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for the Study of Bioethical Issues

TRANSCRIPT

Medical Countermeasure Roundtable

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SESSION 5: MEDICAL COUNTERMEASURE ROUNDTABLE

DR. GUTMANN: We're missing Lisa and John, so we'll wait a minute. Okay. I assume -- do we know where two of our panelists are? Well, we will just -- we'll get started.

This is always a treat for the Commission to have these roundtables of people who have already presented, so we can both hear from you if we're going to focus on -- if there's one thing you want to make sure we say or focus on or one set of data that you think is very important to inform our report, what would that be? And it's really not -- you've already given us your overview, but really we always think it's important to make sure our reports are properly focused. And don't neglect the most important parts of the topic. So this is your chance to tell us what is, in your minds, most important that we convey in our report.

And I would just go quickly down and then open it up for the Commission members to ask you any questions. And since in the Biblical form, the last shall be first, James Hodge, why don't you begin?

MR. HODGE: Well, sure, thank you.

I don't know if -- do we need to talk into the microphone here?

DR. GUTMANN: Yes.

MR. HODGE: Is it switchable?

DR. GUTMANN: Because this is also webcast, so --

MR. HODGE: Okay, very good. I didn't realize. So it's great to know that.

Listen, if there's one takeaway message that I would think this

Commission would find helpful, it's the idea that at the moment you get to some product that can be distributed, some vaccine that's available, some manner of medical countermeasure that you know will work, after all the legal and ethical concerns you're going to have to pave through to get to that point, you're not remotely done in relation to the significant national challenges of actually allocating it to the individuals that might need it most, or any other bases for which it will actually get in the hands of Americans.

That I think might be the hardest question and often it's kind of the afterthought. Well, we'll work hard to produce this countermeasure and surely when it's available, we'll get it out. CDC, HHS, DHS, they all produce excellent guidance on this. It doesn't mean the states follow that. It doesn't mean hospitals follow it. In fact, we've seen documented over and over, they don't. They follow their own plans, their own approaches. It's wildly divergent across the United States. And while you all can't solve that, I don't think, acknowledge it. Know that you've got that challenge of making sure that the distribution of that allocation will be an equal test for this country.

DR. GUTMANN: Okay, thank you.

Holly, if there is one -- I'll repeat the question but I think Dr. Parker and Dr. Kaplowitz know, if there's one thing we should be sure to say or take into account, what is that?

DR. TAYLOR: Sure. So I'd like to answer it by saying, the thing about making the decision that makes me most nervous, or the thing that I find it hard to wrap my head around is how to balance on one side, making a decision about exposing identifiable children to a potential risk when you're balancing that against some highly uncertain benefit in the future. That it's new to our sort of calculus about research ethics, and I think that's -- there needs to be a justification in particular if a decision is

made to put that into the balancing of whether or not to go forward with a trial.

DR. GUTMANN: Okay, thank you.

Lisa?

DR. KAPLOWITZ: I would want to make sure that we're thinking about the best interest of children, not only before an event but after an event, and to factor that into our planning which is, you know, part of our charge being in emergency preparedness, that we look at the whole spectrum. And what can we do before an event to really facilitate providing medical countermeasures to the entire population after an event?

DR. GUTMANN: Right. Thank you.

Dr. Parker? I should call you John. I have to get over -- yes -- General, because otherwise I'd call you Major General.

DR. PARKER: John works really well.

DR. GUTMANN: Thank you.

DR. PARKER: Because as I've told a lot of people, I got my first name back after I retired.

(Laughter.)

DR. PARKER: In my mind, if we look at this balance, is that if there is an outbreak, we are in fact probably going to give antibiotics and vaccine to the adults. And with or without a pre-event study, probably going to give vaccine and antibiotics to the children.

So if we know we're going to do that, there's two ethical questions. Is it ethical to just give the vaccine to the children on the basis of what we know about the adults, and not do any studies? Or is it -- does it weigh on the side of the scale to

be -- there's no "more ethical" -- but if that's going to be the scenario, shouldn't we try to get some data pre-event? And then you mix into that -- and I don't know how to say this.

The American public doesn't want to tolerate much risk. But as we look to the future, I think there's going to be a lot of things where we're going to have to engage not only ourselves but the American public and others into measured risk. And they've got to get used to that.

You know, we send astronauts to the space station, we've sent them to the moon, we're planning to send them to Mars. You can't imagine the risks involved in that. And so those people that want to do that exploration, and those people that want to support that measure those risks and say, "Yea, verily we'll take them."

If we could raise the risk level across the United States about getting away from this expectation of zero risk, I would say that the government plan is sound.

DR. GUTMANN: Thank you.

Nicola?

DR. KLEIN: Just two short issues. First of all, I don't think there's any question that, while challenging the -- doing studies now is certainly feasible, and we certainly could do those studies in children looking at the immunogenicity in studies.

But actually the point that I would like to mention that I did not mention earlier was that, if it does come to -- as other people have mentioned -- that there is a vaccine that is in use. And if the panel decides that it moves forward, I think an absolutely critical thing to consider, while talking about risk, is that to have an active vaccine safety monitoring plan in place that is going to be ongoing as vaccines are being delivered.

DR. GUTMANN: Yeah, thank you.

Michael?

DR. ANDERSON: Just a follow-up on what General Parker said, and it's always been General Parker to me. I think that we have an obligation to keep America's children safe. I, as a pediatrician, think that each and every day.

And what's concerning to me about the hypothetical "God forbid" scenario about an attack tomorrow is, yeah, we'll give out vaccine and antibiotics based upon what we know. We don't know anything. What dose do we give that six-year-old? Is it 1/70th per kilo? Is it 1/18th per year? I really think we as a community need more data to feel comfortable, and this is the safest way possible.

DR. GUTMANN: Skip?

DR. NELSON: Yeah, I guess the one point I would encourage you to think about is that all medical countermeasures are not created equal. And by that I mean that the facts of each one of the development programs for these are going to vary. Anthrax is not smallpox, is not pandemic flu is not sarin, and so forth. And the kind of pathway towards getting the data that all of us I think believe are necessary is going to vary depending on those fact situations.

So as you think through what are the sound ethical reasons to sort of move beyond the standard paradigm, I think keeping those facts in mind are very important.

DR. GUTMANN: Yeah. So let me just -- before we get to David, because David presented a framework. What you're -- the way what you're saying factors into our work, and what all of you are saying in some sense, but what you really put to a head, is that we can do -- we can provide an ethical framework for how a decision would be made. What the decision would be will vary with the particular

countermeasure that's being considered and the data available on that countermeasure.

DR. NELSON: Yeah. When I reflect on my work --

DR. GUTMANN: To say that one vaccine, research on one vaccine should go forward really requires having facts, not just the framework.

DR. NELSON: Right.

DR. GUTMANN: And if it should go forward on one, it doesn't entail that it should go forward on everything else, or every -- not all countermeasures are vaccines, either.

DR. NELSON: No, I agree. Most of my work in the consulting that I do is probably 80 percent getting the science straight and the facts straight, and then the ethics begin to fall into place as you get some of that data before you. And a lot of the conversation this morning was around getting the facts on the table. So I think, you know, make sure you're working with good facts.

DR. GUTMANN: Yes. Although I should say, I don't know how you do the 80/20. I mean, if you don't get the ethics right, all the facts in the world aren't going to tell you what to do.

DR. NELSON: That's true.

DR. TAYLOR: I think what he's saying is, you can't make the ethical decision until you have all the facts in front of you, right?

DR. GUTMANN: That's true.

DR. TAYLOR: And absent that -- you know.

DR. NELSON: And even then, there's judgment.

DR. GUTMANN: Yeah.

David?

DR. DeGRAZIA: My take-home lesson, and the one that I suggest, is to drop the balancing metaphor. I'd like to emphasize that because it's tempting to talk about balancing the risks to research subjects against the risks of other children out there, the general public and so on. But to put it that way is to miss the -- the comparison of the rights of research subjects, not -- these are negative rights -- not to be subjected to unnecessary harm against the goal of protecting people out there. And the balancing metaphor I think invites a crude sort of consequentialist reasoning about this issue, which I think almost everyone working in ethics would reject.

So I would just say, remember to keep our eyes on whatever it is we think the children subjects have a right to. I don't know what the right way forward is. I think the factual picture is really difficult, as well as the ethical picture. But I just wouldn't want us to lose sight of the fact that we're talking about individuals who may or may not be subjected to significant risks.

DR. GUTMANN: Okay, good.

DR. DeGRAZIA: Yes.

DR. GUTMANN: Let me just ask, not -- this is not a question for you to answer but a request on behalf of the Commission. Since very many of you have said the facts really matter and there's nobody here, nobody on this Commission who would disagree with that, I don't know what percentage to put, but I would definitely agree you can't come to a decision in this matter without having the facts.

I would request that all of you who work in the domain of the facts here get us the relevant facts with regard -- all of the relevant facts that are known or any that are unknown that we -- that would need to be gotten. We would not -- the ones that are not known are not going to come to our Commission, but that would have to be known

before a final decision should be made on specifically a vaccine, an Anthrax vaccine for children.

And then I was going to open it up for Commission --

DR. TAYLOR: I just want to make a clarification. David and I don't disagree at all. I think I skipped to the chase and talked about balancing in the context of how you make a decision.

DR. GUTMANN: You made that clear. You made that clear.

DR. TAYLOR: Thank you.

DR. GUTMANN: But he still wanted to emphasize how important it is, but that's – now where -- so please, we'll follow up with you if we don't hear from you. Because it's really important for us to know what is the state of knowledge of the facts in this matter? And I know Alex has really emphasized that, how important that is as well, given the uncertainties and the confidentiality in some -- about the risk.

Okay. Now, Dan?

DR. SULMASY: Yeah, one question about the science. I'm not certain that we know whether or not Anthrax can be reengineered to have antibiotic resistance. And if that's the case, does that help us in balancing the idea that, well, antibiotics are a good alternative to the vaccine? Do we know the people who are smart enough to weaponize Anthrax could also, you know, transform the genome with resistance to Ciprofloxacin, let's say?

DR. PARKER: Want an answer?

DR. SULMASY: I would never refuse an answer to this question.

DR. PARKER: Well, I can't answer specifically. However, I will tell you about an experiment that occurred on the space station where we -- not we, I had

nothing to do with it. But salmonella was sent up to the space station and allowed to be sexual. The result was that we got a salmonella that was very, very, very infective, several times more than the normal salmonella bug.

And so if we're allowed to extrapolate, I would say that Anthrax, either through normal mutation or through scientific encouragement could be taught to be resistant.

DR. KAPLOWITZ: I'll add to that that it's something that has been discussed, continues to be discussed. It hasn't happened yet, but with the ability of genetic engineering I think that we're assuming that it could. There's always the question of what capabilities are out there. But more and more, there's very sophisticated science that can be done in garages or with not too much trouble in terms of getting the necessary equipment. So we're assuming it's theoretically possible.

DR. GUTMANN: John?

DR. ARRAS: So David, so you've urged us to reject a consequentialist analysis and to accept a rights-based approach to the problem. Now if it were simply a consequentialist issue, I think it would be a slam dunk in favor of doing pre-event research, right? Because I mean, I think most people here are acutely aware of the benefits that that could bring. And of the harms to be inflicted upon people after an event, if we don't know what we're doing, okay?

So with Leon Isenberg, I would argue that we actually have a social obligation to do this kind of research if we can. But if we do -- but if we adopt a rights-based approach, I'm wondering how that spins itself out? Like what are the rights of children that are in play here? I mean, is it a right not to be experimented on for the benefit of other people if the risk is above minimal?

DR. DeGRAZIA: A couple things. First, I have recommended a rights framework, which I think is the one that makes sense, at least in the context of protecting subjects' interests. I haven't really rejected consequentialism entirely --

DR. GUTMANN: But that's not really the question. The question is, what are the rights? I mean, because --

DR. DeGRAZIA: What's the content of the rights? Yeah.

DR. GUTMANN: Just assume you have the right. We don't -- with all due respect --

DR. DeGRAZIA: Yes.

DR. GUTMANN: -- whether you a consequent -- it doesn't really matter.

DR. DeGRAZIA: Right.

DR. GUTMANN: What are the rights? I mean, because if you say there is a rights-based thing and you can't --

DR. DeGRAZIA: Oh, sure.

DR. GUTMANN: -- put substance, so what are the rights here, say?

DR. DeGRAZIA: Well, the most relevant right for minors who are not mature minors, who can actually give informed consent, is a right to adequate protection from harm which then needs to be specified. And I suggest that, as a starting point for reflection, how to specify that thinking about what good responsible parents, with the protections that they would afford their own children.

And so the question to ask is, would a good responsible parent allow his or her child to enter into a study in which, you know, dosing is being tested, or the like. This is a somewhat different angle from asking whether it's exactly minimal risk or a minor increment more than, and I'm not sure exactly how to relate those two

frameworks.

But I haven't gotten much farther than that in terms of specifying what the right -- I mean, I think it would be, you know, relatively low risks or there's no direct benefit.

DR. GUTMANN: Let me ask anyone on the panel to answer this. This is a statement but it goes right to John's question from a parent here, Dawn Loughborugh, U.S. citizen mother against proceeding with Anthrax trials. I am concerned if you open the door to ethically perform pre-event clinical trials of drugs and vaccines for low bio-terrorist threats, high impact, low -- you know, low probability, high impact, you are not protecting children as a vulnerable population for adverse events related to the current perceived treatment.

Dr. Parker said the military perception is fraught with bio-terrorism threats as being real. As for -- you cannot -- I can't read this word. But I understand -- you cannot simulate outcomes. So you cannot simulate outcomes without testing on children, protect -- and this is a statement, "protect children from becoming guinea pigs for terrorism. My child suffered a life altering adverse event to a childhood immunization. It's devastating. We need to prevent it."

So that -- I mean, I think that's the argument that needs a response. So Holly?

DR. TAYLOR: So I think it's a great point, and I think it is exactly what needs to be answered. And you know, it's setting a precedent. And when we set a precedent, we sometimes can't control where that precedent might leave us. So the calculus that we may allow in this setting may merge into other settings. So it's the implications of making the choice in this setting, and how it then may relate to other

situations.

DR. GUTMANN: So can we -- Nicola and Michael, since I think you've really had to address this concern and care about it, given your own -- so would you respond?

DR. ANDERSON: I care about it very deeply as a pediatrician and a parent. Obviously having parents involved in this discussion from the beginning is so key. And it's just on whether the balance analogy is appropriate or not. It's a balance, what's the risk of not doing these trials, and God forbid there is an attack and we have no data versus doing the trial. And I think we have to have these open and very cogent discussions.

I think as a scientist and a pediatrician, I look at the data from the military, millions of doses given to, you know, one would argue older adolescent, 18-year-old and above military recruits with excellent safety data. And I think we have to figure out a cogent scientific and safe way to study this and get the data.

But having parents at the table asking these important questions is very important.

DR. GUTMANN: Nicola?

DR. KLEIN: I don't think I have too much more to say, other than what Michael just said. But I think parents are always going to have these concerns. And I think these come up, not just with Anthrax, but this is an issue that comes up routinely with many vaccines, that we have to address all the time when parents come in. And I think I sort of referred to that when I said, you know, parents come in with some misinformation. I'm not saying that that is the case in this particular statement. But I think that we do need to continue to educate and communicate with the families and talk

about why it is that we think that this is going to be --

DR. GUTMANN: But this is safety trials, right? So how many children would have to be enlisted in these trials, and where will you seek the consent from the parents and children? It would not be a required vaccine, so --

DR. KLEIN: So when you say this --

DR. GUTMANN: Well, the first step.

DR. KLEIN: So the first step would actually be an immunogenicity study --

DR. GUTMANN: Okay.

DR. KLEIN: -- because a safety study is going to be much, much larger. The requirements are going to be much, much larger than what would be required for an immunogenicity study.

DR. GUTMANN: So how --

DR. KLEIN: Well, this is a tough question. It depends obviously -- it's a complex question. But it can be, we do safety studies on the order of tens of thousands of children, ten, fifty, hundred thousand or plus doses of vaccines. Because, as was discussed earlier, there's a very low risk tolerance for vaccines and vaccine safety. And we are giving vaccines to healthy -- typically to healthy babies usually. So before they even get to that point, they have been tested up to 70,000 people for the largest pre-clinical studies for safety.

So we have -- so when you get to the point where you're looking at safety in a -- not the Anthrax vaccine but the other vaccines that are licensed in routine use, we do do safety studies up to many, many tens of thousands in order to check what would be rare outcomes. Because local reactions and fever, you don't need those kind of

numbers.

DR. GUTMANN: Okay.

Jim?

DR. WAGNER: The conversation that got us here was John, I think, your question about consequentialist versus right-based approach addressed to David. And I'd really like to hear a little more about that. It seems to me we cut you off after you named the first right. And the first right on a right-based approach was adequate protection against the consequence of harm.

It seems to me the -- you got back to a consequentialist mentality to try to support a rights-based process. And when the mother writes, you know, she's worried about the consequence of the vaccine doing harm, or -- yeah, the vaccine itself doing harm, there is also our responsibilities are not to the right to protect children against the consequence of infection in the case of a bio-terrorist event.

DR. DeGRAZIA: Right. As you said, there is limited time so my answer got cut off a little bit.

Right. I talked about the subject's right to adequate protection from harm leaving it somewhat open exactly how to specify that. It's important to understand, though, that's a negative right. It's a right not to be treated in a particular way. It doesn't matter that it's protection from harm, that doesn't make it consequentialist. It can still be a side constraint.

And by the way, again, I'd be more in favor of strict rights, not absolute rights. So there are possibilities of some exceptions. But the right to -- if the general public has a right to adequate protection from harm, which sounds pretty plausible, that's a different kind of right. That's a right to be provided with services and, you

know, provisions that can protect their safety. But that's not -- that's a right of a different kind. And generally, negative rights take priority over positive rights.

It's a little bit like the different -- people have an adequate right to safety or the like, public safety, you know, in the context of gun control. It doesn't mean no one can own a gun, right? It's rights -- so negative -- it's helpful to think about the negative right of adequate protection from harm of the subjects, not to be treated in a certain way is different from the public, if the public has a right by the same name, a different kind of right.

DR. WAGNER: I guess what I come back to is, if we are helping, you know, the White House decide how it is they exercise their responsibility to provide for the common defense?

DR. DeGRAZIA: For the common?

DR. WAGNER: Defense.

DR. DeGRAZIA: Yes.

DR. WAGNER: It is -- and we are also -- and I'm sorry to be so thick on this, are we not being asked, how is it that we protect the population, including the population of children from harm?

DR. DeGRAZIA: That is the question, yes. But then the answer should take into account whatever ethical limits, set the appropriate limits of the means that can be taken towards that end. Because that protection from harm for the public is a kind of goal. It has a different ethical shape than a right, at least a negative right.

DR. GUTMANN: That's why I asked what the particular rights that would block that.

DR. WAGNER: So what are some others of those, if we're going to get

into that?

DR. GUTMANN: One that you said was the protection of children as subjects of research, to --

DR. DeGRAZIA: Not to be exposed to more risk than good parents would allow for their children.

DR. WAGNER: And you think that's sort of the key one? There's not another one on your list?

DR. DeGRAZIA: Well, another one is a kind of qualified autonomy based right of at least assenting, if assent is appropriate, and there's no -- again, I think there are exceptions that we could talk about. But I think that's also relevant.

DR. WAGNER: And that was in your talk?

DR. DeGRAZIA: Yes. And my--one third idea I might throw out is, universalizability. Whatever the policy is, it should be one that everyone can accept from their point of view. And that would include the point of view of the parents of the children who might be test subjects.

DR. WAGNER: Got it.

DR. GUTMANN: Skip?

DR. NELSON: I'd just add to this conversation, when I look back at the way the National Commission sort of conceptualized our current regulations, the definition of minimal risk, though it looks like a data-driven definition, was really frame, I think, to try and capture this notion of responsible parenting. And I've argued with Lanie Ross that one could understand both minimal risk and minor increase over minimal risk, those categories as the way parents -- these, you know, sort of responsible parents make decision making.

That opens up the interesting question, the extent to which the regulations frame this negative right to be protected as to whether or not we would allow parents who believe they're making responsible decisions in certain formats. I mean, John talked about first responders, military families, et cetera. Is that responsible parenting for them to make a decision to put their children into a small immunogenicity study? When I say small, 100 to 200.

No one's putting on the table the safety study prior to an event. Seventy thousand was what we did for Rotarix. No one's talking about that. So I would hope we don't put that on the table. It's really just a small immunogenicity study as a pre-event.

DR. GUTMANN: So what -- when you say "I hope we don't put that on the table," though, if you get beyond the first you go to the second, right?

DR. NELSON: Well, maybe I'm showing my hand. I can't imagine --

DR. GUTMANN: No, don't, you have to show your hand. I mean, we don't have -- you know --

DR. NELSON: It would be hard for me to imagine doing that large scale safety study outside of an actual event. That's what I'm suggesting.

DR. GUTMANN: Oh, okay. Well, that's important to --

DR. NELSON: It would be hard for me to imagine that possibility. I think, at least in my mind, what's been on the table and --

DR. GUTMANN: That's why I ask these questions. So you have to show your hand, because we need to know what --

DR. NELSON: Right. And I think the NBSB was just talking about their small -- about the immunogenicity study. I don't think they had a 70,000 large-scale safety study in mind.

But let me get -- make two --

DR. GUTMANN: May I ask John if that's correct?

DR. PARKER: We were not definitive about the size of the study at all because we did -- we did want to see immunogenicity data. And although you may have to give several thousand vaccinations to see one Guillain-Barré but if that number of children were vaccinated to get that data, we would have at least a clue about the safety. We might not have a definitive answer about the safety, but we would have a clue.

DR. GUTMANN: Okay.

DR. PARKER: So in medical countermeasures, we might have to put in the mix that, you know, we're not going for an FDA license on safety here. Is a snapshot good enough, than 10,000 people?

DR. GUTMANN: Yeah.

DR. NELSON: And could I just add one more thing? The Commission did some work previously where you talked about compensation for research injury. I might point out in the vaccine segment --

DR. GUTMANN: Yes.

DR. NELSON: -- we do have a compensation for vaccines that tries to reflect that balance between individual risk and social protection. And I might suggest to you, you could think about how that might be applied in this arena in a much more concrete way in terms of subjects placing themselves at risk for social good.

DR. GUTMANN: Good point.

I have a list, and Anita is the first on it. Anita, yes. Anita.

DR. ALLEN: So I want to follow up on this children's rights issue

because I was made to think about the question of whether or not, in your view, David, parents have their own independent rights. For example, a right to parent in sub-optimal ways, right? So you might have conflicts between your ideals about children's rights, which might include the right to be not exposed to risk, which a responsible parent, ideal parent wouldn't expose their child to. And yet, I think many ethicists will say, well, parents have their own independent rights which include a right not to be perfect parents.

So tell me how you think about children's rights as potentially bearing on what we might be able to do in the context of medical countermeasures.

DR. DeGRAZIA: Okay, right. Good topic to bring up.

Yes, parents have rights, too. I think I may have covered myself when I suggested that we interpret best interests, not in the literal maximizing way which implies perfection, perfect protection of the interests of the children, but as protecting the essential interests of children. I do think children do have a right to their parents protecting their essential interests, and we can go into what that list would consist of.

Parents also have a prerogative to some extent to parent as they wish, to raise kids in a particular religion and so on, to school them in certain ways. But there are great limits to the parental prerogative. They can't, for example, just not have their kids go to school at all or they can't bring -- they shouldn't bring them up in a religion in which there's terrible abuse as part of the religion. So the -- I think the children's rights set limits to the parental prerogative.

So I don't see a conflict there. I think, you know, there are parenting prerogatives but there are children's rights to have their essential interests protected. And they help to define the limits of the parental prerogative. Sorry, that's very abstract,

but I think it helps to avoid a picture in which there are some really hard conflicts where parents' rights may really conflict with the children's right to have their essential interests protected, including adequate protection from harm.

DR. ALLEN: Yeah, I'm afraid, though, that we might be avoiding some hard questions which could arise in this particular context. Because we're not talking about food, clothing and shelter, we're talking about research and about experimentation, right?

DR. DeGRAZIA: Yeah.

DR. ALLEN: And so we're not talking about what I think are the obvious cases of essential interest.

DR. DeGRAZIA: Right.

DR. ALLEN: That's why I think there may well be some interesting conflicts that we will come across as we look into this more carefully.

DR. GUTMANN: Nelson?

DR. MICHAEL: Okay, Nicola, you're up again.

Just to be granular, since you are a person who's tested lots of vaccines, aren't we really talking about a study maybe of a couple hundred individuals? Assuming you wanted to look not only at immunogenicity, where you round up the usual suspects, I'd imagine humoral immunology in this case would probably be more dominant than cell immediate or innate. You wouldn't probably need to look at mucosal responses. So these really wouldn't be technologically complex, and most importantly just from a safety standpoint, you're talking immunology about -- in terms of follow-up, you're talking about -- or additional harms of phlebotomy.

But really, dose ranging is important as well, then maybe now you're

talking about N equals 100 in each arm times three, perhaps. So you're looking at a study of about 300 individuals. In terms of safety, I know you're really talking about homeless phase four kinds of concerns. I mean, in my field, a safety study is less than 100. Even the phase two-Bs I've done for HIV have been as low as 2,200 and as big as 16,000, but nothing like 70,000. We wouldn't conceive ever to do that until we were in like phase four.

So I'm just wondering if a minimalist approach would be a dose ranging/immunogenicity study of around 300 potentially followed by, as General Parker mentioned, some sort of more expanded safety trial of maybe 1,000 individuals. So is that essentially what you would think in a concrete way, as the studies we're actually talking about?

DR. KLEIN: Right. That's what -- that was what I thought we were originally talking about, these types of studies. And I think that's in the range -- you know, you could probably go up or down a little from 1,000 in that second stage. But I think that's probably the range you're talking about.

The other thing to consider, I think, is what ages we're talking about, because you may need to do it in different age groups as well.

DR. GUTMANN: Raju.

DR. KUCHERLAPATI: So I've been looking actually from all of the members sitting here, the answer to -- the recommendation, actually. And I can guess what the recommendations from, in just listening to you, all of you, but I don't know what the recommendation is. Would it be possible just to go around the table and be able to say -- the question is very simple question, very narrow.

DR. GUTMANN: You have to tell us the question, Raju.

DR. KUCHERLAPATI: The question is very simple and narrow. And that is, is it your recommendation, based upon all the ethical considerations, all the other considerations that you thought about, to proceed with the pre-event, you know, in a research study of the kind of magnitude that we just talked about, to obtain information about one vaccine, Anthrax vaccine?

So is it possible, Amy, to go around the table --

DR. GUTMANN: Absolutely.

DR. KUCHERLAPATI: -- and say --

DR. GUTMANN: Immunological --

DR. KUCHERLAPATI: -- yes or no. And maybe there is some compelling reason as to why you say yes or no.

DR. ARRAS: Could I add a codicil to the question?

DR. WAGNER: An escape hatch?

DR. GUTMANN: Go ahead, John.

DR. ARRAS: No, I want to close the escape hatch, because --

DR. GUTMANN: Quickly. Quickly.

DR. ARRAS: -- like in John Parker's committee, you know, basically said we recommend going forward with this on the condition that some group, you know --

DR. GUTMANN: No, no, that's not the --

DR. ARRAS: Yeah, yeah, on the condition that some group like us, you know, give a conclusion on the ethics. I want -- I mean, to make this a really interesting question, I want you to roll in your ethical interpretation as well as your --

DR. KUCHERLAPATI: You use the term many times this morning and this afternoon of cutting to the chase.

DR. ARRAS: Yeah.

DR. KUCHERLAPATI: So let's cut to the chase.

DR. ARRAS: Yeah, with no escape hatch.

DR. GUTMANN: Well, the question as I understand it is, do you recommend to our Commission that we recommend that this study go forward and -- yeah, all things considered.

MR. HODGE: Are you literally interested in a yes or no answer here?

DR. KUCHERLAPATI: Yes.

MR. HODGE: Okay, no.

DR. TAYLOR: No.

DR. KAPLOWITZ: I can't answer the question, really. In my role here, my role is to make sure this Commission looks at the whole scope. I am representing the secretary in a sense, and so --

DR. GUTMANN: You could say -- put a condition -- you could give a conditional -- you could give a conditional answer. Yes, if; no, if. You could. I won't let everybody else off the hook.

DR. KAPLOWITZ: I don't think I can, to tell you the truth.

DR. GUTMANN: Okay, fair enough.

DR. PARKER: John essentially put me in a position where the -- I'm speaking for the board, and we did recommend to go ahead with that caveat, okay.

Now why did we recommend to go ahead? Because the majority of the board felt very strongly about children and that if we contemplate giving drugs or vaccines to children, even under extenuating national emergencies, we should know something about that drug --

DR. GUTMANN: Okay.

DR. PARKER: -- and vaccine.

DR. GUTMANN: Nicola.

DR. KLEIN: I'm going to give a condition that if I'm convinced that there actually is a credible threat -- because I'm not convinced that there is -- but if I am, then I say yes.

DR. GUTMANN: Okay.

DR. ANDERSON: The American Academy of Pediatrics believes it would be unethical not to proceed with this, so that's a yes.

DR. NELSON: My answer will be a little bit more complex. I was ex-officio member of the working group on the NBSB report, and I'll say what I said in that context.

First of all, I don't think any such protocol could precede except under review by a federal panel under 21 CFR 50.54. This could not be approved by a local IRB. And you are not a local IRB. So it would need to go a federal panel review, which would be the Pediatric Ethic Subcommittee and the Pediatric Advisory Committee of the FDA.

I staff that committee. I would be the one responsible, unless I move into a different job, of writing the letter to the Commissioner and to the Secretary as whether the trial should go forward. So I think it would be inappropriate for me to say whether it should or it shouldn't.

DR. GUTMANN: That's fair.

DR. ANDERSON: However, I will say --

(Laughter.)

DR. ANDERSON: However, I am not compelled by the logistical arguments that are put forward by some that it would be difficult to do a study under IND in an actual event. So unless in my mind there's compelling scientific reasons, things you could do in a pre-event setting that you couldn't do in a post-event setting, I would find it less compelling.

And let me give you an example. Bridging studies. I don't have -- I don't believe we have data on adult dose sparing and different dosing strategies to where you could do a pediatric pre-event study that could show you whether or not doing some dose sparing or different approaches would actually lead to sufficient immunogenicity to allow bridging in adults.

If the argument for doing the pre-event is to able to do something different than you do in the post-event, then get the adult studies to show that, in fact, you could do something different in pediatrics. In other words, the science would drive the ethics. I would find it more compelling if there was a scientific reason why a pre-event study. I don't find the logistical arguments compelling.

DR. GUTMANN: So it's no?

DR. ANDERSON: Under -- unless I saw an adult study at this point that you could --

DR. GUTMANN: In other words, not at this -- right now you would say no, until you saw an adult study?

DR. ANDERSON: Not as currently designed.

DR. GUTMANN: Okay.

DR. ANDERSON: I would hope that a committee that reviewed it --

DR. GUTMANN: It's a very -- by the way, I really appreciate all of you

being willing to -- we understand all of -- you know, all the complexity behind it. But it's very helpful in focusing what's at stake here.

DR. DeGRAZIA: I still don't think I have a clear enough factual picture about the degree of risk in comparison to alternatives. So I guess I have to say no, at least not at this time. But I'd want to know more about the factual picture, the relevant facts.

DR. GUTMANN: Okay. Thank you very much.

Christine had a question. We have a few more minutes.

DR. GRADY: Well, mine had actually a little bit to do with what we were just talking about in the sense that, I think the details of the study as proposed matter in terms of whether there's a go or a no-go. And so I was very curious, General, Dr. Parker said, we are prepared to give antibiotics and the vaccine to children in a post-event right now. So what would a study change about that?

I can imagine if a dosing study was clearly -- showed us that, you know, the dose that we're giving adults is ineffective in some way -- I don't know how we'd know that -- in terms of generating an immune response, then we change the dose. But then we have the problem that you laid out before in that we're treating children and adults differently. So that's one possible scenario.

I can't imagine we're going to get real safety data that -- enough children in a pre-event study that we would find something safety-wise that would then change the plan about giving vaccines post-event. So what do you think would -- a study would tell us, could tell us that would change the current plan?

DR. PARKER: We debated that question. And the -- it boiled down to a very human type thing that, if we're talking to a parent about giving a child a vaccine, it

would be a much better situation to be able to say that we know the vaccine is safe. And in a counter-argument to that debate, we also -- we also said that, well, maybe that's not terribly important, if people are going to die all around you, if you don't take the vaccine. And that's a little coercive, but real. It's real.

DR. GUTMANN: That's not coercive on your part. It's -- I mean --

DR. PARKER: No, no, it's the event --

DR. GUTMANN: When you're facing death by natural -- you know, by causes that you --

DR. PARKER: You're going to take anything that may avert that, yes.

DR. GUTMANN: Yeah.

DR. GRADY: But also the message could currently be, we know that this vaccine is safe in adults. We don't know the threat. If there was an event, we're going to give it to children because it's the best thing that we have.

DR. GUTMANN: Let's hear from Michael, because he came down on the other side on this. So let's -- okay.

DR. ANDERSON: A rarity in the group on the yes side. I think if, God forbid, D.C.'s dusted today, we have .5 mLs to go under each of our arms, and we heard the reasons why. Because 60 days of antibacterials has a whole lot of risk, and that we believe that this vaccine will save lives.

The six year-old down the street at the daycare center, we have no data on what dose to give. So we keep saying, in an event we'll give vaccine -- could give .5, but I think that the problem is what is the right immunogenicity? What does that .5 actually get you? What is the timing?

So I think just like my slides I threw up before, we had such great strides

over the past 10, 15, 20 years, that studying things with a very cogent professional and safety-oriented look in kids. I believe the NBSB was very courageous in their recommendation to say we really should look pre-event. And I give them a lot of credit for that courage because you've seen, you know, there's a lot of things to take into account.

It just makes me as a pediatrician, an advocate for kids, very nervous that .5 mLs is the answer. And that's why I said yes.

DR. GUTMANN: Holly.

DR. TAYLOR: So this was a question that I had for myself that I did a little -- I spoke to someone who I consider an expert. And I would suggest that the Commission look at the history of past use of vaccines. That the most common reason for not using a vaccine in a child was that there was no efficacy. Not that it was so unsafe as to not be tolerable.

So it seems like -- I'm not sure what position we would be in, what we actually can gain based on previous history of documenting the way in which children respond differently than adults to be able to give you some confidence about what a preliminary dose might be.

DR. GUTMANN: Nicola, go ahead.

DR. KLEIN: Yeah, I would just like to ask, when you say that the most common reason for not giving a vaccine is for efficacy, are you talking about during clinical trials?

DR. TAYLOR: No, I'm talking about once there's a vaccine on the market, there are some vaccines that there's a recommendation that says, "don't give this to a child under six months" because there was no evidence of efficacy in children that

small.

DR. KLEIN: Right. So that's -- the particular situation of flu vaccine, that's correct. But I don't know that you can make that argument and translate that argument to an Anthrax vaccine. In fact, I think it almost makes the counter argument that you actually need to study them because you don't know what the response is going to be, and you can't just assume that half an mL from an adult is going to actually be efficable (sic). And perhaps children need four doses, or perhaps they need to have them, you know, a different schedule than what an adult needs.

DR. TAYLOR: Then I guess my recommendation would be to look at the historical record about that and maybe learn something from there in order to inform whether or not that would be true.

DR. GUTMANN: I have Steve and Nita. Yes.

DR. HAUSER: So maybe I would ask Dr. Anderson, but others, Dr. Klein or Dr. Nelson, I think you had mentioned 55 vaccines, all of -- all but three of which had been tested in kids. If you look at those 52, are there lessons there that would help sway decisions about the potential need for this Anthrax trial?

DR. ANDERSON: Dr. Klein?

DR. KLEIN: Well, I mean certainly, I think the lesson is that -- well yeah, there are lessons for sure. Children have a very immature immune system as they -- in the first year of life, the first years of life they develop -- that develops over a course of time. So what that means is that a vaccine that is given to babies to prevent illness that happens in babies needs to get three doses, perhaps.

But if that -- but that same vaccine may give a comparable immune response to a three year-old if it was just given a single dose. So that's one lesson.

Another lesson is sometimes when you -- you don't know what happens to vaccines. We've seen that when particular vaccines are taken -- two separate vaccines and put them in the same vial and then give them to a child, they don't respond the same way that you think that they will. Perhaps they're not as efficacious or they may need a lot more of one type than if you give them separately, so they don't respond -- they don't function the way you would expect them to do so.

What else? Well, I'll stop there for now.

DR. GUTMANN: Skip on to --

DR. FARAHANY: Can I just add to this, because we were -- this is -- so just to be even more specific on this, if we're looking at the vaccines that are currently on the market which have -- you know, we now know the difference between dosing in adults and children, is it not enough information for us to be able to say the dosing would be different in this particular way for the Anthrax vaccine? Is it that specific and idiosyncratic per vaccine that we've seen such that, you know, while you have these generalizable lessons, you wouldn't be able to come up with any sort of dosing recommendation without having to do such a study?

DR. GUTMANN: Skip, did you want to answer?

DR. NELSON: Yeah, two quick comments. First of all, it occurs to me looking at those 55 vaccines, one of those would be Gardasil, so that's not something we would give to neonates. So there's -- you know, if we look at the different vaccines, there's different reasons to do testing. Most of them are tested early because that's, in fact, the population that you want to treat.

The -- you know, again I'm not an immunologist and I'm not a member of CBER. But let me try to respond in general to your question. I think there may be

some knowledge that can be gained through knowing how the immune response occurs in response to different antigens, depending on whether that's primarily cell mediated or humoral mediated, et cetera. Yes, we can draw some general lessons.

But will you get to the point where you'll say, let's just put it out there with no data? No, I don't think that will happen. And so that's where this immunogenicity data, even if it is to confirm one's original hypotheses about what that exposure response would be, at this point there are no data for Anthrax at all.

And so it's not that this data set would have to be large, but it has to be greater than zero to the point where you would release that at least under an EUA, which would move it out of the IND setting in the case of an event.

DR. GUTMANN: Steve, do you want --

DR. HAUSER: I thought I'd just follow up, and this is a slightly separate question. But I believe there's some recent data that sleeplessness dramatically affects whether a vaccine takes or not. And when these trials are contemplated, would they be contemplated under conditions that might mimic what could happen in an emergency?

DR. GUTMANN: So here, instead of the -- this has been -- first of all, I want to thank Raju for posing this question to you, and thank you all for your willingness and the lucidity of your answers. This is -- we're going to conclude now. But before we do, I just want to go back to the earlier requests I made. Because on the basis of your answers, you could now tell us what are the facts that you are taking as essential to the conclusions you came to in all cases. But Lisa, you're off the hook here. But you are not off the hook on giving us your response to what are the facts that you -- that are out there that we should know and what are missing that would be important and possible to know to help us come to a recommendation here.

That is a recommendation within a framework which we are -- we have a responsibility and we certainly will also want an ethical framework which we'll be more than willing to step up to the plate on the basis of what the board requested.

So with that, I want to thank you all so very much. You really were terrific. Thanks.

(Applause.)

DR. WAGNER: Wow. I'm almost tempted to have us all stand up and sit back down again. We've got to shift gears at this point. But don't drift away from the table, but I think it's worth standing up.

DR. GUTMANN: Just to stretch. So I declare a stretch.