



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

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DR. WAGNER: Okay. If we can have the Commissioners take their seats?

And we will begin our Session 8, after a very productive Session 7. Thank you, Amy. That was excellent.

And so, at this point in our meeting, we do switch gears. We have been talking about genomics and whole genomic sequencing. We are going to shift to medical countermeasures.

This, the Commissioners will recall, is at the request of Secretary Sebelius. The Commission is conducting a careful and open review of the ethical considerations of conducting clinical trials of medical countermeasures, specifically focused toward children.

We began the work in May and are looking forward to some informative sessions today to help us draw towards some of our conclusions. We begin with a session on assessing pediatric research, specifically how to consider individual risk and societal benefit in the pediatric research context.

As is our format, we will hear -- you don't know what our format is -- but the three of you, the three experts, we will hear from you each individually and hold questions for a period after the three of you have had a chance to speak.

Our first speaker this morning is Dr. David Resnik, a bioethicist at the National Institute of Environmental Health Sciences within the National Institutes of Health. Previously, he was Professor of Medical Humanities at the Brody School of Medicine in East Carolina University, an Associate Director of the Bioethics Center, also at East Carolina, and the Director of the Center for the Advancement of Ethics at the University of Washington. Dr. Resnik has authored eight books, over 170 articles, on philosophy and

bioethics.

We look forward to hearing from you. Thanks for being here, Dr. Resnik.

DR. RESNIK: Thank you for inviting me out this morning.

One correction. It was the University of Wyoming. Having lived there for eight years, you don't want to forget that place.

Anyway, I want to have my quick disclaimer that I am representing only myself and not the views of my employer or anything like that.

So, I want to try to go over this pretty quickly here, looking at minimal risk and the role that it plays in the federal regulations first.

You can see there are four types of research that are approvable under the federal regulations, the Common Rule. The first is when the research involves not greater than minimal risk. So, obviously, minimal risk is there.

The second one is involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. Again, minimal risk appears there. And these are the kinds of studies where we can say cancer clinical trials or something where there is a prospect of benefitting for the child.

Then, you get into more controversial categories: research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. And again, minimal risk is in there.

One of the requirements in there is that this kind of research must present, must be only a minor increase over minimal risk. Again, minimal risk appears; whatever

minor increase means, minimal risk is this sort of baseline standard.

And then, finally, research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. That doesn't mention minimal risk, but, by definition, it is kind of the last option that is possible. These are sort of rare kinds of things. You have to have a national panel put together to look at this kind of research to approve it.

So, minimal risk is kind of a threshold concept in the regulations. If something is minimal-risk research, it is classified as such for pediatric research. It is not regarded as ethically problematic at all unless the research is so poorly designed that you are really not going to learn anything at all. But, usually, that is not that much of an issue.

So, when you get more than minimal risk, you need some kind of additional justification, such as direct benefits to the participants, benefits to their class, or there is a really important problem affecting children's health that we need to deal with.

Here's the definition of minimal risk in the federal regulations: "Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during a performance of routine physical or psychological examinations or tests."

There are really two parts of this. It is either the routine physical or psychological examinations or tests part of it. You can use that as a test for minimal risk. Or you can use the risks of daily life.

So, what are some of these risks? Well, if you are looking at a research protocol, you have to consider the physical risk, such as medical harm that can happen to a

child, the bleeding, bruising, loss of consciousness, or whatever is going to happen to a child medically. There are also psychological risks, pain, distress, embarrassment, and so forth. You could also look at social risks or legal risks possibly to a child of loss of confidentiality.

And when you are evaluating the risks, you look at the total risks of the whole protocol, not the risk of just one particular part of the study -- let's say the blood draw -- but all the risks put together in the study, the net risks of the study.

And you also look at the risks of the research, not the risks of the clinical procedures that are already being done as part of therapy. So, for instance, if you have a study, let's say you have children that are getting, say, kidney transplants for kidney disease, and you are looking at the genetics of those children, and all you are doing for the genetics study is you are just collecting blood from the children. Well, obviously, you are not looking at the risk of the kidney transplant because they were getting that anyway. You are just looking at the risk of, say, the blood collection going on in your study.

So, these are some of the, as I mentioned earlier, the risks of routine physical and psychological examinations or tests. What are these things? Well, the OHRP has provided some expedited review categories. That is basically the same thing. You can approve minimal-risk research by expedited review.

So, the OHRP will tell us that, if you take a certain amount of blood, you collect toenails, or you record a videotape of people, these things are things that basically can be approved by expeditable review, and they will count as minimal risk.

These lists are 14 years old, and they need to be updated. At the NIH Clinical Center, we have guidelines that we use for the amount of, say, blood, for instance,

that you can draw from a child or adult, or whatever, per their body weight and the amount of time, and so forth, that we will consider to be minimal risks.

But not all risks can be assimilated under this concept. For instance, we have had studies where spraying for insects, pesticides are sprayed in the home. And pesticide spraying is not a routine physical or psychological exam. So, you have to look at something like the daily life standard.

The problem with this is, whose daily life are we talking about for the research risk evaluation? Are we talking about children living -- the risks that you find if you live in Harlem, let's say, or are you talking about the risks that the children would be exposed to in the suburbs of Washington, D.C.?

If you use what is called a relative standard of minimal risk and you say that, well, it is just the risks of the children that we are looking at, then that is opposed to a sort of an absolute standard that sort of general risks to children in some population. This could lead to unfairness and exploitation because, if you had a population that was already at high risk, given their conditions, you could use it to justify exposing them to higher risks than you would other children that were not in that population. So, that has been some criticism of using this relative standard, and people have urged going to the more absolute standard.

There is also a problem -- this is whether you can quantify the risks of daily life. What in the world are these things? There is a lot of evidence, as you might expect, since minimal risk is subject to different interpretations, that it has been interpreted differently.

There was an interesting study of IRB Chairs, and 81 percent classified a single blood draw as a minimal risk. That seemed to have some consensus. But, then, we have categories where there is not consensus. Fifty-three percent classified electromyogram as minimal or minor increase over minimal. Forty-one percent said it was more than minor increase over minimal, and you have some other differences here about allergy skin testing, and so forth.

So, this suggests that there are a lot of disagreements about what minimal risk means. As an IRB Chair, I can tell you that I have witnessed a lot of these.

To try to provide some guidance on this, there is an interesting study by David Wendler and colleagues. What they tried to do is quantify the concept of daily life's risks by looking at typical children's activities. So, they were able to figure out the cumulative risks for children per day at certain ages, risk of death, hospitalization, ER visit, things like that.

I think this is an interesting study, but it is unclear to me how this would actually be used in IRB practice. Would we actually have to quantify the risks of a study and then compare them to these risks that Wendler and colleagues have provided? I doubt that would happen. Knowing IRBs, it would be some much more qualitative assessment of minimal risk which typically goes on.

So, let me briefly discuss an example of a minimal risk that we looked at on our IRB. This was a study involving the NIH and the Children's Hospital of Philadelphia. We are collaborating on an observational study of breastfeeding versus bottle milk, cow's milk, or bottle milk soy milk in infants.

The parents already had their feeding choice prior to entering the study. We are trying to understand how soy isoflavones, which have estrogen-like activity in the body, affect infant development and health. There is a variety of measurements that were taken for boys and girls. They were followed, boys followed nine months, girls for seven months. Then, they were at the toddler phase which they enrolled in. The infants had to be healthy and full-term in a singleton birth.

Is that my time being up (referring to buzzer)? Okay. We are getting there.

Now here is where the risks sort of got dicey for us. Blood had to be collected at weeks two, four, six, eight, 12, 16, 20, 24, 28, 32, and 36. So, that is a lot of blood collection for these young children. So, the IRB was concerned about the risks of blood collection.

There was a single collection of 6 milliliters which was within the Clinical Center guidelines for minimal risks, but there was concern about the cumulative effect of collecting that blood, especially at eight weeks when the infants were at increased risk for anemia due to switching from fetal hemoglobin to adult hemoglobin.

So, what the IRB decided to do to minimize this risk was to require a heel stick at six weeks to measure hemoglobin, and infants that were anemic at eight weeks would not have their blood drawn at eight weeks.

There was also the concern about repeated venipunctures on infant and mother. This IRB decided to limit the attempts at three times per blood draw.

And so, with these and other things, we were able to approve this study as

minimal risk.

What I want to get at here --

DR. WAGNER: Would you wrap this up pretty quickly?

DR. RESNIK: Yes, this is the last slide. Okay.

We felt the study was justified because it was addressing important pediatric health concern. Since there was no direct benefit to the infants, risk was an issue. And it was not at all clear to us this study could have been approvable if we had not managed to classify it as minimal risk. So, we sort of juggled, we sort of worked with the study to where we could be comfortable with classifying it as minimal risk.

So, I think that is all I will say. Thank you.

DR. WAGNER: Thank you very much.

Dr. Neal Halsey is Professor of International Health at Johns Hopkins Bloomberg School of Public Health, with a joint appointment in Pediatrics at Johns Hopkins University School of Medicine. Dr. Halsey is also Director of the Institute for Vaccine Study. He has served on vaccine advisory committees for the CDC, the Pan American Health Organization, the World Health Organization, and the American Academy of Pediatrics. He has published over 200 peer-review articles, 40 chapters in textbooks on infectious disease and on vaccine.

Dr. Halsey?

DR. HALSEY: Thank you very much for inviting me. I appreciate the opportunity to talk with you about a subject of interest to me.

I was asked to participate, I am certain, because of my participation 10

years ago in an OHRP review of a protocol for the use of smallpox vaccine in children.

Just a bit of background: smallpox vaccine was used universally on a routine basis in children one year of age and older up until 1972, when it was determined that the risks from the vaccine exceeded the potential risks from exposure to smallpox, even though that was eight years prior to the declaration of eradication of smallpox.

With the events of 2001, including 9/11 and the anthrax exposures, there was fear of additional bioterrorism, including the use of smallpox as a weapon for bioterrorism, which *Variola major* has a case fatality rate of 30 percent.

An exercise was put together for the National Security Council and participation by three federal agencies called Dark Winter, where there was an imaginary exposure to 3,000 individuals who contracted smallpox in three different cities, an aerosol exposure. It really was a maximum-risk or worst-case scenario with assumptions that there would be a tenfold increase in the number of cases with each generation, overwhelming the healthcare system, the public health system, and communication, transportation, and everything else, called Dark Winter.

The Administration made the decision that there would be vaccine made available to immunize the entire population of the United States. And a survey conducted in December of 2001 revealed that 75 percent of adults would take the vaccine. There was also demand for people to release the vaccine for use in children at some of the public meetings that were held.

The vaccine that was available had been made many years ago by Wyeth Laboratories and stored, and then given to the government. There were 15 million doses

available. The population was around 300 million at that time. So, there was consideration as to how to expand that by doing dilutions and that they would have 75 million. And also, a large amount of money was invested to make available second-generation smallpox vaccines that are listed there.

NIH coordinated a multi-center trial of diluting the vaccine in adults, 1 to 5 and 1 to 10, and they got very high take rates, 97, 99 percent. Therefore, they moved forward to developing a study at three institutions for dilution vaccine in children that would be conducted, sponsored by the NIH, conducted under an FDA IND. There would be 40 children vaccinated, 20 of them undiluted, 20 of them diluted 1 to 5, and comparison of the take rates and the side effects from the vaccine.

I forgot one point on the previous slide. This was approved by the IRBs at Cincinnati Children's Hospital and Kaiser Permanente. But under review at Harvard/UCLA, and consideration under 46.405, there was a tie vote, 5-4, 5 against and 1 abstained. The Chair broke the tie by voting against it, which, then, by regulation, had to go to OHRP for review under 46.407, which the Committee felt that it would be approvable under that.

Therefore, a panel was put together of 10 reviewers, as was mentioned. Smallpox vaccine, is the most reactogenic vaccine that we have ever used in children or adults in this country. It causes a high rate of local side effects. This is a normal take with redness, swelling, and you can have robust takes, which involve what looks like lymphadenitis, and so forth, but it is actually still part of the normal take.

Also, you can have transmission to other parts of the body, which is

common, just by scratching, putting in the eye, all over the body, and you can imagine everywhere that it did take place; and also, transmission to contacts within the family and other close contacts.

Children and others developed rashes. This is Erythema multiforme, an immunologically-mediated rash. There were occasional more severe ones. Stevens Johnson Syndrome did occur and was associated with the vaccine rarely.

People with underlying conditions, such as eczema, were subject to more disseminated skin disease due to an underlying T-cell deficiency, T-cells in the skin. So, they would get Eczema vaccinatum. And there was mortality associated with this, very difficult to treat and manage.

Those with underlying systemic T-cell disorders, such as this child with leukemia, suffered from progressive Vaccinia, which did require amputation and did lead to death in a number of individuals every year.

In 1987, there was a military recruit who developed disseminated Vaccinia, who was then found to have had HIV infection. That was prior to the universal screening of the military population. He was treated and recovered and did fine.

Back in 1968, a survey was done by Mike Lane at CDC which revealed these rates of complication. There isn't time to go through all of them, but I draw your attention to the last two lines, encephalitis and death, which occurred more commonly in children than they did in adults.

In the NIH trial of adults, they used an occlusive dressing to minimize the risk of transmission, autoinoculation or transmission to others, but there was concern that

this may have increased the rates of local side effects. This is one person with a robust take, if you will, and a fairly honest swelling that was there.

Other side effects are listed here. I would draw your attention to the fact that one-third of the adults said the pain was moderate to severe and interfered with their ability to work or go to school or participate in recreational activities.

So, the panel of 10 reviewers, of which I was one, in review of the protocol, came up with a number of concerns. They felt the risk was understated. The encephalitis risk was actually higher in children than adults, but wasn't reflected in the consent form or protocol. And the statement that serious complications were remote was really not correct, and the risk of transmission was understated. The potential benefit to the individuals was overstated.

And 407 requires consent from both parents, which they had only had for one parent. And the safety monitoring was criticized by some as not being adequate; plus, there was not an adequate discussion of what the alternatives were for families, including non-participation.

With regard to trying to reduce the risks, there was pretty decent screening for underlying conditions, but it could have been improved, based upon a couple of assessments. In order to minimize the exposure to a highly-reactogenic vaccine, I suggested that they could study the undiluted vaccine first -- excuse me -- they could study the diluted vaccine first because we already knew that the undiluted vaccine resulted in very high take rates in children. And therefore, if the diluted vaccine resulted in high take rates, you wouldn't need to expose children to the undiluted.

With regard to trying to maximize the benefit, I suggested that they could select children for participation whose parents had already received the vaccine. That way, you would have maximum parental knowledge of the vaccine, and for those parents who are getting the vaccine -- in Hopkins, we were immunizing 50 to 60 laboratory workers a year, just because they were working with vaccinia -- you could select children whose parents had had the vaccine. There was a theoretical risk of potentially bringing the vaccinia home and exposing your child to an inadvertent site.

These criteria have all been reviewed. One of the 10 reviewers felt that the protocol could be reviewed under 405; nine did not. All agreed it could be approved under 407, and you have already been through the guidelines. So, I won't spend the time on that issue.

Interestingly, within three months after the review, the protocol hadn't been implemented, and the Secretary of HHS issued the following statement. I will only highlight the green that is on here, that "Bioterrorism preparedness plans have evolved such that, under current plans, the potential to use diluted Dryvax in children will no longer exist."

Basically, it was determined that the theoretical risk of exposure was much, much less than what the concern had been when the protocol was developed back in June of 2002. And therefore, there was no justification for this particular clinical trial to proceed.

A few months later, we had a multi-state outbreak of monkeypox. This is just one child, acquired due to importation of exotic pets from Africa, rodents primarily, and

then people bringing these pets home, including prairie dogs that got subsequently exposed, developed monkeypox.

CDC worked with FDA and they did release the smallpox vaccine and given to those children and adults who were exposed. And I forgot to get the numbers of children who did receive the vaccine under the IND. And I think that system worked pretty well.

Smallpox vaccine is known to protect against monkeypox. There are a half-a-dozen studies; I didn't show them to you. But there is an endemic area of continuing monkeypox transmission in Africa.

It raises another interesting question about other potential bioterrorism agents. I mean, could you study the vaccine in that setting where you would be providing substantial benefit to children? And I am talking about the second and third generation of smallpox vaccines. But that raises a bunch of other ethical issues you are not prepared to discuss.

Since 2002, there have been a number of developments, including identification of myocarditis as a risk factor which wasn't appreciated in 2002, although historically there was some evidence for it. And it actually occurs at a rate of about 1 in 10,000. Most recover fine, but there are some with sequelae.

Dryvax is no longer available. The ACAM2000 has been licensed, is in the stockpile, but also MVA vaccine is in the stockpile. It is not yet licensed.

The last slide, I think this experience amplifies the issue of what constitutes sufficient estimated risk to the general population to justify studies in children for

countermeasures. And I do support the concept that FDA has pushed, the pediatric rule, that there is a need to study vaccines and drugs in children when there is anticipated use in children. But the difficult discussion that I think you should have is this latter part: how do you estimate the potential use?

Thank you.

DR. WAGNER: Thank you. That is very helpful, Dr. Halsey, yes.

And our third speaker I am pleased to introduce is Dr. Ruth Berkelman, Director of the Center for Public Health Preparedness and Research and Rollins Professor at the Rollins School of Public Health at Emory University. Dr. Berkelman is Board-certified in pediatrics and internal medicine, and after serving with the CDC for 20 years in the U.S. Public Health Service, she retired as rear admiral in 2000. While at CDC, Dr. Berkelman served as the Deputy Director for the National Center for Infectious Diseases.

She is a member of the Institute of Medicine and the American Academy of Microbiology. She has served on the National Academy's Board for Life Sciences, the National Biodefense Science Board, and as Chair of the Public and Scientific Affairs Board of the American Society of Microbiology. She is currently the Acting Chair of CDC's Board of Scientific Counselors for Infectious Diseases.

Ruth, it is always good to be with you in Atlanta. It is a delight to have you here in D.C. and be with you here.

DR. BERKELMAN: It is an honor to be here today with you. I am actually very gratified that this distinguished group of individuals -- and you are -- is taking this on, and you are taking it vigorously and thoughtfully.

The Commission has been asked to consider whether there are ethical grounds to proceed with safety and immunogenicity trials of medical countermeasures in children. We face the tension that arises when potential public health and societal benefits of research are juxtaposed with some risk to clinical participants who would be expected to receive little or no benefit from the research. And to make matters more complex, these clinical participants are children in this case.

And perhaps it would be helpful to see the issue at hand today within a broader context. The ethical framework guiding scientific research is primarily aimed at studies involving individual participants and assessing the potential benefits and risks to these individuals. If we rigidly adhere to guidelines developed for such studies without consideration of the societal benefit and risk, then the best decisions may not be made.

The issue facing the Commission today highlights the need for greater consideration of an ethical framework to guide research that may pose a risk or benefit to the population and society and may or may not involve human participants. There are an increasing number of scenarios in which the current ethical framework may be inadequate. For example, there has been relatively-less attention to the ethical review of life science research conducted in the laboratory and not involving human participants, but that may pose a substantial risk to society.

Controversy over potential risk to a population recently erupted over research on H5N1 influenza virus, a virus known to be highly lethal in humans but easily transmissible only in birds. The research sought to make the virus more transmissible among mammals. It did not include human participants, and it received no ethical review

before it was initiated.

In another case, individual participants in research may have a potential benefit that greatly outweighs potential risk to them as individuals. And the greater risk may actually be borne by the population. Today we are faced with the opposite issue in which society would benefit and individual participants have most at risk.

All of these scenarios share a need for consideration of societal risk and benefits. Some organizations have made significant inroads into considering these societal issues and research. Yet, I submit scholarly assessment and training of researchers in the ethical conduct of research has generally not focused on societal benefit and risk. And the Commission may want to consider the need for a broader ethical framework that explicitly considers societal risks and benefits as well as individual ones.

I will now confine my remarks to the issue of research that would involve testing medical countermeasures in children. It is recognized that children participating in such research would be faced with some potential harm, with little expectation of benefits. So, why should such research even be considered?

We start with what is public health and what is public health's responsibility. The Institute of Medicine report defined public health as "what we, as a society, do collectively to assure the conditions in which people can be healthy." In the event of a catastrophic event, the government is responsible for assuring that society continues to function and that the government remains stable. Protecting the public's health and welfare is an essential component of its responsibility.

Public health officials may rely heavily on non-pharmaceutical measures to

protect the public's health in many crises. In some circumstances, such as a widespread anthrax release, utilization of medical countermeasures may be urgently needed.

Due to its responsibility to protect health, and with its best assessment of threats, the government has put numerous resources into developing medical countermeasures. The development and stockpiling of these countermeasures does not translate into an ability to utilize them during an emergency. The information and infrastructure needed to be able to utilize medical countermeasures during a catastrophic event is frequently, if not consistently, underestimated.

So, a vital question is, what is the minimum information needed for the government to distribute a medical countermeasure for use in children at the time of an event? It is important to recognize that public health is used to dealing with scant data in its decisionmaking during catastrophic events. The public accepts greater risk during these events than during routine circumstances.

Public health, however, is not likely to be able to deliver a countermeasure without knowledge of relative safety or potential effectiveness, what dose. There is a huge difference between limited data and no data. The government does not need the extensive testing that would be done for acceptance of a routine vaccination in healthy babies. The sample size should be only enough that there is some assurance that the vaccine may be beneficial at a certain dose and that severe outcomes are not common.

Study design would also be important. Trials conducted pre-event would be best if initiated with older children who can assent, and the study results of which could inform any subsequent testing in younger children.

In the absence of data, the response to a major event would likely be quite confused and ill-informed and may undermine not only the health of many children, but also the public's health and well-being of the general community.

Data that are quite limited can still provide a practical basis for moving forward expeditiously. There is a very pragmatic streak in most public health practitioners. It is particularly required when faced with the need to make sound decisions quickly with limited data.

An important issue is that medical countermeasures are all different. A green light for testing one countermeasure in children is not a green light for testing other countermeasures in children. The societal benefits and individual risk of testing these countermeasures need to be considered on a case-by-case basis. The threat, the potential benefit of the testing to public health decisionmaking, the consequences potentially of not doing so to children at large, and the risk to the children who participate all need consideration.

Other avenues of acquiring the minimum data should be explored before proceeding. Can the testing be done in less vulnerable populations and extrapolated to the pediatric population? If no testing were done for a countermeasure pre-event, could necessary data be rapidly acquired during an event through proposals that are preapproved, they are ready to go? The effect of a delay in the distribution of potentially helpful countermeasures to children and a significant increase in difficulty of conducting research during an event must be considered.

If the decision is made to proceed with a trial on a countermeasure pre-

event, we should openly acknowledge that the well-being of individual children enrolled in such a study is being put at some risk, and we should share the reasons and ethical grounding for doing so. Both a societal and individual risk must be considered.

The challenges are really daunting, and the careful deliberations you are seeking today are part of meeting that challenge. And I want to thank you for the opportunity to be here today.

DR. WAGNER: Ruth, thank you for those thoughts. In fact, thanks to all three of you.

The floor is open. Nelson, do you want to begin?

DR. MICHAEL: Yes. My question is for Admiral Berkelman, if I can call you that.

DR. BERKELMAN: Or Ruth.

DR. MICHAEL: You will always be an admiral, though.

(Laughter.)

So, we had some discussion about what I am going to ask you in a previous meeting. So, I think I will go right to the heart of the issue.

I thought it was very helpful for my decisionmaking -- and I run the military's HIV vaccine group, so I struggle with these issues a lot. We essentially do research around the world with experimental vaccines in adults, knowing that eventually, once there is a licensed vaccine, we would want to deploy it, obviously, in pre-adolescents, especially in Sub-Saharan Africa. But, for the most part, the clinical equipoise still at this point is that we don't feel that we have enough data to be able to do studies in children,

although that, hopefully, will change at some point.

You talked about study design pre-event, and this also goes to some of Dr. Halsey's comments about using diluted versus undiluted vaccine. And especially you began to divide, I gather you were dividing children up into older children who would still be under 18, but would be more in an area where assent would be closer to consent, although not legally at that point yet, but at least ethically you are closing in on that.

Let me see if I could carry this one step further. If there were to be pre-event studies done with anthrax vaccines, I think that you would probably want to do, from a clinical standpoint, you would want to do dose finding kinds of experiments to see if you could do immunologic bridging to spare doses for lots of reasons, for safety reasons as well as for extending the ability to take a limited amount of vaccine and to distribute it to a greater number of people.

Do you think for your clinical decisionmaking it would be useful -- yes, it applies to Commissioners, too (referring to the buzzer) (laughter) -- whether or not it would be useful to consider doing some of these pre-event studies in geographies of the United States where, if there were to be a catastrophic exposure with malfeasance by anthrax, to actually test or consider testing in geographies where the attacks would be more likely to occur? And by that, I mean suburban Washington, D.C., or downtown New York City compared to rural Kansas.

DR. BERKELMAN: I think you are touching on some really important issues here. One is the age where you would creep down and can extrapolate further down. You can use the adult data to extrapolate to teenagers, if you will. And you start with the

lower doses, as Dr. Halsey mentioned.

The issue of geography, we certainly have in this country identified some areas at higher risk than others. So, it seems to me that would be a very reasonable thing to do, is to include that as well as a way to potentially identify some targets.

Again, I am interested in your group's thoughts on this. But we have spent considerable effort saying some cities are at higher risk than others of a major release. And these cities would need a lot more coverage, if you will.

DR. HALSEY: I would just comment that, given what we have learned about bioterrorism and terrorism in general, surprise is usually the factor that everybody is looking for. So, if we were to guess as to which cities would be the most likely, they would probably become the least likely. So, I would be skeptical about anybody's ability to predict where these things may occur.

But, also, let's take anthrax, for example. There is anthrax that does occur in nature in Texas and some other locations. If there were to be studies, and anthrax would be a lot easier than smallpox, I wondered whether they could be done in a place where the agent occurs naturally.

I was involved in the study of Argentine hemorrhagic fever vaccine in Argentina. That has never been studied in children, but if it were, it could be studied in that population where there is at least a potential for risk.

DR. WAGNER: Yes, Ruth?

DR. BERKELMAN: I just wanted to mention that at one point there was some consideration given to studying this in Russia, some of the Eastern European states,

because there is a risk in humans, unlike in the United States where there is relatively-low risk to anyone from naturally-occurring anthrax. It is there, but it is pretty low.

DR. WAGNER: Amy?

DR. GUTMANN: There are facts that are very hard; indeed, it has been impossible for us to get answers to. The most important one perhaps is the government's estimate of what a probability of an attack would be.

In the cases that we have before us -- this is why case studies are both important and actually very difficult in this case -- there is no example that has been called to mind in which the potential hasn't also been an actual in some sense. So, polio vaccine, polio was known. There was the risk, the real, not hypothetical risk of polio in the population. On top of that, it is communicable.

So, do any of you have something to say about how one weighs, which one has to weigh in this case, known risk which we have on testing anthrax -- we know it is above minimal -- versus totally unknown. At this point, no government agency has been willing to make public what their estimates of risk are of an actual need for the vaccine.

That is one question. The other question is just simple. Why wouldn't one start, as several of our previous presenters suggested, why do we have on our table testing safety in children when several of our presenters have said we could start with testing -- there is an absence of further tests on younger adults and refinement of dosages on adults. Why wouldn't that be the first place one would start and see what one learned? There is not that much known right now about that.

DR. WAGNER: So, the first question is about the motivation. Why

bother at all if we don't have a genuine concern about risk?

DR. GUTMANN: By the way, we still have a job of discussing the framework of how a decision would be made. But since we also have been asked whether we recommend the testing of children in the case of specific countermeasures not only, but including anthrax, my questions are to that specific question.

DR. WAGNER: Dr. Halsey?

DR. HALSEY: I personally would favor the approach Dr. Berkelman mentioned, and that is preparation of protocols to be able to study a multitude of agents in an event of bioterrorism, keeping those protocols renewed and revised, because new information does become available, and ready to go. Because as soon as you spend a lot of money and time and expose children to some risk, no matter how big it is, that may not be associated with any benefit, and most likely would not be associated with any benefit, I really think, because of the multitude of agents and interventions that are out there, it makes a whole lot more sense to prepare the protocols.

You are going to have to fund -- you are not the right people -- but somebody has to fund the development of those, keeping them up ready to go quickly and get the coordination between the agencies that are necessary. That is the right approach as a general rule. There may be some exceptions where you would need to go ahead.

But if you look at all of the interventions, the cost of trying to develop enough numbers, and you really do need -- I study safety -- you need large numbers in order to really get an assessment of safety. And if you are going to use something for the entire population, studying 40 or 100 or 200 or 1,000 is really not enough to rule out the less-likely

events.

DR. GUTMANN: Thank you. That is very helpful.

DR. WAGNER: Well, we haven't heard from Dr. Resnik.

Yes?

DR. RESNIK: I would just like to second that suggestion. At the NIH, we have been looking at developing emergency IRBs and also emergency protocols. We have looked at it specifically in terms of public health disasters.

And basically, what we do is we have a protocol already approved by, the idea at least is that you would have a protocol already approved, a generic protocol already approved by the IRB that just basically in very broad terms describes sort of what you are planning to do.

And then, when something happens, then you implement something under that protocol that can be done pretty quickly; quickly develop what your plan is to go do some testing, or whatever. And so, it gives you more of an ability to do these things on an ad-hoc, emergency basis. I am very leery of trying to do something well in advance of some actual event.

DR. GUTMANN: That has the added cushion in this case that we know that antibiotics could be initially an alternative response before the vaccine, not that antibiotics are without the risks, but they are a more known factor in children.

DR. WAGNER: Dr. Berkelman, did you have a --

DR. BERKELMAN: Yes, I just want to follow up and say, again, I think is a reasonable alternative for many countermeasures. Is it a reasonable one for all? I have

actually gone back and forth in my own mind on this. I have thought about the fact that, if you put this emergency, these protocols at the time of an event in place, if you have no data to begin with, essentially, in children, you are starting with what dose in the event? I mean, you can't start with dilute doses and then work your way up because you don't have the cushion of time, and you are probably starting simultaneously in all age groups.

So, I would just caution that, again, it is case-by-case, and think about some data versus no data. Because, for example, in the case of smallpox, we had quite a bit of data on children before that trial was ever anticipated. That is not the case with anthrax, for example, where there is no data, and antibiotics do pose problems.

DR. WAGNER: I have got Christine, Dan -- oh, you had a second question?

DR. GUTMANN: There are too many other people.

DR. WAGNER: Okay. Christine, Dan, and John.

DR. GRADY: Thank you all very much.

I would like this notion of case-by-case assessment, but I would like to talk further about what the things that you would assess should be. Dr. Berkelman listed a bunch of them: the threat, what we know about a threat; the benefit to the society of having some data; the risks or consequences of not testing, and the risks to the children.

So, I guess one question is, can you think of others that should be on this list? And a specific question is, what is not on that list is this notion of how old the children are and the relevance of their ability to understand or assent to the research that is being proposed.

Because I have often wondered, in the case of anthrax vaccine, for example, and the smallpox data actually made me think this is even more important, it seems like we are looking at safety with the expectation that the immune system of younger kids is more different from adults than the immune system of adolescents, right? So, maybe we should skip the adolescent study and just do younger kids, unless assent is an important part of this list.

So, two questions. Should there be other things on this list, and what is the role of assent, if any, in this assessment?

DR. WAGNER: Ruth?

DR. BERKELMAN: I am sure there are other things that should be on that list, and you have named one.

I want to actually get back to your question about the threat and is it a hypothetical threat. I think most people who, not most, many of us believe that the threat is real. It is not quantified. It is not predictable, as Dr. Halsey said. But it is a real threat.

And also, the threat does change depending on which issue you are looking at, what event is more likely. But even though we get some issue of relative risk, we don't get the numbers, and that's what you are seeking. And that is what we all are at a loss for.

The issue of going directly to younger children, I will be interested in what Dr. Halsey has to say, but I would still prefer going down the scale gradually, with what I know of vaccine safety and looking at immunogenicity, than just starting with the younger children.

DR. GRADY: And trading off possible risk to the children for the value of

the knowledge that you are getting?

DR. HALSEY: Yes.

DR. GRADY: Sort of?

DR. HALSEY: Yes.

DR. WAGNER: Dr. Halsey?

DR. HALSEY: Let me address just two of the issues and questions that you raised. One is moving down in age. I have studied vaccines at all of the phases. And especially in phase 1, FDA has almost always required to move down in age. Sometimes you can skip some age groups, but I don't know of any vaccine that has been successfully licensed that went from adults immediately to the youngest age group where it would be used, like infants. Almost always there is some intermediate testing, and for good reason, because there are differences in safety.

With regard to vaccines, there's a half-a-dozen of them that have higher rates of adverse events in very young children than they do in older children and in adults. Certainly, you would want to minimize the discovery of a new adverse event for an agent or a vaccine which you may never need. So, I think almost certainly the FDA would insist upon a stepwise moving down, but you can skip some ages.

The other thing is that it is really not possible to give a complete and detailed answer to your first question about what needs to be included. There are so many differences between the potential bioterrorism agents that it really would require an expert panel, who really has the knowledge about the infectious agents and the preventive measures, to come up with what you really need to put into the protocol. I couldn't come up

with, even in a week's time of studying hard, all the details that you would want there. You would need to put together panels of experts to do each one.

DR. WAGNER: Dan?

DR. SULMASY: Dr. Berkelman wisely observed that all countermeasures are not the same. And Dr. Halsey told us about the risks of vaccination with smallpox, and they were pretty substantial.

So, I was wondering what we know about the risks of the vaccine for anthrax. We have some data at least from the military, and some of those are post-marketing surveillance, which are not necessarily as reliable perhaps as the pre-marketing data. So, what do we know? Is it as dangerous a vaccine as smallpox? Is it less so? What do we know in adults?

DR. HALSEY: I have served on the Safety Monitoring Board for CDC in studies they conducted in the civilian population. The military has far greater experience, and I have reviewed some of the information there.

The simple answer is that anthrax vaccine is not associated with anywhere near the level of risk of adverse risk that smallpox vaccine is. It is an inactivated vaccine. There are local reactions. There were hypothesized many other serious adverse events, the vast majority of which have not panned out in careful studies. But I didn't come prepared to really give you a precise answer in terms of what the risks are, but there are no substantial risks associated with the anthrax vaccine, although there are a couple of things that are further under investigation by the army right now, but rare events. But it is a totally different ballpark, a totally different vaccine and game.

DR. WAGNER: John?

DR. ARRAS: Now I am very confused.

DR. WAGNER: Do you want me to have somebody else go?

(Laughter.)

DR. ARRAS: So, I can appreciate that there is a big difference between the side effects of an anthrax vaccine and smallpox vaccine. Okay? I get that.

But I just heard you say that you don't see any major side-effect issues associated with the anthrax vaccine, which prompts me to ask, well, then, why are we talking about this as something that is categorized as being more-than-minimal risk that requires a review by a panel of this sort? Why is this not, you know, something that could be handled on the local level by an IRB?

And if, indeed, there is good reason to bump it up to this sort of a national commission, that means to me that there is more than minimal risk. And so, the question that I was originally intending to ask here before my confusion set in was, if it is more-than-minimal risk, how much more? I mean, you know, is it a minor increase over a minor increase in minimal risk or is it a major increase over minimal risk?

DR. GUTMANN: We should just say that John isn't confused because he tends to be confused.

(Laughter.)

DR. ARRAS: No.

DR. GUTMANN: But he is confused because we have not gotten consistent information on this. We have been told it is certainly more-than-minimal; we are

told now that it isn't.

DR. ARRAS: Yes.

DR. GUTMANN: So, the amount of information and the consistency of it that we are getting is peculiarly inconsistent.

DR. ARRAS: Yes, and I ask this question because I have really been vacillating on this issue. You know, I have changed my mind two times already on this. First, I started out being very skeptical, very much opposed to this research. I had a long talk with my pediatrician friend Alan Fleischman who softened me up a bit on this, you know, and I was really beginning to think that there may be nothing sacred about something a bit above a minor increase over minimal risk.

But, then, I was reading some other materials prepared by staff that really shocked me in terms of the possible risks of an anthrax vaccination. So, this is a really important issue for how we think about this, and I really would appreciate some clarity on the facts.

Dr. Halsey?

DR. HALSEY: Yes, I would be happy to elaborate a little bit and try to address the concern.

I agree with you that there is a zone that exists that going from a little bit above minimal risk to like the risk from the smallpox vaccine, which I think is much more, and I don't think there is an adequate gradation that is brought into play.

Vaccine testing -- and I have been involved in the testing of a number of different vaccines that are now routinely used in children -- but at the beginning, before the

vaccines have been studied, the IRBs and the FDA and everybody else has always determined that it is greater-than-minimal risk and the risk is unknown.

Because when you give a vaccine, the live vaccines are different than the inactivated vaccines. We have a number of live vaccines. I can talk about those, if you want. Anthrax is an inactivated vaccine. So, there is no agent that is going to replicate or going to cause the disease in any way.

But, yet, we have to mount an immune response in order to be protected against the potential infectious agent. The immune response itself can in rare individuals cause undesirable side effects, and it may be unpredictable.

So that we do see rare cases -- and when I talk about rare, 1 in 100,000, 1 in a million -- of serious complications from some of the vaccines that we do routinely use. But you don't know in advance -- I mean, you are being asked to answer in advance how much of, and you are asking me how much of a risk, of immune risk. And the truth is, until the vaccines have been studied, and studied fairly widely, you don't know for sure. You don't know that answer, and that is the reason why the studies are done in a carefully-staged, progressive manner.

I can share with you, if you want the time, half-a-dozen examples of adverse events that were not appreciated at the time the vaccine was put into general use. But, then, after you have immunized hundreds of thousands or millions, then you have enough exposures to detect the rare adverse events.

DR. ARRAS: But I take it that we are being asked to pass judgment on a much smaller study that I gather is targeted primarily at dose response rather than safety,

right?

DR. HALSEY: That is correct.

DR. ARRAS: Yes.

DR. HALSEY: You will be monitoring safety anyway, but that is really what you can answer with small studies.

DR. WAGNER: And presumably, there are larger study safety questions, safety data available from the military's experience?

DR. HALSEY: That is correct.

DR. ARRAS: Can I have one additional follow-up? On this interesting issue of launching the study during an event rather than before, there are obvious advantages to that because, then, you are talking about a group of people who really are already exposed, right? They are at risk?

DR. HALSEY: Or potentially going to be exposed.

DR. ARRAS: They are potentially, yes. So, there is more benefit on the horizon there.

But this is a technical question. What is the likelihood that that kind of a study launched during an event could yield the information that we are looking for in an expeditious way, to give the society the information that it says it needs?

DR. HALSEY: We have some newer methods, and Dr. Berkelman must have been involved in some of these, especially following the anthrax exposures where there was a lot of problem with communications. But there are newer methods that you can, in fact, actively track individuals on a large scale who are participating in such a situation.

And I think if there were to be an anthrax exposure now and people were to be giving drugs, ciprofloxacin or whatever, I mean, it would be much simpler now than it was a decade ago to bring those people involved, into studies where you could track them on a daily basis and look for side effects and put it into a database. We have actually done something like this with influenza vaccine on a large scale.

DR. ARRAS: But I guess, again, the question is, could that data be adequately analyzed --

DR. WAGNER: Turned around fast enough to be --

DR. ARRAS: Yes, yes.

DR. HALSEY: You can do it in real-time.

DR. WAGNER: Ruth?

DR. BERKELMAN: We have a number of instances in which it has not been able to be turned around as fast as we have needed it or wanted it.

And I agree with Dr. Halsey that we have much better ways to track people and be looking at safety of things over time. But to actually have no knowledge of the immunogenicity upfront is going to be somewhat problematic if there is an anthrax release.

And I think the reason it actually was brought to this Commission is because there are a lot of people who really would rather consider or would see the risk as zero or close to zero until it actually happens, and then they are willing to throw everything at it. But it is difficult during an emergency to get some of the data that you really want.

On the other hand, I have got to share I would not want to see huge trials of children right now when we don't know the risk and the threat.

DR. GUTMANN: Who would the children be who you would like to see trials of? I mean, give me some sense of who would likely to be the children?

One of the things, we are struggling with a lot of facts in this case. For example, we were told that we still don't have dose responses for adults the way you would ideally want before you started doses for children.

And we were asked because there was a group that recommended that children be tested pending an ethical assent by this group. Well, I think it is our responsibility -- I am asking you; I am just stating this; I am floating trial balloons here. That we should first recommend dose responses for adults before you test children for doses, and there isn't some magic difference between an 18- and a 21-year-old. I mean, there is a sliding scale here. So, you could do dose responses for young adults, and we would at least get more information; that is, you all who are in the position would get more information.

And then, also, preparedness, as we know from other catastrophes that happened, like Katrina, preparedness has a lot to do with non-medical preparedness as well, which is preparedness on the ground to deliver, which you all, Ruth has written about as well.

But just on the adults, why not do dose responses in adults first?

DR. HALSEY: I can give a very quick answer. If the vaccine is licensed, dose responses have already been done, and they have been done for anthrax.

DR. GUTMANN: Okay. Okay.

DR. WAGNER: So, we have it for adults.

The final question is Lonnie's.

MS. ALI: Thank you all for a very enlightening presentation.

Just to follow up a little bit with what John said, I was confused as well because we thought that there was more than minimal risk. That was one of my questions.

But another thing I wanted to ask, because one of the things we were talking about when we were talking about alternatives to this, actually, giving or exposing children to risk, regardless of whether it is young adults or younger children, Dr. Berkelman, you said something about the antibiotics having issues and causing problems. And that is one of the things we were talking about here as a Commission, is rather than present these risks to children, expose them to these risks, to use a course of antibiotics.

And I would like to hear from all of you or maybe just you, Dr. Berkelman, whoever can offer the best insight into this, why you would think that a course of antibiotics would not be viable in this situation.

DR. BERKELMAN: A course of antibiotics would be needed, and it certainly would be utilized. And it also is dependent. How much of a problem it would be would be dependent somewhat on how widespread the release was, whether there was a happening in many places at one time, whether there was consideration that was happening over time very quickly.

But antibiotics themselves do have problems. I think this Commission has been informed of some of them. Compliance is one, getting the delivery out.

Some of this is the exposure later, because you would still need antibiotics immediately. The vaccine would not be delivered immediately and get immunogenicity

immediately.

So, I think antibiotics will still be a major course of action. Do you have enough? For how long? What is your recourse?

The vaccine would be, if you will, a co-dependent measure. It would not be one or the other. It would probably be both in the setting of a very large-scale release. But you would not include the children if you did not have -- until you had some data, is my understanding; that with no data, it would be hard to proceed.

If you will indulge, I want to get to this issue of minimal risk because my sense -- and again, I would lean on my colleagues here as well -- is that if you proceeded gradually down in age and you looked at low doses, you would have less risk, minimal-over-minimal risk, if you will, than if you proceeded today to go with a fairly-sizable dose in a toddler. I am not so sure that I would agree with that, and I would not want my toddler tested today.

It is a different issue if you have got all these data going down gradually and looking at it.

DR. GUTMANN: Could you just say, could someone answer my question about who -- suppose there was a preceding, a pre-event with testing on a small number of children. Who would be chosen?

DR. BERKELMAN: Well, I have heard General Parker's answer. I am looking at parents who are informed of the risk, of the threat, and there are a number out there. There are people working in the anthrax vaccine area.

And I am talking about anthrax.

DR. GUTMANN: Yes.

DR. BERKELMAN: And yet, I think the issue is really general countermeasures. It would have to be entirely voluntary. I mean, nobody would be chosen, if you will, outside.

And would a parent do that? Would they consider societal good? Would they consider risk? And I think they would because, even to think about your teenager, you would be thinking about that. And there are instances in which children have been known to do things for others' benefit. It puts them at somewhat-more-than-minimal risk.

It is difficult, though. I don't think there is an easy answer here.

DR. GUTMANN: Could I just pursue it? I am asking just to give me and others a sense of how the government would go about, who the government would approach and ask to be tested.

There is experience here, and I want to know whether the experience gives us the groundwork for knowing and, if so, who? Because you don't do a lottery. What do you do?

DR. WAGNER: Dr. Resnik has an --

DR. RESNIK: Well, if this were to be done in our IRB, in our area, there would be advertisements that would go out to the public, solicitations to the public, notices in medical clinics and things like that.

And my worry, my concern is that the parents that needed the money the most, if there were some money involved in getting your child in the study, would be the ones most likely to be in it.

DR. WAGNER: Dr. Halsey?

DR. HALSEY: I gave an answer in my review 10 years ago for smallpox vaccine, and I think the same would apply for anthrax and some of the others. I think you might start with, for the small studies, children of parents who have already gone through the process of getting educated about the vaccine and receiving the vaccine. I think that could apply to a number of the different agents where the vaccine is in use.

DR. WAGNER: Dr. Berkelman, anything to add to that?

DR. BERKELMAN: No, I agree with Dr. Halsey, and I agree with Resnik. I would not make money the motivator here. This has got to be people who are well-informed.

DR. GUTMANN: Does that mean you would recommend against any payment? And does that mean you would recommend against advertising as opposed to going to military families who have had the vaccine and --

DR. WAGNER: CDC employees?

DR. GUTMANN: -- CDC employees, and asking them?

These are serious -- they are not just practical -- they are serious ethical questions in this case.

DR. RESNIK: I wouldn't recommend against no money. I mean, people have to pay for parking or whatever like that, obviously.

DR. GUTMANN: Yes.

DR. RESNIK: But nothing where money would be --

DR. GUTMANN: That is reimbursement.

DR. RESNIK: -- a motivating factor for sure.

DR. HALSEY: The same answer.

DR. WAGNER: You have given us a lot to chew on. And given that it is lunchtime, we need to get to that.

(Laughter.)

But, no, your comments have been most stimulating. We know where to find you, because we may have some followup questions.

To all three of you, Dr. Resnik, Halsey, Berkelman, thank you very, very much for a great session.

(Applause.)

(Whereupon, the foregoing matter went off the record for lunch at 12:15 p.m. and went back on the record at 1:13 p.m.)

