



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

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DR. GUTMANN: Welcome, everybody. I'm Amy Gutmann. I'm President of the University of Pennsylvania and Chair of the Presidential Commission for the Study of Bioethical Issues. On behalf of myself and our Vice Chair, James Wagner, the President of Emory University, I'd like to welcome you to our 12th meeting.

We have now met several times in DC. We've met in Atlanta; at Emory University in Philadelphia; at the University of Pennsylvania; in Chicago, the University of Chicago; in San Francisco at UC San Francisco. Where am I missing, folks? Harvard. My alma mater, absolutely. Harvard at Harvard Medical School, there we go. And New York, Where was it; where were we in New York?

(Laughter)

The Warwick Hotel. No wonder I didn't remember, the Warwick Hotel in New York. And now, I say that all, because now we are at the University of Miami and I have to say the weather has never been better.

(Laughter)

And I also seriously have to thank Dr. Ken Goodman, Head of the Bioethics program here and everybody at the University of Miami for having us. Ken, why don't you stand up so we can recognize you. Thank you so very much.

(Clapping)

Before we continue, please let me note the presence of our designated Federal Official, Commission Executive Director, Lisa M. Lee. Lisa, please stand.

(Clapping)

Thank you also for all you do for the Commission. And I also want to take this opportunity to thank, um, the staff for all the great work they have done.

At this meeting, this will be the last meet where we discuss our ethical review of pediatric Medical Countermeasure research. You'll hear us saying MCM research, standing for Medical Countermeasure research.

Earlier this year, the commission received a request from Secretary of Health and Human Services, Kathleen Sebelius. Actually not true, earlier this year. Early last year, we received a request and Kathleen Sebelius asked us to thoroughly review the ethical considerations of conducting Medical Countermeasure research with children. She asked that we consider both pediatric medical counter measures broadly and anthrax vaccine to be used to treat children in the case of an emergency, more specifically.

Over the course of our last three meetings we've heard from many experts, including experts in pediatric research and emergency preparedness, in ethics, and they have assisted us immeasurably, as have the public comments we have received. We have deliberated extensively and will continue our deliberations today.

Later today, we'll hear from two additional experts as we consider the ethical grounding of our approach and because this is our last meeting devoted to this topic, we'll spend most of this meeting engaged in member discussions as we formulate and refine our response to Secretary Sebelius' charge. I look forward to an engaging and thought-provoking discussion as we address a very complex and important set of issues.

Before we get started, let me just take a moment to explain how we take comments from the audience. Both at the registration table out front, there are comment cards, and our staff come equipped with comment cards, and would staff members stand up? So, if you want to make any comment, there are staff members, just pick up a card, or if you think you might, take a card. Actually anybody can just point to, and Hillary is back there, she has cards. So, write your comment or question on a card. Someone will make sure I get it. And either Jim or I will, should be able to get to it.

So, thank you in advance for all of those of you who are here, and now our Vice Chair, Jim, would you say a few words before we get started?

DR. WAGNER: And only a few words before we get started. First of all, it's good to be with the Commission again, welcome back, in this young year, young new year and I want to thank our staff, in particular, there has been a great deal of conversation, obviously. It's great to be together as committee as a whole, to kind of knit all that together. But a great deal of conversation facilitated by our staff over this subject since last we were together. So, great thanks to you.

The Commission will also be let in on a fact, it is not really a secret, but our Chair has worked especially hard in helping to frame up our conversation for this particular meeting and Amy, I'm very, very grateful for that. So really, with no further ado, why don't you kick it off for us.

DR. GUTMANN: One thing we need to know, is we can have two of these on at a time, but no more. So, if you see mine on when two other people are talking, just hit me and we'll do the same. But right now, let me try to frame where we are on the basis of our deliberations.

Today and tomorrow we're going to formulate our conclusions and recommendations. We will still have more work to do in writing a full sum report, but we will be formulating publicly the framework and our recommendations regarding Medical Counter Measure research with children.

We have several sessions for discussion on the agenda. So let me begin by laying out how we will structure our time. We focus first on the overarching structure of our analysis and next we turn to issues associated with post-event studies because that's what we've spent the least time on as a Commission deliberating, that is Pediatric Counter Measure research that would take place after a terror attack occurs. That also includes, by the way, any research or any measures that would be taken if an attack were imminent, because if an attack is imminent, we would, um, recommend, and it's just the nature of what imminence means, that it be treated as a post-event. Imminence means that something is happening; predictively happening quickly and there is no time for deliberation. So, that would be post-event. We will then devote the afternoon and tomorrow to discussing pre-event studies, which we've already spent a good deal of time on

or Pediatric Counter -Measure research conducted before a public health emergency happens or is announced to be about to happen. And we have an excellent panel joining us this afternoon, as well, to inform that discussion. And we're setting -- first we have a video conference with one member of that panel, Tom Beauchamp, who is an important part of the National Commission, when it deliberated, and Dennis Thompson will join us, as well.

So, let's begin by framing our analysis. And here I will spend some time in the framework and then Jim, turn to you for elaboration.

So, as we've discussed at prior meetings, as a country, we generally confront and accept, both a fundamental duty to protect individual children from undue risk during research and an obligation to protect all children as far as ethically and practically possible during an emergency by being prepared. Such preparedness includes: the fruits of scientifically and ethically sound research, and also a full sum national readiness to respond. And our task is to advise the government in its mission to be fully prepared to treat children in the event of a chemical, biological, nuclear, radiological attack on the ethical considerations of conducting Pediatric Medical Counter Measure research.

Pediatric research is ethically distinct from research with adults, which is why this issue before us is as important and as complex as it is. Although competent adults can consent to accept risks for the benefit of others during research, children are ethically and legally unable to consent. A child's incomplete autonomy and related vulnerability necessitate additional protections during research. For that reason, absent exceptional circumstances, children generally cannot participate in research that presents more than minimal risk, that is, more than the level of risk encountered in daily life. Although that statement itself we need to make clear by giving examples, unless there is a prospect of direct benefit to them as a result of research participation. Umm, even when there is a direct benefit to them, the level of risk must be proportionate to the level of benefit to an individual child.

Pediatric research involving Medical Counter Measures presents additional ethical challenges and additional practical challenges. We are the Bioethics Commission, so I'll focus on the ethical challenges, but they actually intersect with the practical ones. It's important to distinguish here between two types of Medical Counter Measure research; pre-event and post-event research. Each presents distinct ethical issues and for that reason, our analysis covers each scenario separately.

There are at least three characteristics of pre-event Medical Counter Measure research that challenge traditional research ethics. First, pre-event Medical Counter Measure research involves gathering information for the potential treatment or prevention for highly disabling or lethal condition. That, in general, no one has yet contracted, that is because an attack hasn't yet occurred. Second, this research is aimed at a condition that results from an event with an unknown and perhaps unknowable likelihood of occurring. And many people, including the gentleman next on my right, have driven home this point to us. And third, and in an intellectual way, most interesting in some sense, but it presents a paradoxical ethical and practical concern that, while the risk-laden knowledge to be gained for the sake of being useful, what the research is for knowledge that is intended for the sake of being useful, we hope and the government hopes never to have occasion to use it.

And to put all of those three things in a nutshell, the reason they present an ethical challenge is, that what it means is, the children as research subjects, cannot be said to directly benefit from this research, were it to go forward, and hence the importance of minimizing risk. Because pre-event Medical Counter Measure research generally offers no prospect of direct benefit and would involve healthy participants absent exceptional circumstances, it can be conducted only if it presents no greater than minimal risk to children who cannot provide Informed Consent. Even under exceptional circumstances, no direct benefit is expected to accrue to individual children; research risk must remain limited and low.

For Medical Counter Measure research, this means that the research risk imposes a narrow expansion of minimal risk, and should, and I quote, “pose no significant threat to the child's health or well-being.” Any greater risk is ethically unacceptable.

Post-event Medical Counter Measure research should also be limited to minimal risk, where possible. Importantly, however, post-event Medical Counter Measure research may offer the prospect of direct benefit to participants. That makes a significant ethical difference. Because they would have already been exposed to a pathogen during the event or in the case of imminence, could be with a high degree of probability at risk, quite immediately for such exposure. The ethical analysis is thus markedly different. Children exposed to a pathogen, who contract an illness, can enroll in research is likely to yield information of vital importance to understanding or ameliorating both their own condition and that condition more generally, as it affects other children. That is a characteristic that carries both ethical and regulatory weight.

When the threat of an attack is imminent, that is as a practical matter, there is not time to test the Medical Counter Measure with children before an attack occurs, the ethical concerns surrounding proposed research would track those of a post-event study. Although technically before an attack, for practical and ethical purposes, this scenario more closely resembles a post-event situation because children are imminently at risk of exposure resulting from a specific threat.

The Commission analysis is guided, now I'm going to move to a more general level, by the foundational principles of the Belmont report, issued by the National Commission, the three principles articulated there, which we have carried forward are: respect for persons, beneficence and justice. We're guided by a fourth principle, as well, which was implicit in the Belmont report and is embodied in their approach, their recommendations, as well as in our approach to our subject, and that is democratic deliberation. And indeed, that is what we have been practicing over the past several years and it is also the means by which we can get public input, expert input, bring them together and really show both respect for the diversity of opinions out there, but also try to do our very best as the National Commission did in integrating as much of that as possible into our final report.

In addition to our analysis of the ethical consideration of pre and post-event MCM research generally, we will separately apply this analysis to a case study of anthrax vaccine absorbed or AVA. And that is to respond fully to Secretary Sebelius' request.

Now, we must keep in mind, we do not have a research protocol before us. We're not equipped to sit as an IRB or a national review panel under section 407, and it is outside the purview of our charter to do so.

However, Secretary Sebelius did ask us to address the specific the case of anthrax vaccine, and I think it is clear that is one reason we have this general topic before us. So, the question we must address is whether the U.S. Government could ethically support a pediatric AVA study under any circumstance. We're not going to render a final decision as to whether a particular study should move forward, nor are we working to justify any particular protocol or outcome. We're giving our ethical analysis of both the general question of MCM research and of the particular question of AVA testing before pre- and post-vaccine.

That said, I should also emphasize that we're advisory, and we're an advisory Bioethics Commission. So, with that framing in mind, I'd like us to turn now to the ethical considerations of post-event pediatric MCM research. Okay?

So, post-event studies are ethically distinct from pre-event studies in a very important way. They may present the prospect of direct benefit to participants or the likelihood of yielding information of vital importance to understanding or ameliorating the participant's condition. Although application of the current regulatory and ethical framework for pediatric research is clarified in a post-event study, there are inherent complexities in designing scientifically rigorous studies and streamlining the logistics of Medical Counter Measure distribution and administration.

Community engagement, and I look to my left on this, because NELSON MICHAEL has been a leader in speaking about this, and the whole commission has agreed that community engagement is one important tool that can be used to ensure the success of the research and uptake of the intervention within the effective community or communities. And indeed, it is not an exaggeration to say that asking us, as a Commission, to deliberate before about post-event studies, is a very important step in the whole community engagement, to alert and to engage communities who would be interested in this.

Under current federal plans, at least one Medical Counter Measure, the one we've been charged to analyze that has been authorized for adult use, would be available for pediatric use in an emergency. We should be clear that post-event observational research not only should, but needs to be, planned in advance. There will be very stressful conditions, were an event to happen, and advance planning is essential. And post-event observational research should be conducted under, really, when, if and when Medical Counter Measures would be supplied to children in an emergency. Post-event research should also be conducted when limited pre-event Medical Counter Measure studies have already occurred.

Nobody, from whom we've heard, suggested that anything more than limited, pre-event Medical Counter Measure research could be done, ethically speaking. Which means that there will need to be post-event observational research. Whether children receive an untested or minimally tested Medical Counter Measure in an effort to save lives, it is ethically imperative that health officials collect data to learn as much as possible about its use from the event.

In addition, for post-event studies, adequate processes must be in place for informed parental permission and meaningful child assent. Again, this needs to be prepared ahead of time. The research design must be scientifically sound. Children enrolled in research must have access to the best available care and provisions must be made to engage communities throughout the

course of research. So, that is my outline of our working framework about post-event and what leads us there. And Jim, I turn it over to you to elaborate and to lead our discussion on this point.

DR. WAGNER: Amy, I'm pleased to do it. I told you she had done a lot of work and that's just the beginning (Laughing) of what you're going to see. So, thank you for that overview. Let me amplify on it just a bit and ask us to dig into this post-event, our framework, and structure there.

I think we've done several significant things, already, at least the direction we're going, there are handful of things I think are significant, not the least of which, deciding in the first place that we were going to use this question, that was specific question, about anthrax, that came from the Secretary, that we were actually in the process of trying to address that appropriately, we decided we would put together a framework that could be used broadly for Medical Counter Measures, I think that is very significant contribution that we've made.

That framework, we've repeated, that framework is going to be based on same principles derived and embellished from the Belmont report, and made note of the special ethical circumstances of children's research subjects. I think that is significant.

We have decided to break the issue down. And, this is significant also it seems to me in pre-event and post-event circumstances, capping risk at minimal and pre-event and minor increment of minimal in post-event. A subject that I am hoping, I'm expecting we might want just a little more conversation on, is that having said we're going to address special ethical circumstances that are associated with pre versus post, I shouldn't say pre. Pre and post as different events as different scenarios. This decision to imagine that imminent, although technically taking place before an event, is tantamount to a circumstance of post, that would put into play our post-event scenario. We may want to talk about that a little more.

That it might be valuable to design protocols aimed at inferring the level of subject risk in young children from test results in young adults and then moving to older children, etcetera, a process in that in our current discussion lexicon we have referred to as age de-escalation, I think that's a significant contribution, as well, and bears some talking about.

Now, our specific, of course, overall what we're trying to do is feel as though this strategy and these points are of service both to White House and to the public, by offering this kind of a framework. And we need to consider its utility to ensure that the best advice is being offered for the safety of our children, both the safety from threats in the event of an attack, and safety from the risk with, associated with ethically ill-advised research.

So, let's talk specifically about post-event studies. We have said that in post-event, we could understand raising the level, to, the level of risk, to some minor increase over minimal. And then we talk a lot about implementation in a post-event scenario. What strikes me and I wonder if we want to have, and Amy, you lean on this pretty heavily I think in the latter part of the comments you just made, but it is not a conversation I've heard us have. I have -- I want to make sure when we talk about post-event, we're not implying that we are suggesting "wait and see" or maybe I need to have that conversation, or we need to have that conversation. In other words, we'll keep post-event in a file until something happens and then we'll pull it out.

As you've just heard reviewed, there are several steps or several important components of responding post-event that require pre-event planning. And -- such as: planning research itself in advance, planning to ensure distribution administration processes are in place, observational research planning, that you spoke about, by getting in place what would be needed for informed parental permission, you spoke to that as well. There is quite a lot pre-event to do in preparation for a post-event scenario. And I'm not sure if we've had discussion there. I'm not aware of the discussion there-- that would conclude by saying who it is and what agencies we expect under what circumstances; those things should be pursued, even today. So with that, I'd like to -- well, go for it. I'd like to throw it --

DR. GUTMANN: I think we made a decision on the basis of what we heard in our deliberations, of how important it is for this Commission to speak to the planning for post-event. Because we heard, without exception, that whatever is done pre-event, there will be much more to do by way of research and understanding post-event, and we also came to the conclusion, in earlier meetings, that anything that's done pre-event can only be justified, a necessary condition of its justification, is for the government to be actually fully prepared in a post-event situation to use the knowledge that is had and also to engage in the kind of research that has to be done, that can only be done post-event. So, it's both in the categories of preparedness, in-- to provide, and post-event research, and also in addition to the kind of engagement that would need to be the case. So, I think there will be a significant part of our report that focuses on how important that is, and Jim raises the question of which agencies, and that always is an issue of coordination, I think. My own sense is, we should ask for the necessary coordination and whatever division of labor makes sense in the government, not ourselves being expert at how that would work.

DR. WAGNER: I want to go to Raju, although having said that, I think some of the strengths of our earlier reports have been specific expectations that there would be follow-ups. That's all I am referring to.

DR. GUTMANN: Yes. Right, and I agree with that entirely. The expectation since Secretary Sebelius, is Secretary of HHS, asked us directly, wrote a letter specifically to me, I think we will ask her, you know, our recommendations will be to her agency as the Department of Health and Human Services, to ensure, to take the necessary steps, to ensure that there is agency coordination.

DR. WAGNER: Raju.

DR. KUCHERLAPATI: I think it is a great start from both of you, it's really wonderful. Before we actually talk about the specifics, I just wanted to raise a question about definition of an event. And so, when I read about this, you know, there are a couple different scenarios one could think about. One scenario, which is commonly thought about, and I think Alex talked about this, is that the event would occur in a specific, a portion of the country. Let us say in Boston, it would effect children, one or two million children, but not all of the country. That is one scenario. The second scenario, of course, is that the event were to occur simultaneously in the entire country.

So, if, let us say the event is restricted to one particular geographic area in the United States, then obviously there are two groups of children; one group of children that are in the vicinity where -- (inaudible)-- that are a different kind of risk than the rest of the children in the

remaining portion, where the event has not occurred. And, of course, the way that you treat those two groups of children might be different. So, much of the, at least the way that I understood, in both Amy and Jim's, and the description of them, is that we're talking about dealing with the children in the geographic area in which the event has occurred. And I wonder whether we should think about both classes of children and whether we treat them differently or any other counter measure research that we would consider in those two groups of children would be different and whether we should address that?

DR. GUTMANN: Do you want to start?

DR. WAGNER: Let me start. I certainly think we should, actually that is what I was referring to when I said I enjoy hearing just a little more conversation on the word "Imminence," because certainly for those children in Boston, they are post-event. But then how is it, I'm wondering if we can't use our understanding of what imminence means to say this, therefore does or does not make an imminent risk for people in New York and Philadelphia and Chicago. I would like to see us address the point that Raju is raising, yes.

DR. GUTMANN: So, the framework that we've set out addresses that point. It doesn't determine pre-knowledge of the event, whether and where another event would be imminent, but at the time, whatever government intelligence exists could establish that. So, we've established the framework, which says quite clearly, that once an event happens, we're in a post-event situation with regard to the children involved. And, in addition, if and when an event happens, there's intelligence that suggests it's imminent for other sections of the country, those would also be treated as a post-event.

DR. JAMES WAGNER: I've got Nelson--

DR. KUCHERLAPATI: I just want to make a comment. I think the distinction is that, at least in times of the way they were considered or treating the children, is that I have read that in the case of an event that all of the children in the affected area would be treated both with a vaccine and antibiotics. Whereas, the other children, where an attack occurred, that would not be the appropriate treatment to those. So, the question is that, what do we do, you know, for those children? And what are the kinds of things that the Commission can --

DR. GUTMANN: So, Raju, what we would do would depend on intelligence about the risks to other parts of the country. I think that's really quite clear with, and I think correct, with our framework. Lonnie.

DR. JAMES WAGNER: Nelson and then Lonnie.

DR. MICHAEL: So, I just want to continue to emphasize something I think is not been, in my view, emphasized as much as it needed to be in past deliberations, which is that, for post-exposure prophylaxis, for individuals really at high risk for having been exposed to anthrax, there are very good and a series of confirming animal model experiments where, of course, this work is feasible, that continue to show that the use of antibiotics, plus vaccine, is more effective at blocking transmission of inhaled anthrax than antibiotics alone. And I wanted to continue to say that, because even though it is animal model research, and yes, it's true, if you look at the differential mortality rates of individuals exposed in two U.S. domestic attacks, there was a difference in use of single or combined modalities. I think it's important for us to struggle with

the fact that the use of antibiotics alone should probably not make us ethically comfortable. 'Cause I just don't think that is not something that makes a lot of medical sense.

DR. GUTMANN: And let me just again, I think it is important for the record, we as a Commission have the knowledge, and we will use that knowledge, that the plan now is to use antibiotics coupled with AVA vaccine for children, as well as adults. Because a lot of, we -- this is also factually the case, a lot of medicine is used with children extrapolating from adults and animal research, but this case there is adult research as well as animal research, and in the case of where there will be direct benefit to children, that would be an ethical protocol.

So, it's very important to recognize that it's not the case that this country is unprepared. It is prepared, with, intellectually prepared, and to some extent practically prepared and we're going to recommend full practical preparation for using a protocol of AVA vaccine and antibiotics. And then doing the appropriate research to see what the effects are. In the case, this would be a case where the rules of proportionality apply, that the slight, somewhat above minimal risk is appropriate given that there is a prospect of direct benefit for the children.

Barbara is next.

DR. ATKINSON: I have is another definitional issue, and it is one as I read the report, we talked about some, and we definitely heard testimony about it, and it's the, what exactly is minimal risk and what is slightly above minimal risk, with real examples. Because when we explain this to the public, if we try to just use those words without the context, I think somehow very early in our report it would be nice to be really clear on the examples, and then what is above minimal over risk, too.

DR. GUTMANN: Barbara, could I ask you, would you like to say something on that? --

DR. ATKINSON: On what they are?

DR. GUTMANN: I think you'll see there is total agreement on how important this is. Or anybody else?

DR. ATKINSON: I'm not real comfortable exactly giving examples. And that was part of my problem in the whole thing, even though we did hear it once. Are you going to --

DR. GUTMANN: Shut off your red --

DR. SULMASY: I was going to bring that up, too. We are all clear, I guess by a definition of minimal risk. We've got sort of a standard Federal definition, sort of activities of life or of education or healthcare. The minor increase over minimal risk, we did begin this sort of stipulative process, and things like, sick enough to miss school or skin biopsy, we've sort of called a minor increase over minimal risk. But I do think we need to sort of fill that out with a couple more examples, and then say what a minor increase over a minor increase might be. And that for me would be things like, lumbar puncture, bronchoscopy, LFT abnormalities, and then, not just as a significant threat to the child's health or well-being, but I think a significant chance of a serious threat to the child's health or well-being, which would be liver failure or death, and those are the kind of things we would want absolutely off the table. That is my, sort of, off the back of the envelope, sort of sense of what those would be, but I think we ought to, as I've urged

at previous meetings, be stipulative about these and sort of give some guidance to any potential 407 committee about what those would actually look like.

DR. GUTMANN: Yes, there's an agreement on that. We are going to avoid anything, language, anything more than minor increment over minimal risk because after that you get on a slope that just keeps going. So, minimal risk, one example of minimal risk, and maybe the best, because we're in the medical sphere, is the risk of a normal, healthy, child having an annual physical exam in a doctor's office, and one thing that we're very clear about is that minor increment over minimal risk must pose no significant threat to the child's health or well-being.

DR. SULMASY: Let me just sort of say that, proceeding only to say what is included under minor increase over minimal risk doesn't give enough, because it doesn't give the ceiling that I think we need to give some examples of things that would be beyond the (inaudible).

DR. GUTMANN: I did give a ceiling, pose no significant threat to the child's health or well-being, or may not be sufficient, but it is a ceiling.

DR. SULMASY: Right. But again, by stipulation, because that language is still too vague.

DR. GUTMANN: Yeah -- Lonnie.

MS. ALI: I just want to go back to something you guys were saying about risk, because it seems to me talking about post-event exposure, and let's say in Boston, where are two million children. The level of risk that is acceptable there may be a little bit different than what it may be said in Los Angeles, where there hasn't been real exposure. And, are we talking about as a Commission, are we talking about actually not giving children AVA vaccine with antibiotics if we do not know what that risk is if it is over a small increment over minimal risk? You know, what are we saying as a Commission? Or is it different for kids over in California, would it be different for them, where the risk would be minimal risk, no increment over minimum risk? And then, also about the process. I think, you know as Commission, I think our huge contribution here will be the process, the preparedness of having this framework in place because there will be chaos after a post-event, you know, if it occurred. So, I think the process, the preparedness is important and how that works, if that is together, and in place, how that works. Would it be different like, would IRBs come into place if they are in an area where there is no actual exposure? Would there be any kind of IRB intervention in like say Boston if it occurred there?

So, um, I just have these questions, you know swirling in my head. I just wanted to find out really about the AVA, do we give it to a child if we don't know the risk and they have been exposed?

DR. GUTMANN: You may want to --

DR. GRADY: I think just in response to Lonnie, my understanding is that HHS plans to give AVA, plus antibiotics to children, if they are exposed, right now, without any additional testing. I wanted to get back to Raju's question. Because I think it's a really important question to think about. It seems to me that, that's where planning comes in, in the event of an attack, let's

just say it is anthrax attack for the purposes of discussion, but it could be something else. It seems to me that the children that were exposed would be given AVA and antibiotics. And so the question that we should be thinking about is, what is the research that is going to inform further use of those modalities or something else? If there is important research question that can be answered by children who have not been exposed, then there might be something important to do, but I can't imagine what that would be. I mean, I think the children that we know that have been exposed would be given the counter measures.

There are lots of very important questions that should be asked in a post-event research design to be sure that we understand what we would do the next time it happened. So then, if children in Los Angeles were then exposed, we would have more information the next time. That seems to make sense to me. And so post-event, I think we should talk about post-event as meaning the people who were part of the event, the children part of the event, but with an eye to any kind of pre-planning that we can think of that might. Given an event occurrence, what makes sense to do in unexposed children? Does that make sense to you?

DR. GUTMANN: Yeah. I think that is really the time when it is -- becomes both ethically acceptable, clearly ethically acceptable and obligatory to get the information through being prepared with the research protocol of "get the information that can be gotten" from the effectiveness.

DR. GRADY: Although I think part of what I'm -- I mean is that it seems to me that the research questions might be very different in a population of children who were exposed and a population of children who were not exposed. So there should be more than one study, if that is the way to think about it.

DR. GUTMANN: Yeah.

DR. WAGNER: Christine, let me ask you for clarification on this because I think in our minds we keep saying let's just use anthrax as an example, and I think in our minds, I hope we are not too limited. The one dimension that I worry about is the time table. Because certainly if there were a, well as in Japan, a nuclear incident where there was an immediate exposure to a regional population, but in that case, a cloud, or a Chernobyl, a cloud of something that was imminently going to fall over someone else, the time table to respond to that is far shorter than the time table we would have with anthrax. And I don't know there aren't other viral agents that most devious selves could imagine that would have a similar sort of opportunity for spreading, in which case I wonder if you wouldn't move swiftly to the at-risk, imminently at risk population, with perhaps different questions than you would have the freedom to ask in that which was immediately affected.

DR. GRADY: I think that is right. It helps us to think to remember that; responding to an event is different than doing research in an event and research, I agree with what you both said earlier, is critical post-event because there are things we need to know about how proceed, but we're going to respond with or without research, with whatever we have at hand. And so, the pre-planning seems critical in terms of thinking about what are important questions that we could ask, in a research way, in a post-event setting and how do they differ from kids who are exposed in Boston and kids who are not exposed yet or may never be, in somewhere else?

DR. GUTMANN: Among other things, there are certain very essential research questions that can only be asked in a post-event, because you can only follow through on a set of questions in the case of an event. We, again, hope never to have to put those research protocols into place, but we ought to be ready to do so in the case of an event.

I have Alex on the list.

DR. GARZA: I think you are entirely correct, Christine, about looking at the different populations that way in developing the research question. And so, if I heard you correctly, Raju, though, it sounded like you were asking the question of, would you consider unexposed pediatric population to be post-event population or pre-event population? So, which ethical framework would they fall underneath? I think that is a valid question. So, my interpretation of that, or my sort of view of the world of that, is there is a phenomenon which we discuss in my line of work called reload, where if a perpetrator--

DR. GUTMANN: I may, by the way, say what your line of work is.

DR. GARZA: I work for the Department of Homeland Security. And so, the conundrum is, if somebody is, if a bad actor has the capability to develop bacteria or a pathogen and able to disseminate it, what is to prevent them from developing more and disseminating more? And so, part of what we view our charge is, is preventing further attack. So, once we know something has occurred, we want to make sure it doesn't happen again. Of course that is what the President is going to have on his mind. So, does that mean that just the population that was exposed is at risk or is everybody at risk? Because again, if you can make a gram, you can make a kilogram.

And so, with those populations that have not been exposed, but yet are still part of the United States or part of, you know, part of the community, should we consider them a post-exposure population or pre-event population? And the ethical framework is different from those, one is going to be a higher barrier than the others. I would tend to think that we should consider them a post-event population because there are different questions that we are going to have to answer. Like Christine was saying, that are going on during the event in the exposed population as opposed to the population that has not been exposed. But the tyranny of time and acquiring that sort of information, in order to protect the rest of the nation, is going to be paramount. And so, at least in my viewpoint, they would fall underneath a post exposure population more so than pre-event.

DR. GUTMANN: Nita.

MS. FARAHANY: So first, Amy, thank you for flushing out this framework in greater detail for us to have this conversation. I think it is really important that we think about the post-events protocol that we might develop. Some of the things I worry about, though, is whether or not having a very well fleshed out post-event protocol and framework diverts us from the burden of feeling like pre-event studies are necessary and important. And so, I say that because if we, for example, take Alex's definition of post-event to include everybody in the United States and say now we're in a post-event study, the standards by which those individuals are subjected to risk is lowered, meaning that we feel more comfortable taking greater risk with individuals because they are all in post-event population. And the way in which parents may feel enrolling children is that they feel more compelled to enroll children in those types of studies. Which, to me, is kind

of concerning, so even if we establish adequate protocols to ensure consents, the emotional reaction that many people have, which would lead to greater willingness to undertake risk is something that would concern me.

So, what I would want us to be sure to do is to look as we develop a very robust post-event framework to see how that guides us and feeds us back into thinking about the pre-event framework means that, because if we see, under current guidelines, that children would have both the vaccine and the antibiotics, and we're worried that it's difficult to do controlled research because everyone is getting it, but that doesn't mean they are enrolling in research to follow the results of their care and their study. And, if we think that those things are likely, while we can have a robust framework and should, it shouldn't divert us from thinking we also would need potential pre-event studies, as well.

DR. GUTMANN: Nelson.

DR. MICHAEL: So, I guess I want to make three major comments about post-event research. The first, I think I really want to echo what Lonnie said from the very beginning because it is in danger of potentially being lost, which is, I think if the best thing we could do as an advisory group would be to ensure that the government really is ready for this to happen. I mean, for those of us who have written clinical protocols and I'm one of them, I can tell you that it's not something that you can do overnight. So, having these studies really spring-loaded is going to be critical, and that is difficult. 'Cause someone has to do it. Some has to do it now during the time when which there isn't the urgency to do, what most of us tend to do, study the night before the exams, in this sense. So, I really think that is a critical point for us to address.

The second I think is that; now imagine going back to Raju's construct where you have individuals that clearly were at risk and were exposed and now on drugs and vaccine. Those individuals would have to still be enrolled in a research protocol to gain the kind of insight that you would want to have, and I would say is that if I could have one piece of information from a post-event situation, it would be to follow a subset of children in a research protocol that had been exposed, have been treated with both drugs and vaccines, and one could gain additional information, operationally, that would allow us to distill at the best medical practice.

And third is, now let's take the situation that you have a major attack that occurred in one large US city, but not in the other. And then you think it raises the risk of having another large American city, or a portion of the large American city put at risk. That might change the ethical debate in terms of how you can do the kind of research that Nita talking about pre-event, which would be looking at safety and immunogenicity, dose sparing as a mechanism to get at those kinds of questions that would be also important to have in order for us to continue to develop the best practice of treating children with drugs and vaccines. Looking at different routes of administration of vaccine, and especially looking at dose sparing, where you could get additional safety information, different increased amounts of immunogenicity, but I think we need to be also mindful that dose sparing also means a logistical benefit to the strategic national stock pile, you just stretch the amount of vaccine that could potentially be used, especially if the attack was major.

So, I think those are three major things I wanted to emphasize, but especially the fact that someone really has to sit down and roll their sleeves up and make sure these protocols are on the shelf.

DR. GUTMANN: Dan.

DR. SULMASY: Two things. One point that was put on the table earlier, I think by Jim, was the question, talking more about the question of imminent, and whether it does in fact devolve to post-treatment. And, while imminent doesn't have a, in fairness, in nature, it does have a definition, right? And we can define it reasonably, I guess, and we ought to, I think, more clearly than we do as maybe days to weeks, or hours to weeks even if it's the Chernobyl cloud. A, if that's the case, I'm certainly convinced that that would be tantamount to a post-event project. 'Cause you couldn't really do pre-event work under those sorts of circumstances. So, if that's how we're going to define it, we ought to define it that way clearly and then I think it follows that pre-event becomes post-event under those circumstances.

DR. GUTMANN: It's technically before an event occurs, but it is for all practical and ethical purposes, predictably happening quickly, there is tradition in just war theory that actually defines imminent, imminent attack, is one that could justify preemptive action. It's very different than preventive action, when where an attack is not, imminent and there's extraordinary controversy over that. But there is not extra ordinary controversy over preemptive action in the case of imminent attack. And, it would be, frankly, foolish if an attack is truly imminent, it is predictably happening quickly. Not to treat it as, for practical and ethical purposes, post-event.

What that means effectively, is that some -- those who know or the agents, the people, the principals of those who know, do need specify that something is imminent and therefore we are that kind of emergency situation. And, I think that's, in keeping with the framework, the ethical framework that we have put forward. I think it's very important to do that. It's also important not to stretch that so that if there are people, and there always are people, who have bad things, and have bad intentions, we treat a situation as one of imminence or emergency. Otherwise we are, in the case, to use the just war theory, permanent war, which is not a situation that is present or one that is compatible with the ethical framework that we've developed.

DR. SULMASY: I'm sorry, I had a second point, which is just to amplify or-- something that Nita said about being careful not to divert our attention from the need for pre-event studies. It's slightly a different variation because if we do a post-event study and put of our marbles in that basket, and we find out that we needed to have twice the adult dose of vaccine in order to get immunogenicity in children, many, many, might have died under those circumstances. So, I do think it is important to make sure that we don't so emphasize post-event that we divert attention from the possible benefit of pre-event testing.

DR. GUTMANN: We've spent significant amount of time on pre-event, including coming up with the help of experts, on a protocol that would minimize, would minimize risk, which begins by seeing what the situation is for young adults. And, as we mentioned earlier, age de-escalation. And, that is something, by the way, that we can and should strongly recommend because it is the case that if the government, as we assume it is, is serious about this, it should start doing this and minimize, which is totally in keeping with normal research protocols with low risk and can go through IRBs in the normal way and there's every reason to, for us to

recommend that and for the government to begin that process, assuming this is a serious set of risks with unknown probabilities attached to them and I look to Alex because you're next on my list.

DR. GARZA: So, I wanted to revisit the term of imminent, though. And the reason for that is I think you are correct, Amy, when you talk about, in war fighting, where you can have some reasonable expectation of when events are going to occur. But that's mostly because we have very good battle field intelligence and things like this. But when you are dealing with intelligence of unconventional warfare and terrorist organizations, a lot of times you can't get to the fidelity of imminence. But what you can do is evaluate the threat. And so, the threat is intent times capability and so if you can –

DR. WAGNER: (inaudible) threat means what, intent?

DR. GARZA: Intent times capability. And so, I would caution using or maybe caveating the word "imminence" and including some sort of or maybe broadening it to the threat definition. Because there's a lot of times where we are not going to know the time and place, but we know the capability and we know the intent and therefore that drives what we do, as a country, to prevent or to decrease vulnerability or to increase capabilities for ourselves. So, I think there should be some way of caveating that language to do that.

DR. WAGNER: Please clarify, because imminent is too high a standard?

Or --

DR. GARZA: I think imminence implies in order to execute this sort of research in a post-event scenario, to me at least, using the word imminent means we know time and place, where this is going to occur. And I'm saying that is a very high burden for people to understand.

DR. GUTMANN: What is presented to us, let me be clear about this, what is presented to us is when is it ethically justifiable to subject children who do not stand to directly benefit from the research to more than minimal risk or more than minor increment among risk. And I, for one, could not, as Chair of a Commission on Bioethics, say that it is justifiable on some vague, unlikely, no emergency situation, to ask children to be subject to more than a minor increment among minimal risk, for no direct benefit to them. At that point, it is at that point, and the reason why I think it is very important to have a strict definition of imminent, is that point that you are using children as mice or guinea pigs, you name it. And we cannot do that ethically speaking. In an emergency situation, where there's imminence and we're in effectively a post-event situation, then the children stand to directly benefit.

That's why, so that is the important line that I think needs to be drawn ethically. But, that is why we have really worked hard, and I think successfully, to come up with a protocol, that if put into place, could begin by having children who are not subject to more than minimal risk, or minor increment, minimal risk being no -- we need to be very careful about it, but we could begin by doing that. And if the government is serious about this, there's every reason for it to begin doing that. And, indeed, If the government doesn't begin doing that, that's a sign that it is not taking this as serious as it -- as you suggested, it ought to be. So, I think we have both a pre

and post-event set of scenarios that are ethically justifiable. I think that's really important for a Bioethics Commission.

DR. ATKINSON: Yes, Christine's comment raised another issue for me and that's deciding to give the AVA and antibiotics in a post-event. If that decision is based on any risk level at all which we're saying it should be, then that has to be made ahead of time. And I'm not sure who's making it ahead of time. If you even think of the risk of the antibiotic, it would be what I would consider more minor over minimal. I mean 60 days of antibiotic is not anything, that doesn't have a fair amount of risk to a lot of people, including anaphylaxis and things like that. So, are we going to compare the vaccine to that risk, and is it Homeland Security decides which isn't done under HHS or it is HHS that decides? I mean, there are administrative things, and who is deciding for everything besides anthrax, and so I'm not sure, I mean I don't know how we want to deal with that, but there is that whole issue of deciding it ahead of time. And, it would be nice to have IRBs for the research that's going to go on afterwards, but we're talking about the treatment of everybody that's exposed, not just the research component of it too.

DR. GUTMANN: Raju.

DR. KUCHERLAPATI: I, thank you. First of all, before I make that comment I was going to make, I wanted to say that I support the comments made by Nita and Dan, about the importance of the pre-event research. But this discussion is focused on post-event and so I have a question. And that's the following: So, the way that Alex defined it, is that once an event occurs in one part of the country, that we would consider that that event would be imminent and the rest of the country and therefore all of the children would be treated with, in this particular case with vaccine. Let me continue; vaccine plus antibiotics. Or, Amy, you are shaking your head, but the other possibility is that those children that are in the exposed area would indeed be treated with those two modalities.

Now, obviously once that has happened, the only kind of research that could be done are observational studies. Then all of the issues about assessing minimal risk, or minor increases in a minimal risk, are out the window. Right? But yet, all of the definitions that we talked about today, you know, include that phrasing, so we have to be sure that there is no reason to further consider any minimal risk and so on. Because all of those children, the only feature that is important for those children to participate in research is consent. All the other issues are irrelevant.

DR. WAGNER: Very quickly, I want to clarify what I thought we were talking about. When we talk pre and post-event, I believe what we're talking about is not pre and post-event response, but what are the set of ethics which would guide a response -- pre-event versus post-event. In other words, we have ethical principles that the ethical circumstances are different in post-event. That doesn't necessarily mean that we start inoculating, immunizing people in L.A. when there is attack in Boston, in spite of the fact we might want to use post-event ethics in deciding what we will do with at-risk children there. In other words, it is important to make, for me it's important to make certain that we are proposing an ethical framework to guide response, rather than prescribing response pre and post-event. Does that make sense?

DR. GUTMANN: Yeah. Let me just explain why, not only I, but several people were shaking their head. It doesn't automatically follow that when there is, we are talking in this case

of anthrax attack, in one place, might not be large as a city. It could be a small attack that ipso facto, it does not follow that, ipso facto, every child in the country is at risk. It just doesn't follow, logically speaking, and that is why I think it is important to separate what our ethical analysis is and what our empirical analysis is. The empirical analysis would have to come through a series of understandings that we're not, now and nobody right now is privy to, as to where there is and isn't imminent risk. It is part of human nature that when an attack occurs, people all of a sudden feel more at risk wherever they are. But it doesn't follow that everybody, therefore, is. So, we cannot say as a Commission, that were there an attack, somewhere in the United States; it would just simply follow that everybody in the United States would be in a post-event situation.

That is the only --

DR. KUCHERLAPATI: That was the question that I posed and actually I'm hearing two different things in response to my original question. But this discussion, Amy, is not about that. This discussion is about what are the kinds of ethical research considerations that one should have, among the population of children who are exposed? And again, I'm hearing two different things now. And, Jim is saying that, first what we're trying to make recommendations or trying to determine -- what is the kind of response that the nation should have among them, but my question is not about what the response is --

DR. WAGNER: I'm sorry, Raju. Raju, I'm sorry. I must have been misunderstood. I am saying exactly the opposite. Our task is to offer the ethical framework. The ethical width, if you will, for consideration. But we are not, and we have said there is different ethical considerations, pre-event and post-event, and our job is not, I want to make sure. I didn't mean to imply our job is to stipulate what a response should be posted.

DR. KUCHERLAPATI: I didn't make myself very clear. Let me explain the scenario much better. There was an event. And in some region, all right? And therefore, the government has decided that those children now should be given the vaccine plus antibiotics, okay? All of the children in that region are given that combination therapy. And now we do want to obtain information from within the population how they respond and a lot of other types of clinical questions. And therefore, essentially, first of all, all of those children are eligible to enter into a study, right? And, what I am saying is that the only kind of study that could be designed would be an observational study, right? And therefore, all of these prior issues that you need, that the research cannot be more than minimal risk. For example, it is not a consideration. That is all that I'm saying.

DR. GUTMANN: Yes. And that's why the ethical, --

DR. MICHAEL: Yes and no--

DR. GUTMANN: yes and no, Ok. There are some considerations as to what you could still do proportionality and so on, apply. But the important feature of that, ethically speaking, is that those children who are at risk, because they have been exposed to anthrax, those children stand to directly benefit, both from the treatment which has not been completed tested prior, they stand to directly benefit, and from any extra procedures that they would be put through in research protocol.

Dr. WAGNER: And from the knowledge learned --

DR. GUTMANN: And from the knowledge learned, yes, from the knowledge learned. That is what I meant to say, thank you.

Lonnie, and then Alex.

MS. ALI: Raju, I was thinking just like you and understood what you said until I thought about, where you talk about immunogenicity in a child, that would put them at risk if you're trying to determine what level of the AVA vaccine would predict immunogenicity. And I was going to ask, my original question was to Nelson, was to ask him, and to Alex – Do we know, because I know there are members of the military who have been vaccinated, do we know right now under animal models, what the levels of AVA vaccines are needed to create immunogenicity in adults?

DR. MICHAEL: There is consensus on the imprecise information we have about correlate risk of infection. That's, the short answer is not really, although there is an accepted standard, in which the level of immunogenicity that you would key, if you did a dose sparing series of experiments. But the practical reality is animal models have not been completely validated for the clinical situation. It's not ethical to do pathogen challenges studies in adults with anthrax, for obvious reasons. So, there really isn't a lot of guess work about what the level of immunogenicity should be. So, I think just from a purely scientific standpoint, there is always that question mark. That said, there is an accepted body of experts who believe that there is, are, certain things that you can measure in the blood of individuals that have been vaccinated, and those bench marks could be looked at in terms of titrating dose or route of administration in adults or children. And that's, to me that is the kind of pre-event research, I know we are talking about post-event, but to me those kinds of questions are probably best looked at in pre-event research studies in adults. But, I think it is a good point that you raise, is we really don't have a strict correlate of risk of protection, which is a very, very high scientific standard to be absolutely certain that is the right benchmark.

DR. GUTMANN: And one of the things in an earlier meeting, this is really important set of questions, one of the things in an earlier meeting we established is how important it is to do and how possible it is, ethically possible it is to do more pre-event studies in adults, so we get at some of those. I just want to underline something that Nelson said because it informs all of our deliberations. He said it's not ethical to do pathogen induced studies in adults for obvious reasons. There are limits to what we can find out, scientifically speaking, because of the ethical constraints of what research you can do. And if that is true for adults, it's true in multiple times in children because they can't give their Informed Consent. So, I think Lonnie's question and Nelson's answer is really important in underlining how important it is to do the studies that are ethically possible in adults, who have been immunized and you could do controlled studies because there are adults who haven't and those who have, and see what immunogenicity, what we can find out.

MS. ALI: Can I add something to that Amy, too. Also, I'm thinking we should be careful about talking about what kind of studies are done post-event. They may not just be observational. Because I was thinking on the same line as Raju, but they could include, like, blood draws and

lumbar punctures, just to figure out what that is. So, actually, there is some additional risk that are incurred, that are not just minimal or risk is thrown out the window.

DR. MICHAEL: That is why I say yes or no.

MS. ALI: Yeah. That's what made me think of --

DR. GUTMANN: Very important point to make. Alex, Dan, and then we'll take a break, but with one interlude before the break.

Alex.

DR. GARZA: Sure. So, Raju, I wanted to, sort of caveat my answer I have before. It sounds like Amy and I were in somewhat disagreement. I think that's what you were picking up on. But, in my viewpoint, I think we were in agreement, we were just looking at it from two different points of view. So, when I was saying other people would still be at risk, even if they weren't in the exposed population. I think directly feeds into the definition that we were using of imminence, as well, or imminent threat. And so, if I think if I came to the Secretary and said, "look, we have this incident in Boston and we have high confidence that it could occur again, we're not really sure where, but we're fairly confident that this group/ organization/ individual has the capacity to do that." I think that would meet imminent threat bar, but I'll leave that to discussion. So, I think we're congruent with that.

Secondly, we have some is history with this, if everybody remember back to 2001. This was multi-state attack more or less. In fact, the first case was here in Florida, where anthrax was mailed, and DC, and New Jersey. And so, I can tell you from experience working in the emergency department, that I had people coming to the emergency department who were absolutely at no risk at all. I mean these were regular people out in the public, had no ties to the intelligence community, no ties to senators, anything like that, who were very, very concerned about possible exposure to anthrax, just because they had a letter that was post-marked from a foreign country. And so, I guess the point of that is, it is going to be very contextual, as well, the environment is very contextual, but the point being, is the rest of the community at imminent risk? Maybe. It sort of depends, and unfortunately that's about as good as you get sometimes with intelligence.

DR. SULMASY: This, more a question actually for Nelson. Would you imagine that some of the, sort of, post-event protocols that you would like to have ready, would include at least small groups in which the dose would be varied so we get information on a dose response, even post-event?

DR. MICHAEL: Yes, but I think that the most important study to do post-event would be the ones that I think we've defined a bit in discussion between Lonnie and I, which would be you really would want to increase the database on the safety and immunogenicity of the vaccine that had been given, that had been distilled in practice and given. It will be observational studies, you would need to do blood draws and so therefore, that's why I was saying it raises the issue of accruing of additional risk. I think the studies that you refer to would still be very meritorious, but ethically more challenging even post-event.

DR. AMY GUTMANN: Very important point. Before we adjourn, I would like to go around and ask each member of the Commission just to, post the original deliberations, introduce yourselves and then we will take a 15-minute break and reconvene, starting with Christine.

DR. GRADY: I'm CHRISTINE GRADY at the Department of Bioethics at the NIH Clinical Center.

MS. FARAHANY: I'm NITA FARAHANY, in Law, Philosophy and Genome Sciences and Policy at Duke.

DR. HAUSER: DR. STEVEN HAUSER, neurology at UC San Francisco.

MS. ALI: I'm LONNIE ALI, Parkinson research advocate and care giver.

DR. GARZA: ALEX GARZA, Assistant Secretary and Chief Medical Officer for the Department of Homeland Security.

DR. WAGNER: JIM WAGNER, serve as President of Emory University.

MS. ALLEN: ANITA ALLEN, Professor of Law and Philosophy, University of Pennsylvania.

DR. MICHAEL: NELSON MICHAEL, A vaccine researcher at the Walter Reed Army Institute of Research.

DR. ATKINSON: BABARA ATKINSON, Emeritus, from University of Kansas medical center.

DR. SULMASY: DAN SULMASY, the Department of Medicine Divinity School in McLean Center for Ethics at the University of Chicago.

DR. KUCHERLAPATI: DR. RAJU KUCHERLAPATI , genetics. Harvard Medical School.

DR. ARRAS: JOHN ARRAS, I'm a professor of Philosophy and Public Health Sciences at University of Virginia.

DR. GUTMANN: Thank you all for very productive discussion. We will take a 15-minute break and we will be -- come back at 10:45 and continue our deliberations. And don't forget that, if you have any questions or comments we would welcome them up here. Okay. See you in 15 minutes.

(15-minute break) --