turn it back over to</p> <p>19 you.</p> <p>20 DR. PETER KIM: Thanks, Michael, and I</p> <p>21 would also like to thank everyone involved, all the</p> <p>22 stakeholders, and thank you for this great working</p>	<p style="text-align: right;">Page 401</p> <p>1 marketing nonprescription drugs, namely the new drug</p> <p>2 applications, abbreviated NDA, versus the drug review</p> <p>3 process through the OTC monograph.</p> <p>4 She provided an example of the</p> <p>5 indication and labeling for a patient preoperative</p> <p>6 skin preparation and described the in vivo and</p> <p>7 clinical simulation testing for efficacy for a drug</p> <p>8 product, for patient preoperative skin preparation.</p> <p>9 Next, Dr. Paul Carlson's talk,</p> <p>10 Regulatory Considerations for Microbiome Based</p> <p>11 Therapeutics. Dr. Carlson touched on the</p> <p>12 investigational new drug application regulations and</p> <p>13 the additional chemistry, manufacturing, and control</p> <p>14 considerations for INDs for fecal microbiota</p> <p>15 transplantation as well as live biotherapeutic</p> <p>16 products and then discussed some of the challenges and</p> <p>17 the regulations of FMT such as how to ensure safety</p> <p>18 and how to characterize the product for consistency of</p> <p>19 an effectiveness and also discussed and noted that</p> <p>20 live biotherapeutic products should contain sufficient</p> <p>21 information to assure the proper identification,</p> <p>22 quality, purity, and strength of the investigational</p>

<p style="text-align: right;">Page 402</p> <p>1 drug.</p> <p>2 Next Dr. Susan Huang. Her talk was</p> <p>3 clinical considerations and operational challenges for</p> <p>4 healthcare-associated infection prevention trials.</p> <p>5 Dr. Huang touched on common features of healthcare-</p> <p>6 associated infection prevention trials such as the</p> <p>7 desire to evaluate a quality improvement strategy,</p> <p>8 determining the group of focus whether it be units or</p> <p>9 hospitals, et cetera, targeting a contagious outcome.</p> <p>10 The trials are spurred by urgent common need and that</p> <p>11 there is limited funds in this space.</p> <p>12 She then discussed common features of</p> <p>13 classical versus pragmatic trials, the differences</p> <p>14 between efficacy and effectiveness trials. She then</p> <p>15 characterized infection prevention populations of</p> <p>16 interest, the importance of defining the question</p> <p>17 under study such as temporary prevention versus long-</p> <p>18 lasting prevention.</p> <p>19 She also discussed the importance of</p> <p>20 partnership within healthcare system and also had</p> <p>21 considerations for minimal risk trials and waiver of</p> <p>22 consent, the importance of choosing appropriate</p>	<p style="text-align: right;">Page 404</p> <p>1 interference between treatment and that there is</p> <p>2 contamination interference between treatments when</p> <p>3 patients' outcomes are influenced by both the</p> <p>4 treatments they themselves receive and the treatments</p> <p>5 others received.</p> <p>6 Let's see. Dr. Weinstein's talk was</p> <p>7 Controlling Pathogens in Health Care, A Way Forward.</p> <p>8 He noted the model of the causal pathway of spread of</p> <p>9 antimicrobial resistant organisms can help to focus</p> <p>10 implementation strategies for pathogen reduction and</p> <p>11 healthcare epidemiology. He noted the relative</p> <p>12 importance of the individual components of infection</p> <p>13 control guidelines and bundles should be evaluated and</p> <p>14 the studies of microbiome should assess mechanisms</p> <p>15 behind the creation of the fecal patina and explore</p> <p>16 the interrelations of different microbiome components.</p> <p>17 Dr. James Kim, his talk was OTC topical</p> <p>18 antiseptics, an opportunity to bring innovative</p> <p>19 decolonization products to market. He provided</p> <p>20 background information on the American Cleaning</p> <p>21 Institute, discussed topical skin antiseptics and the</p> <p>22 regulation of these products, noting that current</p>
<p style="text-align: right;">Page 403</p> <p>1 controls, discussed analysis approaches such as</p> <p>2 difference-in-differences approach, the need for</p> <p>3 accounting for contagious outcomes.</p> <p>4 She discussed the differences between</p> <p>5 the conduct of the CLEAR trial and the REDUCE MRSA</p> <p>6 trial and some lessons learned and she delineated</p> <p>7 special considerations for what may be considered</p> <p>8 minimal risk indication.</p> <p>9 In conclusion, she noted that a wide</p> <p>10 variety of trials with varying durations may be</p> <p>11 pursued and once you consider the value of group</p> <p>12 versus individual randomization, ensure sufficient</p> <p>13 sample size for balancing confounders and assessing</p> <p>14 outcomes, ensure obtaining the best possible controls</p> <p>15 for gold standard comparison, and ensure data for as-</p> <p>16 randomized analysis when groups drop out.</p> <p>17 Next, we had Dr. Ed Bein, statistical</p> <p>18 considerations related to cluster randomized trials.</p> <p>19 Dr. Bein noted that the use of a cluster randomized</p> <p>20 trial is appropriate when evaluating treatments and</p> <p>21 intended to be administered cluster-wide and that CRTs</p> <p>22 are intended to handle within cluster contamination</p>	<p style="text-align: right;">Page 405</p> <p>1 regulatory frameworks may pose a barrier to the</p> <p>2 development of innovative topical skin antiseptics and</p> <p>3 noted that the establishment of skin decolonization</p> <p>4 and pathogen reduction as a determinant of clinical</p> <p>5 outcomes would facilitate new skin antiseptic</p> <p>6 development.</p> <p>7 Nicholas Georges' talk was Development</p> <p>8 of Efficacious Cleaning and Disinfecting Products in</p> <p>9 Healthcare Settings. He discussed the differences</p> <p>10 between disinfectants, sanitizers, sterilants, and</p> <p>11 cleaning products. He noted that testing is dependent</p> <p>12 on the claims and the surface types to be treated</p> <p>13 which results in determining which agency regulates</p> <p>14 the product in question. And he touched on how one</p> <p>15 might select the product for a particular use.</p> <p>16 Dr. Erin Duffy's talk was</p> <p>17 Considerations in the Development of Nontraditional</p> <p>18 Therapeutics, a CARB-X Perspective. She provided an</p> <p>19 overview of the CARB-X program as well as their</p> <p>20 portfolio of treatment and prevention products. Dr.</p> <p>21 Duffy discussed takeaways from her recent</p> <p>22 decolonization workshop including but not limited to</p>

<p style="text-align: right;">Page 406</p> <p>1 thoughts on potential patient populations for studying 2 decolonization strategies. 3 She also noted that there are several 4 challenges and opportunities for decolonization 5 strategies and a coordinated approach would be 6 beneficial. 7 Florence Sejourne. Her talk was 8 Challenges and Lessons Learned Developing DAV132, a 9 Novel Therapy Protecting Gut Microbiota from 10 Antibiotic-Induced Dysbiosis. She discussed how 11 antibiotics provoke intestinal microbiota dysbiosis 12 and how dysbiosis may result in additional downstream 13 consequences. She discussed the DAV132 development 14 program and lessons learned. She noted the 15 association between low diversity microbiota and the 16 risk of CDI as well as the risk of colonization with 17 multidrug-resistant organism. 18 She noted that current regulations do 19 not allow for feasible clinical development because of 20 the demonstration of reduction in colonization 21 followed by reduction secondary infections and 22 dissemination necessitates large, expensive trial.</p>	<p style="text-align: right;">Page 408</p> <p>1 and discussed development programs for SER-109 in 2 patients with recurrent CDI. 3 And then we also heard from our 4 panelists on three questions and we had a rather 5 provocative conversations and a lot of take home from 6 the discussion. 7 So once again, thank you very much for 8 everyone's participation, everyone who made this 9 workshop possible. We hope this is the first of 10 several discussions. I would like to thank our 11 partners CDC as well as academia and industry and the 12 patient groups as well who provided valuable 13 information related to their experiences. 14 Michael, I think you want to -- why 15 don't you go ahead. 16 MICHAEL CRAIG: Yeah, Peter. I just 17 wanted to close by noting, folks, that we have been 18 recording today and it is going to be posted on the 19 registration page for folks to see and it's also going 20 to be on CDC's YouTube page and those will be 21 available and thanks for pulling up the post-webinar 22 information.</p>
<p style="text-align: right;">Page 407</p> <p>1 Next, Dr. Vince Wachter. His talk was 2 Lessons Learned in Developing SYN-004, a Potential 3 Point of Care Preventative for HA-CDI. He discussed 4 the development program for SYN-004 for the proposed 5 indication of prevention of CDI. He also proposed 6 ways to help facilitate CDI prophylactic drug 7 development. 8 Dr. Silvia Caballero. Her talk was 9 Defined Bacterial Consortia, a Novel Approach to 10 Tackle Healthcare-Associated Infections. She noted 11 that microbiota and metabolic alterations 12 characterized colonization and infection with C. 13 difficile and MDRO. She discussed development 14 programs for VE303 and VE707 bacterial consortia for 15 either decolonization or preventing CDI and MDR 16 Enterobacteriaceae. 17 And finally, Matthew Henn. His talk 18 was Microbiome Therapeutics to Potentially Transform 19 the Management of Antimicrobial-Resistant Infection. 20 He noted that encapsulated consortia of commensal 21 bacteria may be designed to establish colonization 22 resistance and target inflammatory and immune pathways</p>	<p style="text-align: right;">Page 409</p> <p>1 If you have questions you can email us 2 at ARX@CDC.gov and we'll get back to you with that. 3 And I also want to close by thanking the planning and 4 logistics teams, Katie, Sunita, Amy, all the other 5 folks who have been behind the scenes who have pulled 6 this together and we've been working on this for about 7 a year, so really appreciate everyone's great work on 8 it. There's a lot of work that happened behind the 9 scenes that folks didn't see. So thank you all and I 10 think with that we can close for today. Thanks, all. 11 Bye bye. 12 DR. PETER KIM: Thank you, everyone. 13 (Whereupon, at 5:22 p.m., the 14 proceeding was concluded.) 15 16 17 18 19 20 21 22</p>

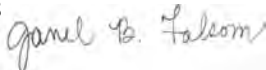
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2 I, JANEL FOLSOM, the officer before whom the
 3 foregoing proceedings were taken, do hereby certify
 4 that any witness(es) in the foregoing proceedings,
 5 prior to testifying, were duly sworn; that the
 6 proceedings were recorded by me and thereafter reduced
 7 to typewriting by a qualified transcriptionist; that
 8 said digital audio recording of said proceedings are a
 9 true and accurate record to the best of my knowledge,
 10 skills, and ability; that I am neither counsel for,
 11 related to, nor employed by any of the parties to the
 12 action in which this was taken; and, further, that I
 13 am not a relative or employee of any counsel or
 14 attorney employed by the parties hereto, nor
 15 financially or otherwise interested in the outcome of
 16 this action.

17

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19 JANEL FOLSOM

Notary Public in and for the
 20 DISTRICT OF COLUMBIA

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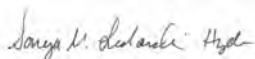
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1 CERTIFICATE OF TRANSCRIBER

2 I, SONYA LEDANSKI HYDE, do hereby certify
 3 that this transcript was prepared from the digital
 4 audio recording of the foregoing proceeding, that said
 5 transcript is a true and accurate record of the
 6 proceedings to the best of my knowledge, skills, and
 7 ability; that I am neither counsel for, related to,
 8 nor employed by any of the parties to the action in
 9 which this was taken; and, further, that I am not a
 10 relative or employee of any counsel or attorney
 11 employed by the parties hereto, nor financially or
 12 otherwise interested in the outcome of this action.

13

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15 SONYA LEDANSKI HYDE

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