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TRANSCRIPT

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DR. WAGNER: So, let's get started.

We are shifting now from, um, uh, pre-event discussions to post event. MCM use, medical countermeasures use and research and post-event scenarios, and we will again, the format, we'll ask each of you to make your presentations, and then open it for questions.

First will be CAPT Carmen Maher, Deputy Director of the Office of Counterterrorism and Emerging Threats within the US Food and Drug Administration. In this role CAPT Maher assists in formulating counterterrorism policy and provides leadership and direction to the office of counterterrorism and emerging threats, as well as, the FDA medical countermeasures initiative. CAPT Maher also advises and collaborates with senior staff in developing, updating and implementing medical consequence management and mitigation programs, policies and plans for response in healthcare – excuse me – public health emergencies. Welcome CAPT Maher.

CAPT MAHER: Thank you very much and thank you for inviting me here to speak with you today. Um, I was asked to, uh, comment or, to be specific about the regulatory landscape for providing medical countermeasures to children in an emergency. And so that's what the focus of my brief remarks is going to be.

The first thing I did want to share and this is something that, um, it's a slide that we have with almost all of our presentations, when we talk about medical countermeasures and emergencies. And, it's the FDA, um, balance that we strike when we're evaluating, um, and in doing that risk benefit analysis with regard to either authorizing use of an emergency medical countermeasure for the population or, um, the reviewers, when they're looking at, um, uh, individual EIND use for an individual patient. And, we, we balance the public health or the medical need, whichever may be the case against the regulatory requirements, and the scientific evidence or the scientific data that we have regarding the product and regarding the intended use.

Um, we're also looking at the circumstances of the emergency, which depending on the situation, the risk benefit assessment might change.

Our regulatory mechanisms for utilizing medical countermeasures in an emergency, um, include the investigation on the drug application, the IND, the IDE for devices investigational device exemption. And, uh, we also have as has been spoken of today, the emergency risk authorization.

With regard to the IND, it's the same mechanism that we have that allows, um, use of an investigational product in humans for clinical trials. But, as you can see, we can also use it if, um, needed

during an emergency. In some circumstances, the IND might be the most appropriate mechanism that we have for the investigational product.

We can use it for individual patient access, which is the EIND. We can use it in an expanded access trial, um, for intermediate sized patient populations, and we can also use it in a treatment IND or, uh, a treatment protocol under IND.

Um, we also have for larger scale events and for authorizing, um, wide scale use of either an investigational product or an unapproved use of an already approved product, the emergency use authorization. Um, a couple of nuances with it. It requires a determination and a declaration under Section 564 of the Federal Food Drug and Cosmetic Act.

In order for the EUA to be utilized, it must meet four conditions for authorization. There has to be a serious or life-threatening condition that's caused by a CBRN agent. There has to be a reasonable belief that the product may be effective. The known and potential benefits of using the product outweigh the known and potential risks of the product. And, there's no adequate approved or available alternative to the product.

Uh, one of the benefits of emergency use authorization, particularly when you're talking about a large scale response is that it does not require informed consent or IRB review, even though you would be using a product that is technically investigational or unapproved for the intended use.

Um, it does require sufficient scientific evidence to support the intended use of the products and for some products, uh, there may not be, um, sufficient scientific evidence to support that use under an EUA, and that's where we are, um, with the AVA vaccine in children.

Um, there are many medical countermeasure challenges in pediatric populations. A lot of them have been discussed at length today. Um, with regard to the EUA, in order for us to authorize use of a product under EUA, in addition to the scientific evidence that we mentioned or that I mentioned, the potential benefits must weigh the potential risk, and you've had a lot of discussion today about the difficulty in making that risk benefit assessment, um, before an emergency because of the uncertainty of the risk, and even during the emergency because of the uncertainty of the risk.

Um, the IND mechanism requires informed consent and IRB approval. During large scale emergencies obtaining this might be difficult. It could hinder the response. We've collaborated very closely with the CDC and with state and local partners to understand what the limitations of, uh, on the ground are with

regard to response, so that we can consider that as we're looking at particularly the, the IND, um, for ADA use in children.

Um, there is a need for clinical studies and, um, I did want to point out, I stole this little bullet from a colleague of mine, Rich Gorman, from his slides at the FDA sponsored Pediatric Medical Countermeasure Workshop. Um, a lot of the information that we have about the use of products and children, a lot of the use is off-label but, a lot of the information that allows us to use the product is extrapolated information from adults. Either we've extrapolated the information and labeled it for children or it's being used off-label based on information that a prescribing physician may have in front of them.

Um, when you talk about CBR and medical countermeasures and the difficulty with developing those, you're talking about medical countermeasures that can't be tested or, um, the efficacy cannot be done in humans. Safety, you may have a very limited safety database. So, you're talking about extrapolation not from adults but from animals, and then, adults to children. So, it becomes even more difficult.

Um, there is extrapolation from adolescents to toddlers and infants but still that is an extrapolation of the data. There's modeling utilized, as well, um, which adds complexity, even though it does inform.

Um, there's a need for bridging studies, safety studies, and there's a lot of endpoint issues when you are dealing with, um, clinical trials or studying medical countermeasures in pediatrics.

I wanted to keep this very, very brief. Regulatory presentations tend to be long, boring and dry. (Laughter) So, I'll be happy to answer any questions you have at the question and answer session.

DR. WAGNER: Thank you very much. And, next, we will hear from Dr. Sonja Rasmussen who is Deputy Director for the Centers for Disease Control and Prevention's Influenza Coordination Unit. She's authored 12 book chapters and over 160 peer review papers related to this. Dr. Rasmussen has received numerous honors including the Arthur Fleming -- the Arthur S. Fleming Award in honor of outstanding men and women in federal government. She participated in planning for a future pandemic, and subsequently in the response to the 2009, H1N1 influenza focusing on influenza's impact on pregnant women in particular. Welcome, Dr. Rasmussen.

DR. RASMUSSEN: Thank you. Uh, it's my pleasure to be here today to talk about some of the clinical research that occurred during the 2009, H1N1, uh, response. And, just to remind you of some of the

timeline associated with that outbreak, in April of 2009, uh, two patients from California were identified with the Novel Influenza A (H1N1) virus. Um, on April 26, 2009, the US declared a public health emergency. Uh, April 27th, 29th, and June 11th, the World Health Organization raised from global pandemic Level 3, where we had been because of H5N1 in Asia, the Avian flu to Phase 4, 5 and 6, and 6 is a full blown pandemic on June 11th. And then, August 10th, WHO declared end to the 2009 H1N1 influenza pandemic.

What was the impact in the United States? Uh, these are estimates. Um, 61 million cases, 274,000 hospitalizations and 12,470 deaths in the United States. And, I think it's important to note that, um, the death, the distribution of deaths was different from what we really saw typically with seasonal flu, which is an emphasis on primarily older people.

Um, there was a, um, big emphasis you can see in the – almost 10,000 deaths in the 18 to 64-year-olds.

So, I'm going to use two examples here. One is the use of intravenous antiviral medications in critically ill patients and the other is use of antiviral medications in pregnant women.

The first issue with intravenous medications. There was no FDA approved IV influenza antiviral medication for treatment of severely ill hospitalized patients at the beginning of the pandemic, and that's still the case now. Um, there was a question of whether oral oseltamivir can be adequately absorbed in critically ill patients. And, the other medication to which the H1N1 virus was sensitive, zanamivir, inhaled zanamivir is contraindicated in patients with, uh, uh, airway disease, uh, like asthma. So, that takes a lot of the population out, and patients that are mechanically ventilated for example in an ICU.

Uh, so the potential emergency use was, uh, investigated. Which possible IV, uh, neuraminidase inhibitors could be used and HHS decided to acquire peramivir and FDA issued an EUA. You've already heard about EUA's on October 23, 2009 and that was terminated on June 23, 2010. This was a first time an investigational, unapproved drug was authorized for use under an EUA.

CDC was responsible for distributing the medication peramivir and, um, they developed an online system, the Peramivir Electronic Request System for clinicians to request peramivir for individual patients. And, really the goal here was to get that medication, that medication that might be lifesaving to patients that were, were critically ill. So, the point was to ensure equitable, rapid access and to get patients who needed the medication, the medication. So, there was web-based information for healthcare providers. Um, CDC connected three post-release follow-up surveys.

Um, we received 1,371 requests for peramivir through the EUA program and over 2,000 adult treatment course equivalents were delivered. It's more than the number of requests because sometimes requests were for ten-day courses rather than five-day courses.

The were delivered to 563 hospital pharmacies in the US and Puerto Rico, um, within 24 hours of the request. And, the median delivery time was 12 hours. So, the goal really was getting that medication to critically ill patients quickly.

Um, there were, uh, in as part of the surveys that were done afterwards, 1,274 distinct peramivir recipients were identified.

This slide shows the, um, frequency of peramivir administration during the EUA and compares that to the percent positive influenza tests reported to CDC, and you can see that these two things mirror each other. Um, you can see the EUA was, uh, issued on October 23, 2009, and you can see there was a rapid increase in requests for peramivir of distribution of peramivir, and then, dropping off as the pandemic, uh, slowed down.

And here, I think this is helpful because you can see these are sick patients. Um, there were 94% of them at the time of the request were in an ICU. Uh, 92% were intubated. Um, 23% were on dialysis. 50% were on pressors. And then, you can see the data at the end.

The difficult thing is that because of the, the way this was done during an event, during an emergency, we don't know if, uh, the fact that it appears fewer people in an ICU, fewer people intubated, fewer people on pressors to support their blood pressure, um, after they got peramivir was related to the peramivir or not.

The same thing you see 23% on dialysis at the beginning, 29% afterward. Did that have anything to do with the peramivir? Uh, it's difficult to know. And that was based on a 127 responses to a clinician survey. So that was a very small proportion of the number of, uh, of clinicians that actually received peramivir.

Um, these are data from the Adverse Events, uh, Reporting System at FDA, and this is the way the data was planned to be, um, received as part of the EUA. And, here you can see adverse events by their preferred term. This is metric term. Um, and then, the different adverse events. I don't want you to look at all

of these but, just to see that most of them are really things that you'd say well that's part of being really sick with influenza. Death, H1N1 influenza, ARDS, acute renal failure, cardiac arrest, etcetera. Um, and, the FDA experts that analyzed these data, uh, um, the only adverse event that they were able to clearly associate with peramivir use was rash.

So, the conclusions about research in peramivir. Many recipients were critically ill and at risk for influenza related complications. Rash was the only treatment emergent adverse event that was attributable to peramivir. It's difficult to distinguish between what was really just severe being really sick with influenza and what was due to adverse events.

And, the data collected were insufficient to assess whether peramivir affected outcome. Did it make people better or not? Or, whether it caused adverse reactions other than rash.

Um, then, I also wanted to talk to you about the use of antiviral medications in pregnant women. And, we knew before the pandemic based on previous pandemics and from seasonal influenza experience that pregnant women are at an increased risk for complications related to influenza.

However, there were limited data available on the use of antiviral medications for treatment of influenza during pregnancy. And, I just want to note that this is really true for almost all medications that are used during pregnant women. That we don't have enough data to know whether those, those medications are safe. So, antiviral medications weren't really that different.

Um, we did have a meeting about a year. It was April of 2008 and that's the paper you can see at the top. We had a meeting at CDC and brought in a number of experts and partners to, um, work on preparing for a pandemic to review the data that were already available and plan for a future pandemic. What sort of recommendations would be made.

Um, that paper, ironically, I got the galley proofs for that paper the same week that the MMWR came out about the, um, the two children in California.

But, it meant that we did have information. We had well thought through information for recommendations. Unfortunately, it meant that we hadn't – some of the research that had been called for in that paper, obviously had not had time to be done.

So, our treatment recommendations were to treat with oseltamivir for pregnant women and women up to two weeks postpartum regardless of pregnancy trimester and not to delay treatment based on negative rapid influenza diagnostic tests or inability to test or while awaiting test results. Physicians were, um, recommended to use their clinical judgment of whether the patient had, um, flu.

Um, we have some data about what happened among pregnant women. These are data that were, um, a collected at states, and then, sent into CDC. So, this is really the work of states, um, that worked very closely with CDC on influenza surveillance during the pandemic.

Five percent of deaths in the United States from the 2009, H1N1 were among pregnant women. And, pregnant women account for about 1% of the general population. So, it shows a higher proportion of pregnant women affected.

We also found that early treatment – early treatment with oseltamivir, um, was associated with fewer ICU admissions and fewer deaths.

And this, just quickly to show you the, um, the – I don't have a pointer here but, the, um, top layer there, you can see women who received oseltamivir, and antiviral medication, uh, five days or more after, uh, symptom onset, compared to those who received it in the first two days were six times more likely to be admitted to an intensive care unit and 53 times more likely to die. You can see a very broad confidence interval there though because fortunately, there were not very many deaths.

And these are observational data. So, these are not the same as data that you could collect in a clinical trial.

So, conclusions about influenza antiviral medication. We have observational data that suggests that pregnant women who received antiviral treatment were less likely to die and less likely to be admitted to an ICU. But, knowledge about the pharmacokinetics, which we know pharmacokinetics are different in pregnant women and about safety of medications during pregnancy remains severely limited.

So, our overall conclusions. Collecting data on safety and performance of medical countermeasures during a public health emergency is challenging and I was actively involved in the part of pregnant women and we were – we were working as hard as we possibly could and it was hard to collect the data that we had.

Investigators are often actively working on response activities. Making sure that people get the treatment that they need.

The goals of providing rapid, equitable access to medical countermeasures may conflict with the goal of performing research.

Research studies in the midst of a response might be perceived by the public as using countermeasures that are not safe, and then, possibly decreasing adherence to public health recommendations.

And then, just a question. Can adequate informed consent for research studies be obtained in the event of a public health emergency response?

Just a few more comments. Um, preparedness is key. If we're going to try to do something post-event, I think you really need establishment pre-event of mechanisms such as clinical networks, and mechanisms of ways to pay for things in the government to conduct real-time or near real-time safety and clinical evaluations of those investigational medical countermeasures.

A systematic mechanism for rapid review and analysis of those data collected is needed so that they can, uh, continue to inform guide usages. The event goes on and studies would need rapid institutional review board review, um, that could be facilitated by a central IRB.

And, I just wanted to acknowledge, uh, Denise Jamieson and Yon Yu and Yon Yu, uh, is the, uh, one of the people that was very involved with the EUA program for peramivir and she lent me her slides.

DR. WAGNER: Well, thank you. Thank you, Dr. Rasmussen. And, the final speaker in this particular panel is Dr. Suzet McKinney. Uh, Dr. McKinney is Deputy Commissioner for the Bureau of Public Health Preparedness and Emergency Response and Division of Women and Children's Health at Chicago Department of Public Health. She oversees preparedness efforts there for the department. In this capacity, Dr. McKinney is the principle investigator for preparedness programs funded by both the CDC and the Office of the Assistant Secretary of Preparedness and Response. She has been the primary force in the development of public health regional plans in Illinois to respond to bioterrorism events and other public health emergencies, and has contributed to numerous programs on public engagement and distribution and dispensing of medical countermeasures. Welcome.

DR. MCKINNEY: Thank you very much. It is indeed an honor to be here to speak with you this morning. I was asked to talk about the challenges associated with local level implementation of the current regulatory framework that the commission is considering, uh, to deliver – for delivering medical countermeasures in children in emergencies.

So, I'd like to start today and frame my discussion around the lessons that we learned here in Chicago from two real-life events. Once I describe each of these, uh, scenarios, I will go into, uh, some challenges that we faced in each of those response efforts. And then, also some potential improvements or suggestions.

In 2008, the Chicago Department of Public Health's Bureau of Public Health Preparedness and Emergency Response, along with our Immunization and Communicable Disease Programs initiated a mass vaccination campaign that was designed to increase vaccination rates against meningococcal disease in children ages 11 to 18 in two Chicago community areas.

This campaign was initiated out of an abundance of caution but due that was after the recognition of increased incidence of meningococcal disease within these two community areas, as well as two deaths associated with this increased incidents.

The campaign required a multidisciplinary response, which included state and local public health, law enforcement, public school officials, as well as, private and parochial school officials and other stakeholders that were instrumental in assisting the department with its vaccination effort.

The campaign lasted for approximately 18 days and included both in-school and community level vaccination sites, covering over 65 schools. In the end there were nearly 7,000 vaccinations that were provided mostly to children during this campaign. However, the number vaccinated represented only about half of the intended population that we wanted to reach.

In this effort, we were providing an FDA approved medication that is also recommended for this age group by the advisory committee on immunization practices. However, this operation was still hindered by a perceived lack of urgency or need, poor perception of the intent by parents, some school officials, as well as the intended population. This made the ability to obtain parental consent particularly difficult despite a full media campaign and joint coordinated messages that were being disseminated by Chicago Public Schools and the Chicago Department of Public Health.

It is very important to note that the two community areas in which we were operating represent multiple levels of vulnerable or at-risk population groups, primarily pediatric patients, low socioeconomic status communities, as well as, primarily African American and Hispanic communities, which in our experience are sub-population groups with high levels of false perception of governmental intent and, um, consequently mistrust.

During the 2009, H1N1 response, our health department provided antivirals to physicians' offices, community health centers and federally qualified health centers, um. Those antivirals were provided to physicians' offices under an EUA. Hence, patients received medications for the most part in their medical homes, which we believe perhaps minimized some of the anxiety around the medication.

But, in the fall of 2009, once the vaccine was available, our health department provided vaccination to city residents under multiple mechanisms servicing any resident voluntarily presenting for vaccination for either themselves or their children.

This response effort was also a multidisciplinary response but one that also garnered local, national and international attention. However, despite widespread media coverage of the – of the event and what should have been an obvious and real threat, Chicago experienced poor acceptance of the vaccine in specific at-risk population subgroups.

Once again, we saw many of these groups as being primarily African American or Hispanic and low socioeconomic status communities. Um, and there was particular concern from parents around the intent for the need of vaccination in children. It was our experience that stigma associated with the Tuskegee experiments and the misperception that vaccines create autism and other adverse health events in children, further hindered our ability to relieve parental concern about the safety of the vaccine, as well as, what our attentions were in terms of securing full participation in the vaccination effort.

So, in each of these response efforts, there were logistical and operational challenges mostly related to the large numbers of persons requiring vaccination and consequently, the number of vaccination locations. However, these are challenges that we plan and prepare for on a daily basis. So, we did not find them as daunting as one might think.

In both situations, public acceptance of vaccination was poor due to numerous factors but, most frequently, religious beliefs, poor perception of both threat and governmental intent, as well as an overall mistrust of what our efforts, our governmental efforts were at the time.

As with any situation, we found that communication was particularly difficult due to the myriad of ways that members of the public tend to access information and receive information. No matter how widespread our communication efforts were, we found that there were, um, pockets in areas that were missed among particular subgroups of the population, and also subgroups who simply did not heed the messages that we were attempting to deliver.

In Chicago, we also experienced difficulties associated with the legal interpretation of the Emergency Use Authorization. Differing interpreting – I'm sorry, differing interpretations among multiple attorneys in the absence of clearly defined guidance for EU implementation and physician accountability, required additional examination and hence caused some delay in the delivery of countermeasures to provider offices.

In the event that the US government makes a determination of the need for AVA and pediatric populations, it is our belief that the challenges that we've seen in these two events will be repeated and further complicated by questions surrounding the different regulatory policies for adults and children.

In the case of the EUA's clear specific guidance for implementation will be necessary to minimize the varying interpretations that we saw here during the H1N1 response effort.

There will be no simple explanation for why MCM's are delivered under one mechanism for adults and yet another for children. However, clear specific and coordinated messages across all levels of government and the healthcare sector, um, may alleviate some of the anxiety.

The availability of medical countermeasures and public POD's, as well as in physicians' offices, as was done with the H1N1 vaccine may also alleviate some concern for parents with regards to their children.

Building upon the H1N1 experience, we believe that local and state public health working in conjunction with the CDC will be well-equipped to accommodate this type of scenario.

The risks associated with pediatric administration of the vaccine will need to be specifically addressed for parents. This should include multiple venues for discussion and a clear comparison of the advantages and disadvantages of the vaccine in pediatric populations.

Without a real credible threat or perception thereof, even the most aggressive and comprehensive efforts will be met with anxiety, fear, protest and apprehension.

DR. WAGNER: Thank you. Thank you all three. Actually, I think Nelson got his hand up first, and then, we'll go to you, John.

DR. MICHAEL: Thanks to all three of you for, for, uh, a great presentations. My question is to, um, to at least, Dr., uh, Rasmussen or perhaps, um, others but, I'm particularly interested based on the information that you showed about what your view would be, of the feasibility of actually doing, um, in a bioethically robust way, a pre versus a post-event study that would be looking at things that would be relatively arcane like dosing and immunogenicity studies of AVA? Not the kind of studies that would be, um, particularly what the public might be more, um, um, expecting that we would ask in terms of efficacy but in terms of, um, more arcane questions.

DR. RASMUSSEN: I don't know that I have the ability to tell you. You're asking – so, you're, uh, you're asking my sense of how this sort of study would go pre-event?

DR. MICHAEL: I'm asking how you could imagine the, um, the robustness of a bioethical, um, uh, framework for a study done pre-event versus post-event that would be say, a relatively, uh, small study of several hundred individuals, children, where you would be asking questions, not of efficacy or even, of significant safety questions in a study that size, but would be asking questions of dosing and immunogenicity, which is really what we're talking about in terms of AVA. So, um, and I'm asking this because of some of the questions that you raised, some of the, um, testimony that, uh, we've heard from the three of you about the feasibility of executing some of the science in the context of a post-event study.

What would be the balance, obviously, between now, a much greater, uh, idea of risk because now, you actually have an event versus the, um, the informed consent process that might be a little bit pressed, um, because of the situation of an acute event.

Do you think that the bioethical framework of asking that kind of question is going to be as robust in a post-event scenario as in a pre-event scenario? And, I think the counterbalance is you're not asking a question that necessarily is going to get the efficacy. Much like the neuraminidase inhibitor study that you showed. You couldn't get to an outcome. Okay? Um, so you're going to be asking questions really that are more arcane, and in my view, might be more difficult, uh, to explain to potential research volunteers, um, and their families.

DR. RASMUSSEN: Yeah, I – I am not a bioethical expert. I'm an epidemiologist and pediatrician. I, um, I think that parents, at least in my experience can understand, if you, if you take enough time and you, um, speak in words that they understand, I think parents -- I, my, um, before I went to medical school, I was a genetic counselor. I think families can understand just about anything you have to explain to them, and I think they can make an informed decision, if the, um, if the informed consent procedure is done in an appropriate way.

Ah, you know, we, oftentimes in genetics explain very complicated things, and families, I think are able to follow it and make decisions that work for them. So, I think from that standpoint, um, it's doable. Um, I think the, the side of things that I worry about in a post-event structure is how hard it was for us to do something in, in a post-event, um -- Now, again, I think, you think, well, all of these people are getting, um, this vaccine. We can study all of them but that's not going to be feasible in a post-event either. It – we're going to have to narrow it down to a fairly small number of people that can be consented to be part of a, uh, some sort of study.

So, I think, um, you're still probably not answering all the questions that you would want to even with a post-event study with smaller numbers. I don't know if that answers your question.

DR. MICHAEL: That's a tough one.

DR. RASMUSSEN: Yeah.

DR. WAGNER: John, how about something easier? (Laughter)

DR. ARRAS: Uh, you can always turn to me. (Laughter) Uh, so, uh, this is just a point of information from doctor or CAPT Maher. Uh, what does it take to get bumped from IND status to EUA status? Uh, so, I heard you say, I think, that, you know, to get EUA status, you have to go through some hoops and you've got to present some real scientific information but, we're not getting the usual meat and potatoes here. We're not getting safety efficacy. We're just getting, at best from the pre-event study, immunogenicity, dosing. So, just as a point of clarification is that sufficient to give you EUA status?

CAPT MAHER: The specific amount of scientific evidence or data that you would need for an EUA is going to depend, and I know that this is not going to be a satisfying answer but, it's going to depend on the intended use of the product, the population that you're intending to use it in, and what evidence do we have

to support that use. And, um, as products are being developed down the pipeline, especially the investigational products, there's a constant look at what the scientific data is showing us about the product, the preclinical data, the early clinical data and, um, an evaluation of at what point do we feel confident that the data that we're looking at, um, allows us to reasonably believe that the product would be effective for the intended use and the circumstances and that's the data that gets you to EUA.

DR. WAGNER: Alex? I'm sorry, Christine was next. I'm sorry, then we'll do Alex.

DR. GRADY: Thank you all. Um, I wanted to pursue one just, I guess also pretty technical question that I have. Um, I've heard it said before and you said it very clearly today, the difference between using an EUA afterwards and using it, a research IND, would mean, uh, consent from the parents and an IRB review.

So, my question really is even with an EUA wouldn't we need consent from the parents? And, is the difference just written or not written or is there no difference? That's one question.

And, the second is couldn't IRB review and approval happen earlier, you know, at least for the most likely protocol that we would use and, and be ready to go. So, in other words, how much of an obstacle are those two things, I guess is the question?

CAPT MAHER: Thank you, and, and from the perspective of, um, what we're planning to do with AVA, and, and how we use IND's in emergencies, I do want to make a distinction between, uh, a research protocol or a protocol that's designed to generate data about the use of the product versus allowing access to the product. And, what we're planning on doing in the pediatric IND is, is a completely accessed IND.

Um, the reason why we have to do it under IND is because as I mentioned before, there's no sufficient scientific evidence to support its use under an EUA. We don't know the safety. We don't know -- We don't know anything about the use of the product in children. And, you know, there's very limited information to extrapolate, if you could extrapolate that information, and it may not even be sufficient.

Um, we have met with CDC and state, local, tribal and territorial partners to understand the limitations on the ground and the differences between EUA and an accessed IND. Um, the information with regard – the information about the vaccine, what we know about the vaccine, what the components of the vaccine are – I heard that that's, uh, uh, something that would be asked, um, is probably the same information that you would be providing under an EUA, which requires you to inform certain information to the recipient.

And then, the recipient can elect to take the vaccine – the, the product or not, um, versus the IND, where you have to actually get, uh, from what I understand a signed informed consent, the typical informed consent. Not your eight-paged, informed consent with all your basic and additional elements, very similar perhaps to the EUA fact sheet but, designed specifically for the IND and to obtain informed consent from the parent.

DR. WAGNER: Interesting. Oh, did you answer the question about an advanced IRB?

CAPT MAHER: We have, um, as, as part of the Medical Countermeasure Pediatric Workshop, one of the things that we wanted to understand and we brought experts in to discuss was, um, the, the situation with the IRB's and, and the difficulty.

Theoretically, if you could preposition a protocol, um, have it approved by the IRB and ready to go, um, then you would be able to do the research intra-event. We, actually, we have, FDA, CDC led Intra-Event Surveillance Action Team that's actually debating all of these questions, looking at the current way, um, safety, efficacy and use of the product is evaluated. How we used some of those, uh, surveillance mechanisms during H1N1 and other emergency responses, and, and what can we do to stand up either pre-event protocols, intra-event protocols, which would include how do we get to that pre-IRB approval.

DR. GRADY: If God forbid, there were an event tomorrow, what would we have to do? We'd have to constitute an IRB and a protocol? I mean what would we have to do to be able to give vaccine to kids because that's what I understand that we would give it to kids, even without data.

CAPT MAHER: Currently, um, as far as I'm aware, the CDC and FDA are already working on, um, the access IND, the development of that protocol to access the development of that consent form.

Um, there's also work, um, going on with regard to developing a nested research protocol to look at it within a subset of the children that received the vaccine to study immunogenicity and reactogenicity, um, to further inform and maybe get us, um, somewhere else with the product.

Um, if it is an IND, it would require IRB review.

DR. GARZA: Well, Christine stole my question about what would you do today. (Laughter) But, I have other ones. Well, it sounds like -- maybe you can clarify this.

So, it sounds like there is minimal difference though between an accessed IND and an EUA. Is that correct what you were saying? It sounds like it was the same sort of information that was being, um, given to parents, um, about the vaccine risk, adverse events and things like that but, one was more formally titled as informed consent and the other one was kind of a FYI.

CAPT MAHER: And, there might be a little bit of different information with regard to the use in pediatrics that we don't know. That would be included in the informed consent about that population, then what you would see in the EUA fact sheet.

Um, but for the purposes of an anthrax response, understanding all the limitations that we have the speed with which one needs to respond, the desire to vaccinate as soon as possible, and the desire to be able to protect all the population including children and, and, um, pregnant women, um, we have been very careful and, and, and listening to the input from our state and local partners of the, um, limitations and the difficulties that the informed consent process adds to being able to do that. Um, we have looked at the, uh, access protocol as being very similar as the access under EUA because the goal is to provide access to the product, to those who need it when they need it.

DR. GARZA: Right, right. And then, maybe a comment and then a question for Suzet. The comment about, uh, is really about the H1N1 vaccine, um, during an event. And, and, it's a little bit, uh, of a different animal, I would say than, uh, than, Bacillus anthracis. And, the reason is because you had already identified people that were ill with H1N1, which is who got the IV drugs. Whereas, the problem with, uh, Bacillus anthracis is you don't want them to get ill because then it carries a very high mortality rate. And so, the whole goal behind, uh, pre-event MCM is to prevent the disease from occurring. Uh, there's, uh, been few cases of pulmonary anthracis within the United States in the last couple of years, and that requires a huge amount of, uh, healthcare resources. And so, if you multiple that by hundreds, it will easily tip your scales.

And so, um, and so, just a bit a caution about, um, trying to compare the post-event from H1N1 to a post-event for anthracis because I think the anthracis would be a much more difficult problem.

DR. RASMUSSEN: Yes, I agree completely and this was really meant to give a perspective. I was asked to give a perspective of being on the ground to try to be doing research post-event. So, you're right, it is not. It is a completely different scale.

DR. GARZA: Agreed, some similarities but -- Um, Suzet, just a question for you. Did you see any difference in, um, in acceptance of vaccine early on in the H1N1 pandemic, as opposed to later on? So, I'm

convinced that once people got comfortable with, "Hey, H1N1 isn't going to kill everybody," then, sort of their interest in getting vaccinated sort of wanes. Where early on, when we were getting very conflicting information from Mexico, where it seemed like, hey, this is going to be 1918, all over, there were people clamoring for, "Why don't we have vaccines? Where is it? How come we don't have it out the door?" Did you see any difference between early on in the pandemic and later on in the pandemic?

DR. MCKINNEY: Absolutely. We saw differences in perception and the desire for vaccine, not only when the priority groups were introduced but, also initially when vaccine began to become available, it was available, initially, in very limited quantities. So, we saw much greater demand. But, as vaccine became more readily available, and, uh, data began to present itself that it was not as virulent as the 1918 type of scenario, we did see a lessening, uh, or decline rather in the desire for vaccination.

DR. WAGNER: Barbara?

DR. ATKINSON: I think my question was a lot answered but, I will ask a piece of it that I think I don't understand.

If we came up with a framework, which I think we're going to try to do of a pre, um, pre-outbreak, um, IND kind of research project, we'd almost certainly want to have some piece of it that would be post, um, episode, as well. If that were all approved together and ahead of time, do you think you still would be able to collect the community information or would you still have the same kind of problems collecting the research data post-epidemic or post-outbreak that, um, you described for instance with the influenza. I mean, will we get data, uh, that way?

DR. RASMUSSEN: I think it all depends on what we plan for beforehand. I think if we plan to collect data beforehand, and have, um, mechanisms to do that, um, either through clinical networks, have ways to get funds out the door, have ways to have IRB approval in advance. I think if we, if we do enough planning we can do it.

DR. ATKINSON: Well, for instance a CTSA effort. If you linked somehow something broadly to that or someway you could envision some ways that you could collect information in a useful way ahead of time.

CAPT MAHER: Yeah, I was only going to comment from an FDA perspective. To the extent that we have, um, data or scientific evidence ahead of time, helps us, um, evaluate the product with regard to its

safety and, and, and potential use. But, also, helps with, with designing and communicating the information about the product. It's a very different situation when you can say, we have even this little bit of information about safety and children because we have it versus we don't know anything about the use of the product in children.

DR. ALLEN: So, this is a question for Dr. McKinney. Um, bioethicist are accustomed to, uh, hearing that, um, African Americans and certain other minority groups don't trust government enough to be enthusiastic about being involved in research or in even some clinical applications of medications that are known to be safe and efficacious.

Um, so, I'm wondering what your thoughts are for us because we, uh, would like to think that both the benefits of research should be shared among all groups, and also that the risk of research should be shared among all groups.

Is there anything you learned from your experience with meningitis vaccine or flu vaccine that could help us understand, uh, for this context and for others that we may deal with in the future, how we can encourage African Americans in particular but, other minority groups to, um, to trust enough to be able to reap the benefits of research and clinical, uh, applications of drugs?

DR. MCKINNEY: Sure. In the situation of H1N1, later in the response effort, when we were trying to increase acceptance of vaccine, particularly among the African American community, we began to engage in a number of community engagement or public engagement, uh, meetings and sessions. And, from our experience and I'm actually dealing with this issue now, we're looking at the issue around crisis standards of care and scarce medical resources after large scale emergencies.

I think what I have learned personally is that all of our efforts in each of those two scenarios, we conducted our efforts because it was what we thought we should do. And, we didn't, at the beginning engage the public to get their ideas and their perceptions and their beliefs on what they thought we should be doing. So, I think a concerted public engagement effort early on might help us in this effort. Um, it would also, I believe, help members of the public, particularly African American communities and Hispanic communities feel as though their beliefs and that their voices make a difference. And, I think that's what we've been missing previously.

DR. ALLEN: So, maybe in an atmosphere of in which we are having to think broadly about medical countermeasures, not just for today but for decades ahead, we should be proactively trying to educate

and to engage all communities in what they might need to do in order to deal with particular threats such as anthrax or other.

DR. MCKINNEY: Absolutely.

DR. ALLEN: Yeah.

DR. MCKINNEY: I believe that all of these communities and these at-risk populations that we're most concerned about have the capacity to understand what they believe is best for them. It's just that their beliefs and their ideas have not been gauged prior.

DR. ALLEN: Thank you.

DR. FARAHANY: That actually answers my questions. Thank you.

DR. KUCHERLAPATI: Thank you very much. I have a question for, uh, CAPT Maher. So, if I understood correctly, uh, in your presentation you said that there is not enough scientific evidence today to declare an Emergency Use Authorization for a vaccine for anthrax. Right? And that suggests that, uh, that we need to obtain such evidence before it can be used in children. And the two options are that, uh, we undertake such, uh, trial now, before, you know, such an outbreak or an attack or that you would initiate such an effort immediately after an attack.

The question for you and other people is, is it an adequate amount of time, without loss of significant amount of life or, you know, morbidity, uh, if you initiate such a trial after the attack and, uh, and if so, is it preferable to have such a trial now?

CAPT MAHER: I think the, the better we can prepare ahead of time, to inform the use of the product, the better off we'll be and the smoother the response will go. I know that in our engagement with, with, um, public health planners, one of the biggest concerns is the dual mechanism for release of the product for pediatrics under IND, for adults under EUA.

Um, we are preparing to rollout, as quickly as possible, a nested research protocol. Um, if that's the only way that we're going to be able to obtain information about use of the product in pediatrics to further inform continued use and, and how we would continue to use the vaccine in the unfolding response, and then, eventually, um, one can imagine if there is a large city that is exposed to anthrax spores, the spores are not

going to go away very easily. So, you have to think about exposure even after the immediate exposure of the event.

Um, there's a lot of difficulty still and a lot of uncertainty around how would you be able to implement that. Um, I don't think it's ever been done to have that type of a scaled event in a rapid response situation with all the uncertainty, confusion, fear, um, and then, try on top of that to do a, a clinical research protocol, however, simple that protocol may be.

Um, the idea from what I understand is that when parents bring their children, um, for access to the vaccine, if they elect to have their child vaccinated, imagine as you will as they're coming out, they're offered the opportunity to enroll their child in this nested protocol, um for reactogenicity and immunogenicity.

Um, how smooth that would go before an event where you have the time to really sit down with the parent, to really talk about the vaccine, to really answer all those questions in a one-on-one situation with time for the parent to sit back and reflect on that before choosing to enroll their child. Or, being in a situation where their child has received the vaccine because they've potentially been exposed and I'm trying to save their life and having to have that conversation in that situation.

DR. SULMASY: This sort of, uh, follows from, uh, the conversation Anita had, uh, with Dr. McKinney because I do think it is, uh, uh, becoming very apparent that, um, part of medical countermeasures has to be community engagement and education.

Um, um, and in that regard, um, I have two questions. One for Dr. McKinney, whether you think that given your experience, data would matter, at all. Would having some data matter in terms of public acceptance and education. And then, secondly, maybe to our other, uh, uh, panelists, um, whether there's been any modeling, um, of what a sort of 25% or 30% acceptance rate for vaccination in the event of a very large scale outbreak would mean, particularly given the fact for something like anthrax, there isn't even any herd immunity that you could achieve from what I understand.

And then, following that would that kind of data help parents, as well?

DR. MCKINNEY: With regards to your fist question, I think the benefits of data and whether or not having data would be beneficial for us really would depend on the subgroups of the population in which we were trying to provide that data to. I do believe that there are certain groups within the population who are interested in data and would want to see data before they made any decisions about whether or not to, uh,

provide the vaccine to their children. However, I think there are other subgroups within the population that won't care very much, at all about data and will really stick to, um, what I would classify as misperceptions, um, and things that they've heard about historically.

Um, so, I think it depends on which group of the population. I think when, um, planning public engagement and community education, uh, meetings and sessions, you really have to look at the community that you're going into, um, the demographics of the members of that community and tailor those discussions to that demographic.

DR. SULMASY: Really for the others, any awareness of any modeling of what this, you know, sort of low – because we saw even for H1N1, one of the papers we had, you know, even among healthcare professionals, a 35% compliance rate with vaccinations, it might be even lower with this. Has anybody really even done the kind of modeling of what that would look like if, you know, there are, uh, a million of population someplace exposed?

DR. MCKINNEY: I'm not aware of any modeling like that having been done.

CAPT MAHER: No, I'm not aware of any modeling that has been done, um, on any –

DR. MCKINNEY: Issue.

CAPT MAHER: Yeah.

DR. ARRAS: If I may just add to Dan's question, uh, and this goes to Dr. McKinney. Uh, um, if you're asking, you know, how much, how many people would be interested in data or what sort of data they would be interested in, it seems to me that given the fact that these are basically technical dosing studies that this isn't going to give parents the kind of information that they would ordinarily be interested in. They want to know whether it's safe and effective.

DR. MCKINNEY: Absolutely. I would agree with that but, I think, um, for those of us who work in this field, um, for perhaps who work in the healthcare field that there might be some interest and some value to having that data but, on a larger scale, I agree with you that most parents just want to know whether or not this vaccine is safe.

DR. GRADY: I guess my question builds on that a little bit because my understanding is that even in adults, we know it's safe, reasonably safe but, we don't know whether it works post-exposure. Right? We don't have data to say this is effective post-exposure in adults, and even the dosing schedule, as I understand it, is an educated guess. Excuse the word but, I think it is.

So, the question is in an event, would we also want to be collecting data from adults? So, would we have some of these same challenges because we would need data from adults, as well as from children?

CAPT MAHER: To the first question, I do know that under the rubric of defense through the NIH and CDC have partnered to conduct some studies to look at, um, post-exposure prophylaxis in animals, um, so that there, there, if not already, there may be data coming out of that in animals. Um, and then, you know, again, we're back to extrapolations. So, from animal to adult and then adult. What does that mean for the child?

Um, and could you repeat your second question, again?

DR. GRADY: Well, I guess my second question was wouldn't we also be interested in collecting data, um, in the, in an event from adults, as well as from children. So, that all of the challenges of collecting data in a crisis, which I understand are appreciable would still be here because we would need data from the adults, as well.

CAPT MAHER: Absolutely, and, um, part of that action team that I mentioned earlier, the surveillance, um, intra-event, we're calling it the intra-event surveillance. So, we're actually looking at what can we do ahead of the study for, um, all populations but, also, particularly for pediatric and maternal and, uh, we also have, uh, an action team that's looking specifically at pediatric and maternal. So, we have an overlap of some of the discussion where needed.

Um, but we are looking at the fact that regardless, we need to figure out how are we going to monitor and evaluate the use of the product to either further provide information and guidance on clinical decision making but, also, um, with regard to the safety of the product in the emergency and the efficacy. Is this working? Are we actually protecting people? Are we providing good treatment? Is this hurting? Do we need to pull it back? Um, so we are looking at that and we would absolutely want to be collecting information. Um, PHEMCE I believe is also, um, looking at the experiences with peramivir.

And, one thing I do want to note with peramivir and it goes back to that EUA and IND. Um, the EUA is an access mechanism that was designed to allow widespread access. There is no, um – it does not enable, so to speak, um, clinical research or any type of research under the EUA. That's not to say that you can't plan to study the use of an EUA product in the population that it's being used. The difficulty with peramivir is that you release – the product was used under EUA, um, so it wasn't under research, it was widespread use, and collecting information during that emergency to inform how well the product worked, we've all heard how difficult that was. That's driven a lot of the most recent conversation over how do we do it better the next time?

DR. MICHAEL: I'll ask a question of Dr. McKinney. Do you think that a process of community engagement in parts of communities, uh that might be at risk of an anthrax exposure are historically less trustful of the medical research community might be in a more, um, salutary posture for accepting a research study post-event had there been a discussion in the community pre-event of the risks and benefits and the advantage to the community to actually consider a study again, of the type that we're notionally considering, which would be one that would not address hammer stroke issues of safety or efficacy but, really getting to some of the first steps along that process?

DR. MCKINNEY: I do, agree. I, once again, believe that from our experience what we have seen and particularly, members of the community that I spoke with directly, um, during the H1N1 response effort. Um, members of the community that had a lot of these misperceptions spoke to me intensively about the fact that the government comes in and tells us what we need to do instead of asking us what we want to do and what we think is best to, uh, provide for the healthcare of our families and ourselves.

So, I believe as early as we can begin those engagement processes and as frequently as we can engage members of the community that we will begin to see a greater acceptance.

DR. WAGNER: Well, on the flipside of the question about the reluctance of certain communities to participate, we have a question from the audience from Ellen Manning, who is Research Compliance Coordinator at the Medical College of Wisconsin. And, uh, she notes from your comment actually, um, Carmen, Captain Maher that you spoke about, um, not about reluctance but is there – should we have some concerns if, in fact, we were going to try to enroll children at the time their parents receive a vaccine? Should we have a concern also about essentially the coercive effect of a respected physician, uh, and, uh, in posing or giving a sense of obligation, uh, to the parents of these children?

CAPT MAHER: Yes, I think that's a very real concern. I think, um, this is novel thinking in terms of responding to something like this on this type of a scale with products that we don't have a lot of

information on and under regulatory mechanisms that were designed for well-controlled clinical trials and studying of product for generalized knowledge.

So, I think those are very, um, real concerns that we have to be thinking about, as we're looking at the mechanisms and the plans that we have for responding to an event, and, and taking, um, steps to minimize or mitigate that but, but I do think there is going to be a different mindset. The risk benefit situation, the analysis that we're doing as professionals, you know, as a parent you're doing that risk benefit analysis for your child, as well, and that analysis is going to be very different, um, in a pre-event setting where there's perhaps maybe in some potential of an event and how much do you believe that's going to happen and your child might be affected versus, "I'm in it right now. My child might have been exposed and we're both getting vaccinated."

DR. WAGNER: Thank you. Well, actually, we will get to hear from you again, right, at this afternoon's occasion? So, I want to thank all three of you for a very stimulating, uh, conversation and we will take a recess for lunch returning. When do we return?

(Applause)