



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

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Meeting 10, Session 10
August 2, 2012
Washington, DC

DR. WAGNER: Gentlemen, welcome. To our panelists, we have been eager -- I was going to say "agonizing" (laughter) -- but we have been eager to have more facts, more information, and to zero-in on what is the key information needed for decision-making regarding pediatric medical countermeasures research. And we are hoping these speakers are going to help inch us -- in fact, feel free to move more than inch -- in this conversation, gentlemen.

We will begin with Dr. Paul Thompson. Dr. Thompson is the W.K. Kellogg Chair in Agriculture, Food, and Community Ethics at Michigan State University; well-published, over 150 journal articles and book chapters on topics such as food biotechnology and world hunger. His work in emerging technology links the values of risk to notions of sustainability. Dr. Thompson is former President of the Society for Philosophy and Technology and has served as a member or advisor to numerous boards and panels, including the USDA Agriculture Biotechnology Research Advisory Committee and Genome Canada Scientific Advisory Committee. Dr. Thompson has been a grantee of awards from the National Science Foundation, the Sloan Foundation, the Rockefeller Foundation. And we are pleased to have you with us here today. The floor is yours.

DR. THOMPSON: Thank you. It is a pleasure to be here. And I guess I should add that it was a pleasure to divert my summer and spend a couple of weeks learning about anthrax.

DR. WAGNER: Ah, teach us.

DR. THOMPSON: George Sternbach begins his history of anthrax by quoting passages from Virgil that describe an ancient plague in sheep and cows, now presumed to have been an outbreak of the anthrax pathogen. Anthrax is, in fact, one of many natural pathogens that affect both agriculture and human health. My testimony is intended to provide the Committee with background information on the way in which plant and animal diseases are approached within the context of agricultural science and veterinary medicine.

My expertise is as an ethicist whose career has been devoted to the study of ethical issues as they arise in the context of agriculture and livestock production.

There are two main points of focus that I would like to emphasize. First, agricultural production and food consumption are potential sources of exposures to diseases such as anthrax, as well as conduits between human and animal populations that can affect the transmissibility and virulence of pathogens. The risk profile of these pathogens that would be derived from an exclusive focus on human medicine or bioterrorism is, thus, potentially incomplete. Second, a straightforward appreciation of the ethical significance of the interaction between agriculture and human medicine or public health is constrained by institutional barriers that limit the interaction among scientists and ethicists working in these respective fields.

So, first, diseases of plants and animals can pose hazards to human beings. The routes of exposure include ingestion of pathogens when diseased organisms enter the food chain, forms of contagion associated with physical contact between diseased plants or animals and agricultural workers, and long-distance transport of pathogens that originate in food and agricultural production through wind and water. In addition, agricultural plants and animals represent a possible route between disease processes that are uncontrolled or endemic in wild populations and the human population.

However, agricultural production operates under procedures and regulations that have been developed to control risk to human populations. Indeed, these procedures may be so successful that people outside of agriculture and agricultural science may not realize how prevalent agriculturally-based hazards have been for people in the past.

Nevertheless, it is crucial to understand that ordinary crop production and animal husbandry have the potential to vector existing pathogens and to provide a context in which evolution of new pathogens can occur. Post-harvest contamination of food by microorganisms, such as *E. coli* 0157:H7,

Salmonella, and Listeria, is regarded as the most serious human health issue for the agricultural supply chain in industrial societies. These organisms do not present as disease in livestock species, but can contaminate food through movement of animal fecal matter through agricultural fields, water supplies, and packing facilities. Some plant diseases, such as Aspergillus, Fusarium, and ergot fungi, are sources of food-borne illness. Inspection, monitoring, and regulation have sharply curtailed the spread of infectious disease from plants and animals to humans. Nevertheless, supply-chain transmission from animals to humans can occur, and anthrax is a case in point.

The human deaths from anthrax in the Soviet city Sverdlovsk during 1979 were originally presumed to have been caused by consumption of anthrax-infected meat. Only in 1996 did a review of the clinical and epidemiological evidence, which included a number of infected sheep, indicate that aerosol released from a military research installation was the likely cause of the Soviet anthrax deaths. One of the more bizarre instances of supply-chain transmission occurs when the hides of anthrax-infected animals are harvested, as they occasionally are in less-tightly-regulated countries. Bongo players have apparently contracted cutaneous anthrax from their drums, and the deaths of drum-makers in the United Kingdom have been attributed to inhalation of anthrax spores while handling hides.

Although contagion from livestock to humans is not generally believed to be a major issue in the United States, agricultural production practices necessarily bring human beings into direct physical contact with animals and, as such, there are opportunities for transmission across species lines. Indeed, our word vaccination is derived from a Latin root that means "from cows", owing to Edward Jenner's 18th century derivation of smallpox vaccines from the cowpox virus known to infect dairy maids.

The large-scale mechanization of agriculture reduced the historical amount of physical contact significantly, and the sheer percentage of national populations engaged in agriculture has declined from perhaps 80 percent in Jenner's day to approximately 1 percent in the United States today.

Human contact with agricultural animals is a perennial concern for the control of fast-mutating viruses that can switch hosts rapidly. Veterinarians monitoring avian influenza have been particularly attentive to the potential for crossovers between poultry and migrating flocks of wild birds. In addition, contact between animals and humans is important to human health in less-developed countries, where it is estimated that each cow infected with anthrax may result in up to 10 human cases of cutaneous disease.

Anthrax itself is not an important source of loss in U.S. livestock herds. Effective animal vaccines have long been available -- I will add that those are live vaccines, unlike the vaccine being discussed here -- though they are seldom used by most U.S. producers. Incidence of anthrax in livestock is generally associated with extreme weather events, such as drought and flood. Both have the potential to mobilize dormant spores from the soil, increasing the potential for exposure to agricultural animals. Spores remain potent for many years, and in some areas present-day cases of anthrax in cattle cluster along trail routes that were active in the 19th century.

Outbreaks of anthrax can and do occur in wild animals, especially when weather conditions allow for dormant spores to become airborne. It is, thus, reasonable to speculate that climate change might alter the current situation. Although I did not find empirical research on such a scenario, an increase in droughts or flooding followed by wind-borne movement of soil could theoretically lead to human exposure from naturally-occurring anthrax spores. Such an eventuality would also create new issues for livestock producers.

Regulatory oversight for anthrax and the anthrax vaccine occurs at the state level, and though reporting of incidences is required everywhere, other regulations vary considerably from state to state. Some states require that the vaccine be distributed by veterinarians. And in states where anthrax has not been observed for many years, even use of the vaccine may require approval from the State Veterinarian or Animal Health official.

The USDA's APHIS National Surveillance Unit collects reports of anthrax cases through the National Animal Health Reporting System. Existing procedures for slaughter and meat inspection in the U.S. make it exceedingly unlikely that gastronomic exposure would ensue in the event of an outbreak, though the emergence of alternative supply chains can theoretically pose new challenges in this area as well. In general, veterinarians' training and experience with the disease in cattle, bison, sheep, and horses should be regarded as a resource, should future exposure to humans occur from any source.

There are, however, numerous differences between the public health context and the way that plant and animal diseases raise ethical issues in the context of food production. The ethical responsibilities of agriculture reside, first, in ensuring an adequate and robust supply of calories and, second, in terms of ensuring the safety of the food supply.

The economic viability of the farm household is also crucial, owing to the prevalence of farming and animal husbandry among those living in extreme poverty around the globe. Indeed, I would add as a global issue approximately 80 percent of the people living under the World Bank's standard of extreme poverty -- that is less than one euro a day in income -- derive their living from some source associated with agriculture. So, in my little corner of bioethics, the phrase "vulnerable populations" connotes something rather different than it does in this context. The economic viability of the farm household is also crucial in the U.S. as well. Although Europe and Japan successfully implemented significant improvements in their ability

to monitor animal disease in the wake of the mad cow and foot-and-mouth outbreaks of the 1990's, small-scale beef and dairy producers in the United States have lodged strenuous protests against such measures. Thus, in many cases the ethically-appropriate strategy for controlling disease in an agricultural context is to minimize economic impact on producers. This may involve culling animals or destroying diseased crops rather than taking measures to restore them to health. Cost concerns also apply to preventative therapies such as vaccination. For example, although vaccinations for foot-and-mouth disease exist, they are not widely used, even in some areas where this highly-contagious disease is known to be prevalent.

In view of the relatively-undeveloped interaction between agriculture and human bioethics, it is simply not clear as to whether these ethical concerns, which are deeply relevant in the context of developing policies for disease management in the food system, have implications for the deliberations of the Committee. Thank you.

DR. WAGNER: Thank you.

Next, we will hear from Dr. Richard Gorman, who is the Associate Director for Clinical Research for the Division of Microbiology and Infectious Disease within the National Institute of Allergy and Infectious Diseases. Dr. Gorman also serves as the head of the Pediatric and Obstetrics Integrated Program Team for the Office of the Assistant Secretary for Preparedness and Response within the Department of Health and Human Services. He has served as the Director of the Pediatric Emergency Room at the University of Maryland Hospital; as Chair of Pharmacy and Therapeutics Committee of University of Maryland Hospital; as a member and a Chair of the American Academic of Pediatrics Committee on Drugs, and on the Pediatric Advisory Committee of the FDA. He has also practiced pediatric primary care in suburban Baltimore for 20 years.

Welcome. It is good to have you with us.

DR. GORMAN: Thank you for that introduction. And thank you, Dr. Gutmann and Dr. Wagner, and other members of the Commission, for the invitation to share my perspective. I come before you in my capacity as the Chair of the Pediatrics and Obstetrics Integrated Program Team, the PedsOB IPT. And I will now explain what that is.

The PedsOB IPT system of PHEMCE. The PHEMCE was introduced to you by Dr. Kaplowitz, and its mission is to advance national preparedness for natural, accidental, and intentional threats by coordinating medical countermeasure-related efforts within HHS and in cooperation with the PHEMCE interagency partners. And the PedsOB IPT is to support and assist threat-based IPTs, those that deal with specific threats, such as anthrax or botulisms, with strategies for identifying, developing, acquiring, deploying, and using high-priority medical countermeasures for children and pregnant women in public health emergencies.

The task of the PedsOB IPT is to understand what is presently in the Strategic National Stockpile and how pediatric and obstetrical medical countermeasure needs are being addressed. The daunting task in front of us is prioritizing and planning to eliminate any gaps. The graphic on the next slide demonstrates how we hope to do this.

To eliminate gaps, information and data must be gathered. As information and data become increasingly abundant, the implementation impediments become increasingly smaller. In regulatory language, the PedsOB IPT hopes to move medical countermeasures from INDs to EUAs to labeled products by gathering more information. I have been asked to spend a few minutes on the Category A infectious agents. The Category A infectious agents make up a small, but extremely important slice of the threats and the medical countermeasures that the PedsOB IPT is considering.

So, what are the Category A threats? These agents are determined to pose a risk to national security. They are easily-disseminated, usually in aerosol form, or transmitted from person to person. They result in high mortality rates and have the potential for a major public health impact. They might cause public panic and social disruption, and they require special action for public health preparedness. The list of the biological agents in Category A: anthrax, botulism, plague, smallpox, tularemia, an assortment of viral hemorrhagic fevers including Lassa, dengue, ebola, and Marburg.

I have provided the Committee in the background materials with sort of a cheat sheet on the Category A agents that sort of lists them in a logical order, and I am going to go over the highlights of that sheet for you now. But I leave that for you as homework, if you wish to do it at some other time.

(Laughter.)

Anthrax is a bacteria, and the spores, as was so eloquently described, can remain dormant in dust for generations. And when the dust becomes aerosolized, it can be inhaled. Anthrax has been weaponized by multiple nations. It is easy to produce, and it is easy to get sources of anthrax. It is transmitted by the inhalation of the spores, the disease that causes pneumonia. Untreated mortality in the pre-antibiotic age was 75 percent. There are both vaccines and antibiotics available as medical countermeasures, and anti-toxins are in development.

Botulism is another bacteria. It also lives in spores. But this creates a toxin that kills people. There is no person-to-person transmission. It is through food sources. The untreated mortality is basically unknown. It works by a toxin that paralyzes your muscles and you die from suffocation, being unable to breathe anymore. Anti-toxins are available for most of the botulism toxin types. There is no antibiotic or no vaccine that has been shown or recognized as effective.

Plague is another bacteria. And when we talked about the Category A's, they have the capacity to generate public panic. This is my personal panicky one. It is passed person-to-person. If you get plague pneumonia, you can cough on someone and transmit it. And it can also be transmitted from fleas to humans from the host, the rats. The untreated mortality of pneumonic plague is about 90 percent. The untreated mortality of septicemic plague is about 50 percent, and the untreated mortality of bubonic plague is 40 percent. And you can die from pneumonia, shock, or sepsis. And this picture, which is not nearly as graphic as the ones that Dr. Halsey showed, but gives you an idea of why this is called the black death.

Smallpox is a virus. It is also transmitted by person-to-person through respiratory droplets. It can also be spread by contact. The untreated mortality of this disease is approximately 30 percent. There is no antiviral therapy at the moment. There are some in development. There is a very effective vaccine that you saw some of the complications for in an earlier presentation. The cause of death is pneumonia; skin, secondary infections where you get bacterial infections on top of the smallpox infections, and throat infections.

Tularemia, or rabbit skinner's disease, is a bacteria. There is no documented human-to-human spread. It is widely dispersed in approximately 100 mammalian species and can be transmitted from these mammals to us via fleas, ticks, or animal bites. The untreated mortality of this is actually quite low, less than 1 percent. But what makes this agent so unique, and so uniquely suited to be a potential biological weapon, is the number of infectious agents it takes to infect you. Only 10 infective particles are necessary to cause an infection that is much like severe pneumonia, severe influenza. And the cause of death, when you do die, is an infection and pneumonia.

Lastly, there is quite a group of viral hemorrhagic fevers, multiple organisms. They can be transmitted to humans by mosquitos, ticks, rodents. The untreated mortality varies by whether you get,

quote, "regular dengue" or hemorrhagic dengue. And the cause of death from the hemorrhagic fevers is generally bleeding.

As a pediatrician, I would be remiss by not bringing up the unique pediatric vulnerabilities. Children are closer to the ground. So, anthrax that lives in the dirt, if you stir up the dirt, pediatric noses are closer to the ground than adult noses. Viral hemorrhagic fevers with their multiple insects, fleas can only jump so high. Mosquitos can fly any height they want. Children breathe more rapidly and deeper relative to adults. So, anything that gets a respiratory pathogen can be more likely to be inhaled by a child than an adult. Because children are smaller than adults, less toxin will be fatal. Children explore their world through taste much more than adults do. Everything goes into the mouth for a large part of childhood. Somehow vegetables are magically excluded from this. (Laughter.) But other than that, it is just basically true. Children are naturally curious. They explore their environment, and this is a risk factor for them. They are more likely, if they see a sick or dying animal, to go and touch it or feel it, and maybe even bring it home to their parents.

For those of you who want a little bit more, these articles were all in JAMA. They were written between 1999 and 2002, and when they were talking about the threat of these as bioweapons.

In preparing to respond for a Category A response, there are several types of studies that could inform both preparation and response, studies of palatability, the routes of vaccine administration for children, liquid formulations of presently-solid materials, absorption, distribution, metabolism, and excretion, basically, dose-finding for children and pregnant women. The execution of any of these studies raises ethical concerns. I would like to spend time on just one of the other ones besides anthrax vaccine, which is a palatability study for ciprofloxacin.

Ciprofloxacin is the treatment for anthrax and pneumonic plague, or the recommended. Both cost and production constraints prevent the Strategic National Stockpile from being able to acquire adequate amounts of liquid medicine to treat all that might need it. Children and adults with swallowing difficulties will get crushed pills.

But if I wanted to study the palatability of ciprofloxacin in children, it is not the first-line treatment for any childhood infection. Palatability could only be tested in healthy children. And using the paradigm that is presently being applied to the study of the anthrax vaccine, the study would present the prospect of more-than-minimal risk with no prospect of direct benefit. And that study would need a 45 CFR 46.407 or a 21 CFR 50.54 review.

As you continue with your deliberations, I will echo one of Dr. Nelson's opening statements. We, the thought leaders and decision makers, must continue to evolve from a view that we protect children from research to a view that we protect children through research. Thank you for your attention and your thoughtful deliberation of this important message.

DR. WAGNER: Thank you very much, Dr. Gorman. I think you are going to be getting some questions also.

Our final speaker on this panel is Dr. Thomas Moore. He is Chair of the Department of Infectious Diseases for the Ochsner Health System. Dr. Moore served as a Clinical Professor and Associate Program Director for the Internal Medicine Residency Program at the University of Kansas School of Medicine on the Wichita campus, and currently serves as Chair of the Anti-infective Drugs Advisory Committee of the FDA. Dr. Moore completed his residency in internal medicine at Baylor College of Medicine and completed his subspecialty training in infectious diseases at the NIH. Dr. Moore?

DR. MOORE: Thank you. I want to thank the members of the Commission for inviting me to speak today. It is a pleasure to see Dr. Atkinson again. I have a couple of disclaimers. First of all, I am not speaking on behalf of the Food and Drug Administration. I am speaking on behalf of myself and as a representative, that is, as the Chairman of the Anti-Infective Drugs Advisory Committee. Also, the topic at hand deals mainly with research in children. I will issue a disclaimer that I am not a pediatrician, although I have been told I am very immature. So, that should count for something. (Laughter.) But, anyway, on April 2nd, 3rd, and 4th, 2012, the Anti-Infective Drugs Advisory Committee for the FDA met in Silver Spring to consider several issues related to medical countermeasures. I have been asked to speak today about the thought processes and discussion regarding the data on which the Committee relied to make some of its decisions.

So, a bit of background. On April the 2nd, the Committee provided advice to BARDA -- that is Biomedical Advanced Research and Development Authority -- regarding types of consumer studies needed to assess the proper use of the prepositioned medikit containing doxycycline to be taken in the event of an anthrax exposure. The next morning, we discussed development of the African green monkey model of pneumonic plague and provided advice regarding its relevance to humans exposed to *Yersinia pestis*, the causative agent of plague. The two sessions following that had to do with discussion of data regarding the safety and efficacy of Cipro and Levaquin in pneumonic plague in both adults and children. All of these discussions, I need to emphasize, were grounded in what is known as The Animal Rule. This is a very pivotal federal regulation. For those taking notes, it is 21 CFR 314.600, Subpart 1, which I will be happy to read again, if you would like, but that is okay. Let's move on.

The Animal Rule, on which all of these discussions were based, has four key elements. One is that there is a reasonably-well-understood pathophysiological mechanism of toxicity of the substance

in question and its prevention or substantial reduction by the product in question, that being Cipro or Levaquin.

The second is that the effect is demonstrated in more than one animal species, and these species are expected to react with a response predictive of humans, that is, unless the effect is demonstrated in a single animal species that represents a sufficiently-well-characterized animal model for predicting the response in humans.

The third is that the animal study endpoint, i.e., death, for example, is clearly related to the desired benefit in humans. Generally, this is enhancement of survival or prevention of major morbidity.

And the last key part of the rule is that the data or information on kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allows selection of an effective dose in humans.

So, with that in mind, there is one other point of which the Committee was mindful. And that is that, in supporting the application by the sponsor, that being Janssen Pharmaceuticals, which is a division of Johnson & Johnson, the sponsor being the manufacturer of Levaquin, in supporting the application, this would enable the government to distribute Levaquin in mass quantities in a crisis, that is, following a mass exposure, without an emergency-use authorization.

The point being that, without the recommendation to the FDA, without the FDA taking action, it would be very difficult for the United States Government to amass significant quantities in reserve of this medication. It would require that a catastrophic event would occur, and then they would have to try to amass the medication.

So, the Committee reviewed two key elements of data. One was the African green monkey model, that is, whether the monkey model was suitable to extrapolating data to human beings. We

considered both humans and adults. (Laughter.) I'm sorry. Sorry about that. Just checking to see if everybody is awake. Sorry. We considered both adults and children. Sorry about that. Wow. The other key elements that we looked at were the safety data regarding Cipro and Levaquin in children.

So, the Committee spent a significant amount of time on the African green monkey model. And we, as a Committee, felt that the African green monkey model did, indeed, satisfy The Animal Rule and did, indeed, provide a relevant model for human exposure. As a result, the Committee took several separate votes. One vote was on whether we voted on -- the initial vote was whether The Animal Model was, in fact, valid. And the Committee voted unanimously that that was the case.

The second was whether Cipro, and then in a separate vote Levaquin, were adequate, that is, whether the data proved the safety and efficacy of those agents for the treatment of pneumonic plague in children and in adults. The Committee felt in both cases unanimously that the data did, in fact, support the approval of both drugs and a formal indication for both the safety and efficacy. That is, the safety and efficacy were demonstrated for treatment of this infection in both adults and children.

One of the problems that we encountered was that, as you might imagine, this is a type of infection which one cannot adequately study in humans for two reasons. One is the exceptionally-high mortality rate of nearly 90 percent of patients who have pneumonic plague makes it unethical to engage in clinical trials. The other is that the occurrence of this particular infection, this particular form of the plague, is exceptionally rare, and it is very difficult to gather data in that regard. So, we had to extrapolate data. In terms of the safety of using these quinolones in children, it is important to note that there really aren't a whole lot of data. And I say that relevant to an anthrax exposure.

Your question, Ms. Ali, earlier today regarding the use of antibiotics concomitant with the anthrax vaccine is one which is well-taken. That is that, following an anthrax exposure, many people

would get the anthrax vaccine, but they would also receive anthrax-specific antibiotics, most of which would include a quinolone.

The children who have been studied who have been given quinolones have been studied only up to 14 days and not beyond. In any anthrax exposure, the treatment has to continue for up to 60 days, sometimes longer. This would be a concern for this panel to address perhaps relevant to that, not so much for the plague. So, the information that we have, the data that we have, the published data on use of quinolones in children is limited to 14 days of treatment, not 60 days. When those children -- and these are children that have been in many age ranges -- when these children have been studied, there is a slightly increased risk of musculoskeletal problems, and these tend to persist for several months. Especially when the children have been re-examined or followed out as long as a year, those findings are robust and persist.

Nevertheless, the Committee took into account that information with the understanding that, in the event of an exposure to pneumonic plague where the mortality rate approaches 90 percent, that was felt to be a reasonable risk to take.

One other point I would make, and that is I was asked to postulate what data would the Committee like to have had to consider in an ideal world for the quinolone approval. I am reminded by my pediatrician colleagues that children are not little adults, and this is certainly true with regard to clinical studies.

I want to echo Dr. Halsey's comment earlier today, and that is that I strongly recommend the creation and maintenance of emergency protocols to study and execute in advance of catastrophic events, keeping in mind, of course, though, that, as Dr. Gorman pointed out, there is a litany of Category A agents which the government would have to consider preparing against an attack. This is almost a Herculean task.

The one other thing I would say is that the studies justifying the experimentation or the enrollment of children for clinical studies, Dr. Gorman and I were discussing this earlier. There is some discussion about using juvenile animal models as sources on which to base further treatment, that is, on which to base clinical trials. My recommendation is that human adults are a better group to study prior to creating studies in children, rather than juvenile animals, because the leap is not as large. That is all I have. I will open to questions.

DR. WAGNER: Thanks to all three of you. And I know we have got some questions out there.

Maybe I can start. Very quickly, these Category A, two of you spoke about Category A agents and threats. What do we know about what makes them a Category A agent or threat? Is it just their virulence, you know, morbidity? Or is factored in there, also, something about the likelihood that they would be used?

DR. GORMAN: It is all of those things, and all of those have been developed by different nations in the world to be used as bioweapons. And some would argue they are still there.

DR. GUTMANN: I have one comment. You may want to respond to it. But I just thought I should put it out there. Much of what you said is very well-taken, but your conclusion, I have to say, we could never, as a Commission, say, "Children shouldn't be protected from research; children are protected by research."

First of all, that makes it sound a lot simpler than our task is. The children who will be protected by research are not always the same children who are asked to engage in the research. And I think you would agree that the research has to be bound by ethical considerations. We have a history in this country in the world of doing research on both adults, but most poignantly, on children that did not protect them, was

not either for their benefit, or even if it were for the potential benefit of children in general, it really violated significant ethical constraints.

So, I guess I am asking you to de-simplify your final statement. I understand that you are part of an organization whose mission is to make sure in the case of these attacks children are protected. That said, I would hope you would have a more nuanced view than children are protected by research.

DR. GORMAN: I was trying to give myself some protection by attributing that comment to Dr. Nelson, obviously not very successfully.

(Laughter.)

I do believe that there is some evidence that there is a fair amount of paternalism in our ability to protect children from research. I also understand that terrible things have been done to children in the name of research.

In the specific example here, we were testing, well, we were thinking about testing medical countermeasures. I think there needs to be a realization that, when there is the next anthrax attack, that I don't want to be the person giving the vaccine to children and saying, "I don't know if it works."

And so, I would think that there is sometimes -- and I have heard hints from multiple speakers who are much deeper ethical thinkers than I am -- that there is more than just this individual concept in play here. And I know as a fact tonight more children will suffer and die from ignorance than will suffer and die at the hands of researchers.

DR. WAGNER: Before I pop over to Christine, I had a quick followup on those agents. Could you clarify for us where you imagine -- any, all of you -- where you imagine we are with regard to antibiotic countermeasures compared to vaccine countermeasures. When you indicate that we don't even

have palatability studies done on Cipro in children, does that mean that we are not even prepared to use that as an effective countermeasure?

DR. GORMAN: We have an alternative for Cipro, which is doxycycline. There is much more data on long-term use of doxycycline. We are hopeful it is just as effective against an anthrax or a plague attack. So, we have an alternative. I used Cipro because it is another antibiotic that people talk about for which there are no palatability studies.

DR. GUTMANN: Are we stockpiling it?

DR. GORMAN: I can tell you that that information is somewhat publicly available. You can look at -- what is in the National Strategic Stockpile is not, but the requisition orders from BARDA are. So, you can figure out what they are buying and you can probably guess where it is going. So, BARDA and CDC are buying Ciprofloxacin and doxycycline.

DR. WAGNER: I'm sorry, did you have a comment?

DR. MOORE: Well, I was just going to say that, just echo what Dr. Gorman said. The antibiotics are being stockpiled. That is a fairly-recent development. There was a pilot study that BARDA executed in the course of the last year having to do with the prepositioning of doxycycline-containing medikits, which was part of our FDA Advisory Committee discussion. So, I know that that is going forward.

The general recommendation I think would be that vaccines would be a much better and much more effective countermeasure than the stockpiling of drugs.

DR. WAGNER: Christine?

DR. GRADY: Thank you all for very interesting comments.

Richard, I am going to pick on you for a second. I want to ask you, I know you have been -- and I admire it in you, actually -- a proponent of research in children and research in pregnant women,

so that we can provide more evidence-based care in general. So, I want to ask you how this feels different or engage you in how this feels different.

You gave us a long list of Category A agents, all of which sound scary, all of which I understand are potential bioterrorist weapons.

Do you think that it makes sense that we, as a society, should do research, including children and/or pregnant women, for each of those agents? And if the answer is no, how would we decide which ones we should and which ones we shouldn't?

DR. GORMAN: The answer is yes. I am fortunate to be able to say that a lot of the things that I want to use as medical countermeasures can be tested in a non-medical countermeasure environment. So, a chemical medical countermeasure for seizures I could test with other people who have seizures. And then, I would hope I could generalize that to the seizures caused by nerve agents.

I can test antibiotics for infections if I have a framework in which to do that. I don't have a framework, and I think there has been a lot of evidence presented here there isn't really a good framework to test an anthrax vaccine, other than to test it in healthy children. And you're discussing whether to do that pre- or post-event.

DR. GRADY: So, can I have a follow-up for one second?

Do you think one criteria for how we decide what is okay to test and what isn't should be, how could it be useful in other settings? I mean, you talked about that a little bit, and you just said that when I asked that question. I don't know - do you think that should be a criteria that we consider?

DR. GORMAN: I think I am going to think about that subtly differently. It gives me another avenue to get to my information. I don't think of that as testing a medical countermeasure, but I will

get information that can, then, inform the decision makers about how they could use a medical countermeasure.

So, if I am testing an antibiotic against a urinary tract infection in pregnant women, I could then have that information for anthrax in pregnant women.

DR. GRADY: Yes, I guess I am thinking, if you had to decide between testing this agent for anthrax and this agent for plague, let's say, and one of them could be used for another purpose, or is already used for another purpose, but you need more data on it, should that take priority, just in terms of what you are exposing people to risk to understand? You know, the value of learning that, the effect of that agent on this side is doubled because you now have more than one use for it. Do you see what I mean?

And it doesn't have to be only you. Maybe the others have some response to this.

DR. GORMAN: It would have both a utility and a practicality argument in the sense that it would be easier to test because I have another use I can test it on, and it would be useful in two situations. So, I would consider that lower-hanging fruit. I would probably go after that first, if I could.

DR. GARZA: So, let me just jump in there about what Christine was talking about. Part of the problem, though, is that these drugs are not routinely used in the pediatric population. In fact, they are rarely used in the pediatric population because of their side effects.

And so, having that sort of triangulating what they are used for in other instances and interpreting that for Class A agents is a little bit difficult. And they are not used in the context, meaning the long span of time that you would have to be taking them, that hasn't been studied, the 60-day course.

But, above and beyond that, I think there are other issues that go back to the effectiveness rather than the efficacy. I think you were trying to allude to that, Richard, which is, if you are given these pharmaceuticals, and most of them will come in an adult form, in a pill, a capsule, whatnot, first, you would

have to figure out the dosing, right, for the children? And then, they would have to actually take it, and there is a problem with palatability of these pharmaceuticals as well. We learned this during H1N1 when we were trying to get antivirals out the door, and the limiting factor was actually the flavored syrup that we mixed with the antivirals in order to give to the children.

And so, I was wondering if you could speak a little bit about not just the efficacy, but really the effectiveness. Like how easy would it be to get children to actually take these medicines or to deliver them to children in an effective form? Because I think that speaks to the broader medical countermeasures enterprise.

DR. GORMAN: I think behavior is somewhat based on what surrounds you. So, when H1N1, to use your example, was coming towards us, people were worried. People lined up for vaccines. People stockpiled their anti-virals and then probably took them. And then, when H1N1 got here and adults sort of got a pretty easy ride off of it, the demand for the vaccine sort of disappeared because they saw what the disease was.

So, if there was an anthrax exposure and children and adults started to sick, were being hospitalized, it was on the nightly news every day, I would think that compliance would be less of a problem, not zero, but less of a problem.

If there was an anthrax exposure and nobody ever got sick, I think that people would stop taking their medicines pretty rapidly, and children would stop taking them more rapidly than adults because they tend to be less palatable. So, I don't think there is a simple answer to that question.

DR. MOORE: That is fine. I was going to respond to Dr. Grady's inquiry just briefly. BARDA prepositioned these doxycycline medikits precisely for this reason. It was a pilot study to determine whether or not medications could, in fact, be dispensed to people in their homes in the event of an exposure.

The point that I am making is that, although the exposure never occurred, thank God, there was valuable information that was gleaned from that study about how many packets to produce, how are they stored, how was this going to work. And they piloted the study both among Minnesota, that is, Minneapolis postal workers, as well as an inner-city clinic in St. Louis. And the effect was the same, that is that indiscriminate use -- the concern was that the people who had the medications would take them when there was no emergency. But the data showed that, in fact, they preserved the medication for the most part and used it only when they were told to do so, had they been told to do so.

In my opinion, you can bankrupt the government by trying to prepare for all of these agents, and I am not sure that -- well, I don't think that that is a good idea, obviously. But, nevertheless, you can perform studies and gather information that is easily generalizable to other agents as well, and do them in a limited fashion.

And, of course, the choice of which agent to prepare against is almost unknown, at least unknown to most of us. I don't know if the Department of Defense has that information, but that is the kind of sort of individual group that would have to make that decision.

DR. MICHAEL: So, I will ask a question that will probably end up being one that could be discussed as well in the roundtable. But there has been some discussion about having post-event studies done because that would change the equipoise obviously for the risks and benefits of doing studies in children that would be affected.

I just reviewed the anthrax-absorbed vaccine dosing schedule. In IM, it is zero-1 in six months, and subcu at zero, two weeks, four weeks, and six months.

So, I guess my initial reaction, when I heard about doing post-event studies, was that might give you information long after the fact that you actually could do something with it.

Now I am reviewing these vaccines schedules. And obviously, even for the subcu approach, you are talking about looking at immune responses in the first three shots within a month. That might be somewhat reasonable, but the six-month mark, if that shot is important to get you to a level of immunity, that is a bit daunting. If it is more to sustain immune responses, and so, therefore, is more for durability, that would be a different answer.

So, have you struggled with that kind of thought process? Would it actually make sense in terms of clinical research to ask the question in that way or, because of the schedule in which you need to give the vaccine, is it just nonsensical?

DR. GORMAN: I really strongly support the idea of having protocols in place for questions that can be answered rapidly. I think you have reached a core issue for immunogenicity. You can't get that answer rapidly.

So, doing it, there will be a different ethical construct of doing it afterwards, but the people who you will be testing will not have any benefit from being in the study, other than the benefits we have already mentioned, because the answer will only be known after the event is over.

DR. WAGNER: Actually, this would be a good time, and gets us nearly back to schedule, to take a bit of a break. We are going to invite you three right back, along with our other presenters in this area, for our three o'clock -- is that right? -- for our 2:45 roundtable. So, we will see you then.

Thank you three very, very much.

(Applause.)

(Whereupon, the foregoing matter went off the record at 2:33 p.m. and went back on the record at 2:46 p.m.)