Drug Development Considerations for the Treatment of Neonatal Enterovirus Infection and Congenital Cytomegalovirus Infection

Virtual Public Workshop

Moderated by Sunita Shukla

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Reported by: Alexandra Hobrecht

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List of Attendees:

Robert Debiasi
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C O N T E N T S

P R O C E E D I N G S

DR. BELEW: Good morning, everyone. It is my honor to welcome our speakers, panelists, and audience to this important workshop on the topic of drug development for the treatment of neonatal enteroviral infection and congenital CMV infection.

It is also my privilege to present the opening remark and set the stage for what I hope will be a productive and valuable workshop.

Next slide, please.

My name is Yodit Belew. I am the Associate Director for Therapeutic Review in the Division of Antivirals, Office of Infectious Diseases, CDER, FDA.

Next slide, please.

So about this time last year, the WHO, among others, put out a disease-outbreak news alert due to -- regarding a severe enteroviral infection in infants and neonates, leading to many hospitalizations, including ICU admissions. Unfortunately, at least one infant died due to this outbreak.

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Next slide, please.

Congenital CMV infection is the leading infectious cause of birth defects and neurodevelopmental disabilities, including deafness. The CDC estimates that 1 out of every 200 babies is born with congenital CMV, with majority being asymptomatic at birth.

With adoption of universal screening similar to what Minnesota has introduced, one can expect that many more neonates with congenital CMV will be identified at birth.

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Both CMV infection and neonatal enteroviral infection can be serious and potentially life-threatening. More specifically, severe neonatal enteroviral infection and symptomatic congenital CMV are associated with higher risk of morbidity and mortality.

Based on the literature and epi data, these conditions can be considered rare; and to provide some regulatory context, Section 526(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act defines a

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rare disease or condition in part as a disease or condition that affects less than 200,000 persons in the United States.

As we are all aware, there are no FDA approved antiviral products for the treatment of enteroviral infection or congenital CMV infection in neonates or infants. So why is that?

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If we step back and think about the regulatory framework, there is a specific evidentiary requirement for establishing efficacy. Sponsors of drug products are required to establish safety and efficacy in both adult and pediatric populations before a product can be approved.

And how they demonstrate substantial evidence of effectiveness is through adequate and well-controlled clinical trials on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the condition of use.

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Outlined here are the elements of

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adequate and well-controlled trials, which include clear stated objectives or hypothesis of the trial well before the trial is initiated, a comparator-treatment group for quantifying or for qualitative assessment of efficacy, clearly defined eligibility criteria, ensuring that the population has the disease of interest, steps to minimize bias, well-defined endpoints for assessing treatment effect, and sound statistical-analysis plan.

Next slide, please.

As many here might be familiar, there is also an alternative pathway for establishing substantial evidence of effectiveness in the pediatric population.

That is to say that efficacy of a product can be extrapolated from adults to pediatric population if there already is an adequate and well-controlled clinical trial in adults, demonstrating substantial evidence of effectiveness.

This extrapolation principle is applied only when the agency has concluded that the course of the disease and the drug's effect are sufficiently

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similar between adults and pediatric populations to permit extrapolation from adult efficacy data to pediatric patients.

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So to bring us back full circle, because congenital CMV infection and neonatal enteroviral infection are unique or distinct conditions limited to infants and neonatal populations, adult data cannot be leveraged to establish effectiveness.

And conducting adequate and well-controlled clinical trials in these populations, while necessary, is undoubtedly very challenging for many reasons.

To name a few characteristics, we have poorly understood or not well-characterized natural history; potential challenges with designing well-powered studies due to small population size; and challenges in trial designs, including selection of endpoints.

Next slide, please.

And that is essentially why we are here

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today, to discuss the challenges and identify the needed additional scientific work to advance drug development for the treatment of neonatal enteroviral infection and congenital CMV infection.

FDA Public Workshop is intended to facilitate exchange of ideas among stakeholders to identify research gaps and help advance the field to address unmet medical need.

To clarify, FDA Public Workshops are not advisory to the agency; and the agency will not provide drug-development advice. It is not for regulatory decision-making; and all opinions, recommendations, and proposals are unofficial and nonbinding on FDA or other participants.

Next slide, please.

So I look forward to a discussion both today and tomorrow. We hope this workshop will move us closer towards our shared goal of advancing drug development to address these unmet needs. You should have full access to the agenda online, but I wanted to briefly highlight the key segments.

So the workshop will begin with several

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presentations on the general principle of pediatric and neonatal drug development.

After we return from about a 20-minute break, the rest of the day will focus on neonatal enteroviral infection with presentations during Session 2 and panel discussion during Session 3. Lunch break will be from 12:20 to 1:00 p.m., and we will adjourn today at around 3:30 p.m.

Next slide, please.

Day 2 will be entirely dedicated to congenital CMV infection with presentations during the morning session and panel discussion during the afternoon. Again, lunch break will be from 12:20 to 1:00 p.m.; and the workshop will conclude at 3:30 p.m.

Next slide, please.

And before I introduce our morning speakers, let me run through a few housekeeping items. So, one, this meeting is being recorded. Speaker slides, transcripts, and recordings will be available on the meeting's website in the coming weeks. So please check this page regularly for updates.

Speaker and panelist affiliations and

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disclosures are also available on the meeting website under "Meeting Materials."

For the general audience, please note that your microphone and video are automatically turned off. Please submit questions using the Q-and-A feature at the bottom center of your screen and Zoom platform.

Next slide, please.

And we are honored to have with us this morning Dr. Prabha Viswanathan, Dr. An Massaro, Dr. Kunyi Wu, Ms. Betsy Pilon, Dr. Lily Mulugeta, and Dr. John Concato to kickstart the workshop.

Next slide.

And it is my pleasure to introduce formally our first speaker, Dr. Prabha Viswanathan, Deputy Director of Office of Pediatric Therapeutics. Dr. Viswanathan's presentation will focus on ethical considerations for pediatric clinical trials. Thank you.

DR. VISWANATHAN: Good morning, everyone. It's a privilege to be here, and thank you for your attendance. We'll be beginning Session 1

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with a brief overview of ethical considerations for pediatric clinical trials.

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I have no disclosures.

Next slide, please.

So just an overview of what you can expect this morning, this is going to be a high-level 30,000-foot view of pediatric ethics.

We'll begin with a discussion of the general ethical framework that we use to analyze our protocols, and then we'll see how that ethical framework leads into the regulations that govern the inclusion of children in research, and I'll be really stressing four key concepts.

The first is the prospect of direct benefit, followed by the assessment of risk, the component analysis of risk, and finally the need for parent and guardian permission; and then we'll end with a discussion about how these considerations impact our development for the two conditions that are the subject of this workshop.

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So let me take you back in time to begin with the late 1970s, where the National Commission was convened to discuss the structuring of an ethical framework that really has two main concepts it is considering: one, the fact that children are vulnerable and require additional safeguards, balancing that with the fact that pediatric research is necessary to safeguard and improve the health and wellbeing of children.

Next slide, please.

So this commission convened and filed a report, and this is a very simplistic view about what they found. So in essence and in a summary, there are four key concepts: first, ensuring necessity; second, limiting risks; third, preventing disadvantage; and fourth, obtaining permission; and I will briefly go into these individually.

So first with ensuring necessity, because children cannot consent to participate in clinical trials, we should only enroll subjects when it is necessary to enroll these younger subjects to be able to meet the scientific objective of the trial.

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Secondly, when we think about risks, we think about how the risks correlate with the benefits that the child might experience in the trial; and this is going to be unique for every circumstance.

Third, preventing disadvantage, when children are enrolled in a trial, they should neither be exposed to excessive risks due to the interventions they -- they experience in the trial, nor should they be placed at a disadvantage by being unable to access care that they would otherwise receive outside of that setting.

And finally, obtaining permission is a critical aspect. Again, because children cannot consent for themselves, they must have parents or guardians that can act as a proxy to provide that consent.

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So next I'm going to transition into a discussion of how this ethical framework led to the regulations that we currently use today.

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I won't bore you with every detail of this slide, but you'll see on the left that the National Commission report that I referenced as long as the -- as well as a Belmont report that were both put together in the late 1970s gave rise to regulations that are both at the FDA level in 21 CFR and the DHHS level in 45 CFR.

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And these are parallel in their structure, but I'm going to focus on the right-upper area that's circled with the additional safeguards for children in clinical investigations, which is 21 CFR 50 Subpart D, which I will be referring to as Subpart D for the remainder of this presentation.

Next slide, please.

So the Subpart D regulations are really broken into five areas, two of which are really relevant for this discussion of the development of antiviral drugs for treating a clinical condition.

A therapeutic such as an investigational antiviral drug would be considered an intervention by and large that confers more than minimal risk to research subjects and therefore must be bound for the prospect of direct benefit for the subjects.

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That's 50.52, and then 50.55 is -- is the element about permission and assent. So we will only be focusing on those two today.

Next slide, please.

So let me just describe 50.52 for a moment. This is the balance of benefit and risk. This is what we do in clinical practice all the time and -- at the -- the bedside level as well as the population level.

So when we're evaluating a clinical protocol, we're looking for some key elements. So does this intervention involve greater than minimal risk? For the most -- by and large for candidate antivirals, that would be true.

Does it provide that prospect of direct benefit to the individual subject? And we'll be talking about the definition of that shortly. And are the risks justified by the anticipated benefit to the subject?

Secondarily and equally importantly, is that anticipated benefit, the risk balance, at least

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as favorable as any available alternatives, including those that are available to the patient outside of clinical research?

Next slide, please.

So I'm going to provide some definitions. You'll have heard me use these -- these exact phrases more than once, such as "prospect of direct benefit"; and so first, I want to talk about -- what does it mean to be direct?

So the benefit that a child experiences really needs to be felt by the individual subject, not the -- the study population in general. Each subject should have some benefit through their participation in the trial; and secondarily, that benefit needs to be arrived -- derived from the intervention under study.

So the simple benefit of increased access to healthcare and potentially enhanced monitoring on themselves do not equate to that direct benefit.

Second, I want to stress that the assessment for the prospect of direct benefit is

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really based on the data that support the activity and the ability of this intervention to modulate the clinical outcome but also how that intervention is used in the trial.

So proof-of-concept data that derive from either clinical human data or nonclinical data, a combination thereof, can support the -- the activity of the drug and the ability for that drug to lead to a change in clinical outcome, but the way that drug is deployed in the trial also must be advantageous.

So the doses that are used and the duration of the treatment should be sufficient to achieve the outcome. There is always the temptation to start low and slow, so to prevent toxicity; but sub-therapeutic doses would not be considered ethical by and large.

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So that was a discussion of benefit, and now I want to turn to risk, and measuring risk is -- is not easy, and -- and the language in our regulations is not incredibly clear.

So first of all, we have the definition

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of -- of minimal risk, which is the risk that normal healthy children encounter in their daily lives and in routine healthcare.

The other distinction that is made in the regulations is a minor increase over minimal risk. Again, there is some latitude here for interpretation; but this is somewhat more than what the child would experience in daily life.

Again, a healthy child would experience in daily life but does not have a longstanding threat to that child's health or wellbeing; and when a risk falls into this category, there's an additional requirement that the knowledge gained by exposing a child to this risk must be generalizable to that child's disorder or condition.

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Now, to -- until now, I've really been focused on the risk and benefit that derive from the study intervention; but when we are looking at a clinical-study protocol, we're looking at every intervention that is part of that protocol.

So there's the -- the drug under study

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but all the other interventions that come with it, and we do the same benefit-risk assessment for each and every one of those.

To -- to analyze those, we use the same framework that we would for the -- for the main intervention under study.

So if that intervention or procedure -- and for example, we could use a blood draw. If it does not hold out a prospect of direct benefit, then it should be restricted to more than -- more -- no more than a minor increase over minimal risk.

On the contrary, if that intervention does have some prospect of direct benefit for the child, then we have a little bit more risk tolerance; and again, a risk-benefit analysis is -- is conducted there.

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I just want to highlight a few examples of where this is challenging, and -- and some of these things that we don't always think about as elements of the protocol, not all of which are relevant to the discussion here; but some of them might be.

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So for example, biopsies that might be done in a clinical investigation either for diagnostic purposes or for measuring outcomes, some of them are simple like a muscle biopsy that might be considered a minor increase or -- or just minimal risk. Others that are invasive -- solid-organ biopsies -- are in a different category.

The same with diagnostic imaging, you have to consider both the risk of the radiation, how many times a child might be undergoing diagnostic imaging. The risk of contrast agents that might be administered and -- and related to imaging in some ways is also nontherapeutic procedural sedation.

So we know there are inherent risks to nontherapeutic procedural sedation. It may be allowable in certain circumstances, but we really look at these closely and -- and determine whether the -- you know, each of these components is -- has both a prospective benefit and a reasonable risk-benefit ratio.

Next slide, please.

I want to just spend a few minutes

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talking about placebo.

And this is the -- the discussion about placebo from an -- from an ethical standpoint, acknowledging that there are going to be many opinions about placebo that are offered over the course of the next two days both from pragmatic and acceptability to caregivers and -- and providers; but this, again, is really from the ethical standpoint.

So when we look at a placebo-controlled trial, the first thing we look at is -- what is the risk of the placebo itself? How is it administered? What is its composition? How long is it going to be given? And make an assessment about that in and of itself.

Second, what are the implications for that child receiving placebo instead of something else in the controller of a trial. So by and large, if there is an established and effective intervention, then all participants in a trial should receive that.

However, placebos are an important tool that we use first when there is no established ineffective intervention.

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And second, it is also acceptable to use placebos when we have an established effective intervention but the administration of that might obscure the treatment and confound the interpretability of the trial and if we could either delay or not provide that drug for a certain amount of time during the clinical-protocol duration and introduce mitigation procedures that -- that prevent that child from experiencing harm during the time that they're exposed to placebo.

Next slide, please.

We will pivot now from the discussion of benefit and risk in the 50.52 regulations to the 50.55 regulations for parent and guardian permission, and the main concept to really drive home here is that -- is, this is a hard time for parents and caregivers when they are caring for a critically ill infant.

And so you might have to come back more than one time to really provide an opportunity for parents to ask questions, understand all the dimensions that are affecting their child's participation; and they should receive follow-up as

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the -- as the trial goes on, if things were to change, if knowledge has been gained.

There are specific requirements for what the documentation looks like, which is available in the references on the slide; but I -- I won't go into those details for this presentation.

Next slide, please.

So I'm going to turn now to how this ethical framework impacts drug development for the two conditions that we're discussing today, enterovirus infection in neonates and congenital CMV infection.

Next slide, please.

And I'm going to go back to the ethical framework that we laid out before, these four core principles: ensuring necessity, limiting risk, preventing disadvantage, and obtaining permission.

Next slide, please.

We'll begin with ensuring necessity, and I think Dr. Belew has already addressed this quite a bit in her opening remarks, but we know that congenital CMV and enteroviral infections in neonates and very young children are -- are unique to this

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population.
It's a population that has an unmet medical need, and efficacy cannot be extrapolated because there is no corollary disease in other populations, including in children.
And so the scientific and public-health objectives cannot be met without enrolling the target population of neonates and young children; and so this element of the ethical framework is satisfied.
Next slide, please.
Second, we'll turn to limiting risks; and this will be possibly a topic for the -- for the next two days. So clinical trials that evaluate most candidate antivirals will need to meet the requirements of 50.52, as I outlined.
Just in summary, clinical and nonclinical data can be used to support the prospect of direct benefits; and then we will be looking at the investigational drug, the risk that is conferred from that as well as the other interventions and being -- making a risk-benefit assessment there about what level of risk might be incurred.

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A reminder that the study design is important in this benefit-risk assessment; and characteristics of the patient population, the risk-mitigation strategies that are deployed are -- are an important part of the assessment.
Next, the component analysis, so the risk-benefit assessment is not limited to that investigational product. We'll be looking at the benefit and risk of every intervention in the protocol.
This might include lumbar punctures, lab studies, diagnostic imaging, and -- and other assessments that -- that the child undergoes either for clinical care or for research purposes.
Next slide, please.
Third, preventing disadvantage, again, this -- I'm not offering solutions or answers here but just food for thought to frame the discussion that is sure to -- sure to -- to take place over the next two days.
So placebo-controlled trials are acceptable if certain criteria are met: first, if

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there's no established effective intervention or if the administration of an active control would make the study data uninterpretable and withholding that treatment can be done safely for the participant.
A reminder that adjunctive treatments should be provided if they are considered standard of care. So for example, in a critically ill neonate, all supportive care measures would be standardized across treatment arms.
Ongoing therapy, you have -- in the case of both enteroviral sepsis as well as congenital CMV, such as physical or occupational therapy and early-intervention services, would be deployed, regardless of treatment assignments.
Next slide, please.
So last, obtaining permission -- and the key message here is that informed consent is a process. It is not a document. The parents and caregivers in the -- in the neonatal intensive-care unit are signing consent all the time for blood transfusions, for small procedures.
So it's important to differentiate

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enrollment in a clinical trial from all of the other informed-consent procedures that they are -- all the procedures that they're -- they're asked to consent for.
Consider strategies that help parents and caregivers really comprehend what they are signing up for, training videos, parent feedback groups, et cetera; and I'll just put a thought in mind that although the focus of this -- of this discussion is really on our very young, our neonates and young infants.
If there was to be studies for these populations as they age and -- and the -- the possibility of antiviral therapy modulating their disease at an older age, then assent may be required in the participation of older children.
Next slide, please.
I'll just end with some resources. So the FDA publishes guidance documents to -- to summarize our views about a number of things, and these four guidance documents all touch on ethical aspects of -- of studies enrolling children.

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Next slide, please.
I'm going to skip my summary because I believe I have mentioned all of the points on the slide.
Next slide, please.
And I'll just end with some acknowledgements of my colleagues in the Office of Pediatric Therapeutics; to Dr. Melanie Bhatnagar, who has provided -- provided a lot of the content for this presentation; our director, Dr. Dionna Green; and all of the Pediatric Ethics staff, both past and present, who also have contributed to the content of this presentation. Thank you so much.
DR. BELEW: Thank you, Dr. Viswanathan.
Next I'd like to introduce Dr. An Massaro, Supervisory Medical Officer.
Next slide, please, Corey.
Supervisory Medical Officer for the Neonatal and Rare Pediatric Disease Team in the Office of Pediatric Therapeutics at FDA, she will be speaking about clinical and regulatory considerations for neonatal antiviral drug development.

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Thank you, Dr. Massaro.
DR. MASSARO: Thank you.
And thank you to the meeting organizers for inviting me to participate, and I hope to set the stage in the next 10 to 15 minutes or so and provide some context from the neonatology perspective that may be relevant to all of our discussions over the next two days.
Next slide, please.
These are my disclosures. My talk today will represent my views on these topics, but they don't -- I don't plan to discuss any specific medical products.
I'll just acknowledge that ensuing discussions may involve off-label use of medications, as this is common practice in the NICU, which is something we hope to change through efforts like this workshop.
Next slide, please.
This is an outline of my presentation.
As noted, my goal is to provide a high-level overview of considerations and challenges really

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that are inherent in neonatal clinical trials with a focus on considerations that may be relevant to the development of antiviral products for treatment of congenital infections but also provide some resources that can be later referenced for both medical-product development in neonates and some considerations for rare diseases in pediatric populations.
Next slide, please.
For background, in the U.S., pediatric drug development is largely driven by pediatric-specific drug legislations.
This includes the 2002 Best Pharmaceutical Acts for Children or BPCA, which is a voluntary-incentive program for pediatric clinical studies, and the 2003 Pediatric Research Equity Act or PREA, which gave the FDA the authority to require pediatric studies for certain drug and biological products.
Together these laws have led to a significant increase in the number of pediatric studies conducted and a subsequent increase in the number of pediatric-labeling changes for drugs and

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biologics over the past several decades.
Next slide, please.
In September of 2022, the FDA announced the historic milestone of achieving over 1,000 medicines that include evidence-based pediatric information and product labeling.
This milestone represented the collaborative effort of the FDA and multiple other stakeholders, who played a real important role in informing the current approach to developing medicines for children.
It's notable that the majority of these labeling changes occurred in the therapeutic area of infection diseases, as you can see highlighted here on the right side of the slide. This is very much in part due to the work of the divisions involved in the planning of this meeting.
Next slide, please.
While it's clear that progress has been made with regard to pediatric-labeling changes and drug development in pediatric patients in general, it's also clear that progress in the neonatal

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population has lagged.

In the NICU, we continue to practice in a setting where, as I mentioned, the majority of medications we prescribe to neonates are done so off label, meaning that they haven't undergone sufficient investigation to establish safety and effectiveness in the neonatal population.

Despite what I had shown you in the prior slides, which is, as I noted, now over 1,000 pediatric labeling changes, only about 5 percent of those have been -- have included studies or indications in neonates.

So we really have a scientific and legislative mandate to address this gap both by conducting clinical studies in neonates for medications that are approved in adults and older pediatric patients when that's appropriate but also by developing new treatments for conditions that are specific to the neonate.

Next slide, please.

There are many reasons for the limited study of drug products in neonates.

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These studies are inherently challenging, not only because the -- of the relative rarity of the disease conditions in the neonatal patients, compared to adults, but also because of the added complexity of clinical factors that can impact evaluation of a drug administered to a neonate.

These include the rapid maturation of organs and tissues that occurs late in gestation, a period that occurs in the ex-utero environment in the case of the pre-term infant; and there's continued significant maturation after term birth and into early infancy or childhood.

Developmental maturation at the cellular and biochemical level also represents a challenge, as many enzymes, receptors, transporters, and other signaling molecules are expressed differently with age.

Physiological changes associated with the transition from the in-utero to ex-utero environment after birth must also be considered, as changes in circulation; oxygen tension; and function of organ systems, such as the lungs and GI tract, are

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triggered after separation from placental support.

Finally, due to many of these factors that characterize the immaturity of the neonate, they are vulnerable to comorbidities and disease conditions across organ systems, making assessment of the safety and efficacy of a drug product particularly challenging to discern.

Next slide, please.

With that general background, I'm going to review a few regulatory considerations for neonatal drug development. As discussed by Dr. Belew, there's a regulatory standard for establishing substantial evidence of effectiveness with adequate and well-controlled studies.

However, this approach is often very challenging and in some cases not feasible in some neonatal conditions.

The other important regulatory concept relevant to our conversations in the need to establish substantial evidence of effectiveness with regard -- is considering that this is with regard to a clinically meaningful endpoint. That is a measure of

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how a patient feels, functions, or survives.

This can be challenging in the neonate, as I'll discuss in the next few slides; but first I want to address the concept of pediatric extrapolation, as it was also introduced by Dr. Belew in her introductory comments.

You see here in this figure where extrapolation is best leveraged is when there's a clinical and pathophysiological overlap between the neonatal and adult disease condition, denoted here by the red area -- arrow.

While the areas where extrapolation has been most successfully used to support substantial evidence of effectiveness in neonates are in anti-infectives and antivirals, as you saw in my prior slide that high number of labeling changes in the infectious-disease space is a testament to the successful leveraging of pediatric extrapolation in this therapeutic area, however, the use of extrapolation is limited when conditions occur exclusively in neonates or in conditions where the natural history or pathophysiology of the condition as

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it manifests in neonates is distinct from the adult-disease correlate.

And as Dr. Belew mentioned -- and I'll just re-emphasize here -- in general, I would consider the conditions we are focused on for this meeting, congenital CMV and neonatal enterovirus that fall into this category, infections with distinct manifestations and clinical sequelae specific to neonates that limit the use of extrapolation.

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So as noted, I wanted to spend some time discussing why measuring clinical benefit is not straightforward in the neonatal population.

And many of these points are very relevant to the discussions we'll have during this meeting when we think about how we will establish whether a drug, quote/unquote, "works" or not for these infections where the clinical sequelae may not manifest until much later, after treatment in the neonatal period.

As we'll hear from our patient and family advocates during the meeting, not everyone

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values the same outcomes similarly.

And the field of neonatology has numerous examples where therapies demonstrated to have positive short-term benefits were later counterbalanced by longer-term toxicities or loss of effective -- effect or seeing that benefit in the long term.

While this may point to the need for longer-term assessments for any investigational therapeutic agent, we'll acknowledge that this approach can lead to potential delays in getting effective drugs through the developmental pipeline to patients.

And there's also inherent complications with these longitudinal type studies for attrition and intercurrent events that can impact the confidence we have in the assessment of long-term drug effects.

While this may point to the need for surrogate endpoints for trials, timeliness and efficiency may be counterbalanced with uncertainty, depending on the reliability of the surrogate endpoint and its relationship to the outcome of interest.

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Those concepts translate into real challenges when defining clinical endpoints for neonatal trials. We're often looking for that unicorn -- what I'll call a unicorn endpoint that reflects an outcome that's common, assessed in a short time frame, and precisely measured.

Unfortunately for most neonatal conditions, we're assessing rare events that occur often late after exposure to a therapeutic agent; and apart from outcomes such as mortality, morbidity, definitions in the neonate represent a challenge.

As I noted earlier, the paradigm of feels, functions, and survives becomes difficult in a neonate. A patient -- it's a patient who can't really describe of course how they feel, and functional assessments in neonates often rely then on clinical or caregiver observations or other tools that may not be well-validated or fit for purpose.

Next slide, please.

So since I've spent a lot of time describing challenges without a lot of solutions, I do

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want to highlight a lot of ongoing work that's trying to address some of these challenges in defining outcomes for neonatal studies.

I've included some references here on several recent coordinated multistakeholder efforts to build core outcome steps for neonatal clinical trials in general, and there's even more ongoing work in specific disease area -- areas.

So one consideration for us in our discussions is whether congenital CMV or enterovirus would benefit from such an effort, and that may start with some of the discussions at our -- at this meeting.

Next slide, please.

Equally challenging to establishing substantial evidence of effectiveness is collection of adequate safety data for drugs studied in neonates.

The size of the safety database needed may depend on several factors, including experience with the drug itself or similar drugs in adults or older children or even previously studied neonatal subpopulations; the serious infrequency of adverse

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reactions observed in other populations, such as those; the rarity of the condition; the potential for unique susceptibility of the neonate to particular adverse events.

For example, when we're talking about an investigational product targeting congenital CMV with the aim to improve long-term sensorineural or neurodevelopmental outcomes, that would clearly warrant long-term evaluation from an efficacy standpoint.

But even when a drug is intended for a short-term effect, this may still warrant assessment for neuro -- long-term neurodevelopmental safety.

And the expectation may be to assess potential safety issues longer than may be potentially expected for -- in a drug development in adults, for example, especially if that drug is known to cross the blood-brain barrier and be associated with high exposure to the developing brain, again, a unique susceptibility to the neonatal population.

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These are some additional study

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considerations. It's important to sure -- ensure that studies are designed to include a spectrum of relevant clinical variability in the neonatal population of interest, and I'll discuss more about this on my next slide.

Another point to emphasize is to remember that the absolute blood volume of a neonate, especially a pre-term neonate, is very small.

So limitations in neonatal blood sampling need to be considered when we're designing our clinical studies, especially when we're considering that we'll need blood for sampling for PK/PD endpoints but also laboratory and safety monitoring in conjunction to routine clinical monitoring.

It's important to remember the environment also that these studies are occurring -- occurring.

As we'll hear from our patient and family advocates, conducting, studies in the NICU, obtaining consent from parents during a stressful time, incorporating study procedures amongst the busy

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workflow for physicians and nurses in the ICU, these are all big challenges.

So multistakeholder input is really needed early in the design process to ensure that these studies are feasible and acceptable to both clinicians and families.

Finally, safety data should be systematically collected. I already mentioned that the size of the safety database may be based on several different factors, but it's important to ensure that attention is also paid to how adverse events are collected.

For example, an adverse event such as hypertension is obviously defined with a different physiological range in the neonate than an adult; and other adverse events may be completely specific to the neonate, such as the occurrence of prematurity-related comorbidities.

So I'll refer you to a tool developed by the International Neonatal Consortium to define and grade severity for neonatal adverse events, and the reference can be seen here on this slide.

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Next slide, please.

As I alluded to on the prior slide, there's a wide clinical heterogeneity that characterizes the neonatal population. Using a common language can allow for methods to stratify patients based on characteristics that can greatly impact the analysis of PK and dose-response data.

This can allow for assurance that the product is evaluated across the range of gestational age, postmenstrual age, or postnatal age, as appropriate.

While of course we recognize that some of these variables may be highly correlated, such as gestational age and birth weight, it's important to recognize that they're all different conceptually, as you can see on this slide; and the information they provide to characterize the neonate are not interchangeable.

Next slide, please.

I've included here additional resources on many of the concepts I've introduced, including tools developed by the International Neonatal

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Consortium, resources from a meeting we convened in collaboration with Duke-Margolis last year on neonatal -- on measuring neonatal benefit -- benefit in neonatal clinical trials, and several of -- neonatal-specific FDA guidance documents.

Next slide, please.

I'm going to end my talk on a brief discussion of rare-pediatric-disease-drug development, as these considerations may also be relevant to our discussions for enterovirus and congenital CMV.

Work to advance drug development in rare diseases is supported by legislation, expedited-review pathways, and voucher incentives. I'm going to focus my comments -- my few comments on the orphan-drug-designation and rare-pediatric-disease-designation programs.

Next slide, please.

So prior to a sponsor receiving a rare pediatric disease, prior to a review voucher, determination must be made that the drug or biologic is actually for a rare pediatric disease.

So a request for a rare-pediatric-

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disease designation includes the data to support that the proposed mechanism of action of the drug or -- of the drug or biologic in that drug is intended to treat a rare pediatric disease.

And that's defined as a disease with serious or life-threatening manifestations that primarily affect individuals from birth to 18 years and that the total prevalence of the disease affects fewer than 200,000 people.

The rare -- RPD-designation portion of the Priority Review Voucher Program is administered by the Office of Orphan Products Development or OOPD in collaboration with our office and the Office of Pediatric Therapeutics within the Office of the Commissioner at the FDA.

Next slide, please.

So I've noted here -- and as Dr. Belew also mentioned -- the statutory definition of a rare disease, as defined by the Orphan Drug Act; and as we just discussed, there's also a definition for a rare pediatric disease; and it has its own statutory definition for the purposes of RPD designation and

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awarding of priority vouchers.

And I just want to emphasize that this is an important distinction when we discuss enterovirus or congenital CMV as, quote/unquote, "rare diseases." We'll be hearing a lot of epidemiologic information over the course of the meeting.

And it's true, and while it -- I'll note that it's true that prevention of congenital CMV infection following primary CMV infection in pregnant women and treatment of symptomatic enteroviral infection in the neonate have been -- indications have been granted orphan-drug designations in the past.

Whether these programs, the Orphan Drug Program or the RPD Program, may be leveraged for a particular development program for an investigational product to treat these infections really depends on several factors or eligibility criteria.

And reviewing all of these nuances in criteria are beyond the scope of my talk today, but I'll refer you to some resources that are available to guide this on my next slide.

You can go to the next slide, please.

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And here you'll find the relevant links to additional information on the programs I mentioned, as well as this first link here is a recently published review of the RPD Program. That has a lot of information about this first ten years of -- of this program being in existence.

Next slide, please.

So I'll wrap up and say in summary that drug development in neonates faces unique challenges due to rapid developmental changes and vulnerabilities that are really specific to neonates.

The FDA and really multiple other sources have resources to promote and support drug development for neonates and for rare pediatric diseases. So with that, I will turn back to the organizers. Thank you.

DR. BELEW: Thank you, Dr. Massaro.

Next I'd like to introduce Dr. Kunyi Wu, Clinical Pharmacology Team Leader in the Division of Infectious Disease Pharmacology at FDA. Dr. Wu will be discussing clinical pharmacology considerations for dose selection in pediatric

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patients.
Thank you, Dr. Wu.
DR. WU: Thank you.
So today I'm going to share the clinical pharmacology considerations for dose selection in pediatric patients.
Next slide.
This is the outline for my talk. First, I will talk about three broad approaches to pediatric drug development; and then I'll talk about modeling and simulation and the clinical pharm considerations for dose selection in pediatric patients.
Then I will use one example to illustrate how to use animal data to select initiatives in pediatric clinical trials and then follow up with challenges and opportunities.
Next slide.
This slide lists three broad approaches to pediatric drug development. First, when disease or disease progression is unique to pediatric patients, then PK, Safety, and Efficacy Approach is used.

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The second scenario is when disease or disease progression is similar in pediatric patients and adults but the exposure response, ER, relationship in peds may be different from adults; and now the PK, Safety, and PD/Efficacy Approach is used.
The third scenario is when adults and pediatrics share a sufficiently similar disease course and response to intervention. Then PK and Safety Approach is used. The third approach, which is the PK and Safety Approach, is the most frequently used approach in infectious-disease pediatric-development programs.
Next slide.
Valganciclovir is an example to use PK and Safety Approach to select and approve those adult, one month, and older, based on similar ganciclovir exposure in pediatric patients versus adults.
As multiple speakers already mentioned previously, for the two disease types we discussed in this workshop, which is congenital CMV infection and the neonatal enteroviral infection, those two disease types are unique in pediatric patients; and this PK and Safety Approach is not applicable.
So the sponsor may need to come to us to discuss before they initiate their clinical program.
Next slide.
Modeling and simulation plays an important role in pediatric drug development. I borrowed this figure from a publication from FDA back to 2019. In this publication, it illustrates the MIDD, Model Informed Drug Development Program, in Pediatric Program.
And they form three parts: first, leverage knowledge; second, dose selection and optimization; third, informing clinical-trial design. So in Infectious Disease Pediatric Program, usually before that we already accumulate some data from adults or other indications.
So a model can help to leverage knowledge, and the model also can help to compare the exposure-response relationship in pediatric patients versus adults. Model can help to select initiatives in pediatric-development programs, and the model also can incorporate pediatric ontogeny in infants and the neonates.
Sometimes model can help to select model, and the simulation can help to select sample size and the PK sampling scheme in the program.
Next slide.
Maribavir is an example to use published PK model to select pediatric dose in adolescents. Even without PK data, this dose has been approved. Of course, most studies are required in adolescents to confirm the simulation results.
Next slide.
So I want to use the rivaroxaban case to illustrate the learning and the confirming cycle in the modeling-simulation practice. Rivaroxaban is an anticoagulant, and it has been approved based on similar drug exposure in pediatric patients versus adults.
And the -- the study design -- the clinical study design is age staggered from older children to younger children. So in older-children cohort, it's older than 6 months. The study dose was

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predicted by using PBPK model, physiologically based pharmacokinetics model.

And interestingly, the observed exposure was way lower than the predicted exposure. So based on this observation, the sponsor increased dose regimen from QD to BID and then matched the exposure in adults.

And also based on this observation, sponsor selected higher than PBPK-model-predicted dose in younger cohort, which is younger than 6 months. However, the observed exposure still though was way lower than the predicted exposure.

Then the sponsor increased the dose regimen again from BID to TID and then matched adult exposure. At the end of the day, all the PK data were incorporated into the population PK model; and the clinical PK data and the population PK model analysis results were used to select dose in pediatric patients.

I hope this example illustrates the practice in modeling simulation as prediction, learning, and confirming the cycle.

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Next -- next slide.

This slide lists some clinical pharmacology considerations for dose selection in pediatric patients.

First, route of administration, for very young children and very sick children, the parenteral-administration route is preferred over oral because for the oral route first we have to have age-appropriate formulation, which takes time; and second, age may have impact on absorption.

So for different formulations, very young children -- absorption in very young children may be different from adults. However, most viability -- viability studies are conducted in adults. So that increased uncertainty for predict -- for -- for dose prediction in very young children.

And also, disease may have impact on absorption. For example, for enteroviral infection, then it impacts GI tracts; and that may have an effect on absorption.

We also view pediatric population as a very dynamic, very heterogeneous population, which

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means their body size, their body surface area, their weight changes on a daily basis, especially in neonates and infants.

So when we think about dosing regimen, we need to think about whether we want to use weight-based dose, which is milligram-per-kilogram dose or we want to use flat dose or we want to use weight-based dose.

Sometimes we also need to think about local drug concentrations. For example, for CNS penetration, central-nervous-system penetration, so if CNS is the target organ, then it is an efficacy concern if it is -- it is not, then it becomes a safety concern.

However, it's very hard to get a PK sample in CSF, cerebrospinal fluid; and even when we get a PK sample, it's very sparse and with high variability.

Another example is for hearing loss. For hearing loss, we need to consider the inner-ear penetration -- drug-inner-ear penetration. However, it's almost impossible for us to get a sample -- PK

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sample in clinical trials for inner-ear penetration. So animal models may become helpful in this case.

When we consider drug distribution and elimination, we need to think about organ maturation, enzyme maturation, receptor-transporter maturation. I have to admit we still have a knowledge gap in this area.

Next slide.

I want to use one example, which is lucinactant's case, to illustrate how to use animal-study results to select initial dose in pediatric clinical trials. So lucinactant has been approved for the prevention of respiratory distress syndrome, RDS, in premature infants because those children -- they cannot produce enough surfactant in their lungs.

So lucinactant is a synthetic surfactant. So because of the unique indication in this population, we don't have any PK data from adults, any clinical adults for -- from other indications. So the initial dose in neonates was directly selected based on premature monkeys and a premature-rabbit model.

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And a range of doses were evaluated in animal models, and three doses moved -- moved on to clinical trials; and eventually, one dose was approved.

Next slide.

We already know for the PK -- PBPK in animal models have been used in pediatric clinical programs. However, the daily challenge we encountered is with the decrease of age in younger cohorts we have fewer data.

So additional data, especially in very young children, will help us understand the physiology in -- in young children and help us to better predict and use the modeling-simulation practice or use some other approaches to estimate, predict, evaluate the dose in pediatric populations.

Next slide.

I want to use this opportunity to thank all the individuals listed on this slide and also thank my colleagues in the DIDP and the DAV in FDA for their help to develop those slides and also stimulating discussions. Without them, this

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presentation would not happen. Thank you for your attention.

DR. BELEW: Thank you, Dr. Wu.

Next I'd like to introduce Ms. Betsy Pilon, Executive Director for Hope for Hypoxic Ischemic Encephalopathy. Ms. Pilon's talk is entitled "Life of a NICU Parent: Decision-Making in Clinical Trial Enrollment."

Thank you, Ms. Pilon, for being here today and sharing your perspectives and experiences with us.

MS. PILON: Thank you so much for having me.

Next slide, please.

So I'm going to talk a little bit about the NICU experience from both my perspective and being a part of a community that very often starts in the NICU.

And I just want to ask everyone what you virtually walked into this room today and what kind of baggage. You know, it varies; and I want you to think in the context of the NICU what families

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might be walking in with.

So, please, next slide.

So families come in with something traumatic happening at birth often, whether it was planned or unplanned, depending on what -- you know, what their situation was.

And they have a lot of questions and a lot of trauma regardless because acute care itself, especially when you're expecting a baby and -- and going through this experience, you know, is definitely not in anyone's plan or hopes and dreams for -- for their child and their -- their parenthood.

Plus, you have to think about the other baggage that people have along the way regarding social determinants of health, regarding any sort of other, you know, developmental trauma or systemic, you know, impact and marginalization that may occur.

Next slide, please.

So this -- this is my story. Max was born 12 years ago actually last week -- or 2 weeks ago now, and he was my first pregnancy. Everything was normal and typical until it wasn't at 37 weeks.

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So the HIE community is a little bit unique in that the majority of our families are full term, but I know that there -- I'm very familiar with the CMV community as well and hope that this is, you know, applicable to the discussion points today as well.

He was born in the community-hospital setting, transferred to Downtown Detroit at Henry Ford Hospital for therapeutic hypothermia. We had no idea that this was even a possibility.

You know, the messaging and representation still remains heavily skewed towards preemies; and, you know, typically, families are counseled that if you get past 36 weeks you should be, quote/unquote, "in the clear."

And any full-term babies that I knew were there for transient observation, maybe a bilirubin level, something that -- that was very transitional and not something neurologically focused. For our -- for our journey, as you can see on the bottom, you know, we did get transferred to the NICU. So that was a layer of complexity.

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I was luckily transferred down a few hours after Max was. Max got into the cooling process -- you can see the little graphic at the bottom there -- on full EEG umbilical line. He was on the oscillator, very, very sick, getting transferred down; and we had to be separated because he was, you know, delivered by emergency C-section.

And then he went through his cooling for hypothermia, which is a 72-hour process, cooldown, warmup, and then on Day 5 received an MRI; and at that time, you know, the MRI, like many hospitals, was on the other side of the moon, it felt like; and they so had to pack him up, reintubated him for stability at that time.

I hope and believe and have heard that a lot of practices have changed over the past 12 years, always the case.

And -- but it was a very stressful time for us; and everyone kept, you know, talking about how MRI day was going to be the sentinel day of information for us to figure out if this was kind of a transient encephalopathy or if this was more

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associated with HIE.

But HIE at that time was not named to us. It was just talking about general brain injury, and so we did have MRI day. It showed moderate damage to the occipital, parietal, and frontal lobes; and we were kind of thrust into what everyone in our community called the dreaded HIE wait and see.

Wait and see how he's going to develop. Wait and see if he'll eat. Wait and see if suck, swallow, gag, you know, coordinates and comes together or if he'll need a feeding tube.

We had no mention 12 years ago of HIE until there was one day where we had non-family-centered rounds and overheard the term encephalopathy.

So I had worked for the health system in marketing and communications, had written a lot of patient-education materials, and had been exposed to a lot of different medical terms; and that was not one that I had been -- that I had been familiar with.

So I reached out to my sister-in-law, who's a pediatric physical therapist. I had asked her what encephalopathy meant. I asked the -- the

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physician what it meant. I flagged him down a little bit; and he said, "Well, it just means it has to do something with the brain; but don't go home and Google it."

So for me, that was a dissatisfier not knowing what, you know, a diagnosis was for my child, what this could mean, what life might look like across a very wide variety -- spectrum of outcomes with HIE. It is very heterogeneous in all ways, I believe.

And I feel strongly about now connecting with over 10,000 families worldwide with Hope for HIE and hearing so many different stories. So, you know, me as a family member, we -- we left the NICU without any connection to any support. I had asked for support. I had asked for other families to be connected to.

So obviously, that was a very isolating and frustrating time; and just the NICU in general is really -- it's a slog, regardless of if you're there for 1 day or 100 days. It's -- it's a very complex acute-care environment.

In our situation, you know, Max was,

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like, the only really sick full-term baby. So that was very isolating; and then when trying to talk to people about the fact that he was full term in the NICU, you know, there was just a lot of downplay or, you know, of course well -- well-meaning but very much -- you know: "He'll be fine. He's full term."

Or even in NICU support groups that we initially connected with, you know, we were told, like, many -- by fellow parents that had been -- there was nothing to worry about 'cause our baby was only in the NICU for three weeks.

So, you know, there's just a lot of interesting things; and when we talk about today -- next slide, please.

The topic at hand, which is neonatal clinical trials -- you know, and in this context of HIE and other -- other very difficult, harrowing potential experiences, there's lots of variables that work against research and -- researchers and families.

Now, Max was born in 2012; and that was at a period of time with cooling in particular that that was becoming standard of care; but it was not

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fully expanded standard of care.
And so we were very fortunate that Henry Ford was a part of the NRN cooling trials and that everyone was very aware that this was a treatment available and that they had the treatment available, you know, not only at Henry Ford.
But obviously, I'm in metro Detroit. There's lots of -- you know, lots of good sites that are -- that we had a lot of great research and -- and access to good care, but the disparity of care is certainly variable out there.
And so, you know, with HIE, in particular with cooling, you need to initiate it within six hours and get the baby started cooling down for biggest chance at efficacy; and I think back to the families that I'm connected to through our organizational support where there -- we have families that participated in the original cooling trials.
And I think about what a science-fiction, you know, discussion that sounds like to, you know, do an experimental treatment to cool a baby down for three days. You can't touch them, can't -- you

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know, have to keep stimuli low. At least, that was what the -- the experience of -- of us and those that went through those trials.
So it's, you know, very high stakes and, again, time sensitive. Resource variability I mentioned a little bit. You know, with HIE and a lot of neonatal clinical trials, there's the mother-baby health and separation aspects.
So I mentioned I'm very lucky that I was transferred, you know, with Max; but many people are not; and mother's health is often very impacted as well, depending on the causation.
There's an overwhelming well-intentioned and necessary consent that's insisted by the -- you know, the IRBs out there; and you have to really build quick health-literacy lessons to build consent to have informed consent. You know, with -- with HIE or many others, something didn't go right.
So a lot of times there's that, you know, fight or flight or freeze in -- in the midst of trauma. That can create a mistrust, and there's just a lot of medical misinformation out there that's

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causing a lot of mistrust. It is trauma.
And then we also come across on the clinical side -- there is -- is and can be bias, gatekeeping, and misperception of families and systemic inequity, so a lot of things -- a lot of big factors from the family perspective of -- and the clinical perspective of -- of trying to enroll families into clinical trials in the context of the NICU.
But we must accept finite disappointment but never lose infinite hope for that.
So next slide, please.
We're going to talk a little bit about the exciting work of the -- that is going on with researchers and families. So on HIE in particular, 'cause that's what I know and can talk about, you know, there's 30-plus years of research with HIE. We've explored cooling with head cooling versus whole body.
People have done additional, you know, studies with longer, quicker, colder gestational modifiers to really explore all facets of cooling.

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There's a PCORI study going on right now called COOL PRIME looking at mild HIE in cooling, which was not originally included in the -- the original underlying cohorts.
And then the HEAL study is another landmark study that now has very powerful secondary analyses going on. There's also -- the Gates Foundation has a preclinical pipeline with various small and large animal models and human organoid.
And they're really trying to look at equity for LMIC because HIE in particular impacts LMIC far more than high-income countries, but -- and -- and cooling is just not something that's feasible for many around the world or effective, given some updated information.
And on the horizon, there's novel and repurposed medication possibilities; and this is where I know the FDA and other regulatory agencies come in. People are talking about stem cells, peptides, biologics, and even melatonin and looking at what could -- caffeine, there's all sorts of things that are being explored.

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And things -- you know, what I -- what I was really struck by, by a previous speaker was looking at, you know, the -- the existing medications that are approved and what could be repurposed and getting also people outside of a specific area.

For HIE, it's very obviously neonatology and neurology focused; but, you know, we have a lot of innovation going on that -- I've heard a story of, you know, innovation going on from infectious-disease immunology as well, you know, in looking at multiple factors. So multidisciplinary collaboration is really essential for this.

And so the next slide, please.

Gap areas to consider from my perspective, silos, bias, and impact to the enrollment -- you know, centering the community that you're studying and avoiding tokenization for funding, that does happen across HIE and other -- and other disease areas.

Having early multidisciplinary stakeholder involvement, thinking outside neonatology -- neonatology, as I mentioned early in the trial-

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design process -- and site training for communication is essential to enrollment success, making sure that people really are building training resources in collaboration with families that have gone through clinical trials to, you know, really, you know, implement best practices in consistency and also have mechanisms of trying to just, you know, find ways to answer common questions to optimize enrollment measures, develop measures that matter.

I know this was alluded to by An earlier. Composite, there's a lot of work being done right now in multiple areas, which is really exciting versus lumping death and disability, which is kind of the comment of, you know, mortality and morbidity.

And NDI in particular is such an interesting definition that I think we're seeing a lot of work that's being done, and Jean Vie [ph] up in Canada and others are looking at what we can do to move to that composite and then looking to help patient and family stakeholders understand those biomarkers too.

We want to be educated. A lot of the

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bias that does exist is that families can't understand or they're not educated. So help us be educated and understand so we can also translate that back to communities.

And then looking at longitudinal engagement and support and looking at proactive communication planning, that should be formalized throughout the entire study, so looking at how your intention -- the intentionality, the key messages, working with a communication consultant.

I -- I can't emphasize -- emphasize that enough to use best practices for patient and family engagement with those considerations for building health literacy and include longitudinal support resources for enrolled families.

Families -- you know, two years is a long time. There's a lot that goes on. You're in the acute period in a neonatal trial in the NICU; but then afterwards you have to figure out life with what you've gone through and process and, you know, deal with whatever impacts might be long-lasting from the NICU.

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Families need those supports so we can decrease attrition rates and make sure that they're really engaged in these studies. So, you know, we've tried to do that with several of the studies that our families have been a part of; and, you know, the HEAL study is a great example.

There's a ton of secondary analyses. I am communicating those back to our community as they come out and continuing to have families be engaged in that process to build this community culture of research.

Next slide, please.

And just to give my own example of Max's journey to share where a lot of these clinical trials stop, you know, so Max's developmental-impact journey, vision concerns early on, 3 months, you know, we were pushed -- we pushed to wean him off phenobarbital, which is now -- there's evidence behind that practice change over the past decade, which is fantastic.

You know, at 9 months old, he got -- received an official cerebral palsy diagnosis. At 2

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years, he got corrective vision surgery. You know, he was in PT and OT and has been for his entire life. He has a slew of specialists down there -- you can see -- from 6 months onward.

Then you can see the black line, and this is where most clinical trial ends because of data and funding and needing to accelerate things through; but of course, kids hopefully go on to live lives; and with Max, he began walking at age 3. At 5 years, he had some delays and suspected ADHD. At 8, he had confirmed inattentive ADHD.

At age 8 and a half, we had epilepsy join our lives, onset at the sleep-wake cycle; 10 years, an anxiety diagnosis; and at 11 years, just this past year, an official CVI diagnosis and had a pretty intensive surgery that he's been doing an amazing recovery with.

For medications, like I mentioned, he was on phenobarb when he was born, which is very standard of care to control seizures, although he had no noted subclinical or clinical seizures; and -- but when epilepsy rejoined, he was on Trileptal -- or he

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is continually on Trileptal.

He has a rescue med. He's on Adderall. He was on baclofen until last year's surgery. So we've been able to take that one off. So just looking at the medication cocktail, what impact does that have? It's really important to families to understand the pharmacokinetics behind that as well.

And that is -- I have the next slide; and I am happy to take questions or connect at any point; but again, I want to thank you for the opportunity to speak today.

DR. BELEW: Thank you, Ms. Pilon.

Next I'd like to introduce Dr. Lily Mulugeta, Associate Director for Policy and Research for the Division of Pediatric and Maternal Health at FDA. Dr. Mulugeta's talk is entitled "Facilitating Neonatal and Pediatric Drug Development: Leveraging Pediatric Trial Networks and Global Collaboration."

Thank you, Dr. Mulugeta.

DR. MULUGETA: Thank you for that introduction.

Good morning, everyone.

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And, Betsy, really thank you for that family perspective, such an important component of what I'll be discussing.

Again, I'm Lily Mulugeta. I'd like to thank Yodit Belew and the rest of the organizers for inviting me to participate in this workshop today.

Again, my talk will focus on leveraging pediatric-trial networks to facilitate pediatric drug developments. In addition, I will briefly touch on some global collaborations in advancing pediatric drug developments.

Next slide, please.

I have no financial conflicts to disclose.

Next slide, please.

So perhaps I'm preaching to the choir a bit here, but I do want to take a minute to remind us of the important principles of pediatric therapeutics' development. So much of what we will be discussing today and tomorrow will be based on these principles.

So firstly, I hope we recognize that it's imperative that pediatric patients similar to

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adults have access to products that have undergone rigorous evaluation. One way to do this is to ensure that pediatric studies are incorporated early into product-development programs when appropriate.

There's also growing recognition that incorporation of regulatory standards into pediatric clinical research really strengthens the quality of the research.

Next slide, please.

So moving on to the challenges in pediatric drug development -- and I think you've heard some of these challenges earlier; but really to emphasize, one of the most persistent issues is the lag between adult approval and pediatric labeling.

This delay, which often averages around seven years, means that children may not have timely access to treatments that have deemed to be safe and effective in adults. Patient-accrual difficulties also pose a significant challenge in pediatric drug development and account for nearly 40 percent of study discontinuations.

Factors contributing to these

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difficulties may include the small size of the pediatric patient population for certain conditions, the willingness of clinicians to use therapeutics off label, and inefficiencies in conducting pediatric clinical trials.

These challenges, which are particularly pronounced in neonates and infants, can result in insufficient evidence to support pediatric product labeling, which really leaves healthcare providers with limited guidance on the use of new therapeutics in children.

Next slide, please.

So the evolution in pediatric drug development over the last really couple of decades represents a paradigm shift; right? It's no longer about protecting children from research but really rather protecting them through research.

And this shift in mindset really recognizes that evaluating both new and existing drugs in pediatric patients requires collaborations across various stakeholders, and I think Betsy really illustrated that very nicely as well.

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So it has to include patients, families, patient organizations, academic researchers, community practitioners, regulators, and industry partners.

The FDA, for instance, has really demonstrated its commitment to improving the efficiency of pediatric clinical trials through collaborative initiatives; and I'll touch upon some of these in my talks; but really this workshop is another example of many collaborations that are aimed at advancing pediatric drug development.

Next slide, please.

So opportunities really for collaboration in pediatric drug development are abundant. One key opportunity lies in precompetitive collaborations where various stakeholders can share preclinical data, tools, and resources without compromising their competitive interests.

These collaborations not only foster innovation but also streamline the drug-development process and ultimately benefit patients, which is really our goal. Consortia and partnerships between

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academia, industry, and regulators are also crucial under -- in driving collaborative efforts.

These partnerships can also enable the development of innovative trial designs that overcome the many limitations of neonatal and pediatric development, including the small sample sizes and the acceptability of the pediatric trial design.

Additionally, which is really the focus of my talk today, pediatric-research networks can play a pivotal role in facilitating the setup and execution of pediatric clinical trials; and I'll talk a bit more about this in the next several slides.

Next slide, please.

So the roles of pediatric-research networks are really multifaceted. Networks in general -- not limited to pediatric networks, but networks in general have been identified as a promising approach to overcome inefficiencies in clinical research, which is particularly important for the pediatric population.

These networks facilitate collaboration among stakeholders who may not have traditionally

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worked together -- right -- such as researchers from different institutions, industry sponsors, regulators.

And so by pooling resources -- and that may include data or expertise or both -- these networks can accelerate research and development in pediatric patients.

They can also encourage innovation, which is highly desirable in the -- in pediatric drug development by supporting the implementation of novel trial designs, use of registries, modeling studies, and platform trials.

And lastly, pediatric-research networks enable the conduct of multicentered trials; and I'm sure I don't have to say too much about this to this group. I just really need to emphasize that this is an essential component for recruiting larger and more diverse pediatric-trial populations.

Next slide, please.

So there is a variety of pediatric-research networks with different organizations -- organizational structures and levels of activities.

Some of these networks are based around

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clinical specialties really focusing on optimizing patient outcomes while other networks operate across geographical locations and really focusing on addressing barriers and inefficiencies in the conduct of clinical research.

And really ideally, these networks are highly integrated -- right -- combining the strengths of clinical specialty-focused approaches really with the broader reach of geographically diverse networks, and I'll provide some examples in the next few slides.

Next slide, please.

So pediatric-research networks have the potential to significantly impact discussion-making throughout the drug-development life cycle, and I think this is really an important emphasis.

In the early phases, these networks can provide valuable insight -- insights into disease prevalence, treatment patterns, patient heterogeneity, and even potential biomarkers that may be specific to the pediatric population of interest.

In later phase stages, pediatric-research networks can influence key aspects of trial

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design; and this can include inclusion-exclusion criteria, treatment duration, collection of supplementary safety data and considerations around data extrapolation from either older children or adults.

And in addition, by collaborating with these networks, sponsors can also potential optimize trial conduct by identifying potential trial candidates, engaging qualified sites, and -- and investigators as well.

Lastly, pediatric-research networks play -- can play a vital role even in the post-approval stage.

And this can be a mechanism to contribute to the expansion of the product labeling to other pediatric populations, generating supplementary safety data, and potential even addressing long-term safety considerations that may not be really fully understood at the time of its initial approval in adults or approval in pediatric patients.

Next slide, please.

So examples of successful active

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pediatric-research networks abound -- right -- showcasing diverse models and approaches to pediatric drug development. There's no way that in my 15-minute talk I'll be able to provide an exhaustive list of these networks, but I do -- would like to highlight a few examples.

One example is the Pediatric Trials Network or the PTN, which was established in 2010 with funding from the NIH. This was specifically to fulfill a mandate under BPCA. The PTN collaborates with academic institutions, industry sponsors, and regulators to provide infrastructure and support for both designing and conducting pediatric trials.

And what's interesting, this network's contribution also includes submission of the collected data to the FDA to update product labeling specifically for off-patent drugs; and you'll hear more about this network from my colleague Rachel Greenberg tomorrow.

Similarly, other collaborative initiatives, such as the Collaborative Antiviral Study Group, bring together multiple centers to conduct

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clinical trials, evaluating new antiviral therapies.

So these really multicenter collaborations, which often can be funded by government agencies or public private partnerships, play a crucial role in accelerating the development and evaluation of both new and old treatments for pediatric patients.

Next slide, please.

I know this is really a busy slide, and I really don't expect you to read what's -- all the information that's in this slide, but it's really to emphasize that the landscape of pediatric drug development is enriched by a multitude of collaborative initiatives and research networks.

Each of these contribute uniquely to the advancement of pediatric therapeutic innovation.

As you can see, some of these networks around -- are modeled around clinical specialties, such as IMPAACT, for example, while others include multiple specialties and focus on addressing inefficiencies in the conduct of pediatric clinical research; and that includes C4C, iACT, and others that

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are listed on here.

In addition, the range of activities of these networks may also vary; and it could include anywhere from protocol development for evaluation of novel therapies to providing collaborative clinical-trial infrastructure, assistance with regulatory submission, and development of consensus and treatment guidelines.

It's also important to note that these networks are increasingly broadening to a global and patient-centered approach, which, you know, given Betsy's presentation, it's clear that this approach will yield to better and efficient pediatric research and development programs.

Next slide.

And just to briefly touch upon networks that are unique to neonates, there are neonatal networks. An example is the International Neonatal Consortium or the INC, which plays a vital role in addressing the unique challenges associated with neonatal drug development.

Many of these challenges were mentioned

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by my colleagues earlier this morning. So really by leveraging multidisciplinary expertise and collaborative frameworks, neonatal networks like INC aim to develop consensus-driven approaches that can enable feasible and practical trials in neonates.

This concerted effort has been particularly -- particularly impactful, for example, in neonatal seizures. This is a space where regulatory waivers for required pediatric studies in neonates were previously granted due to perceived impracticality.

And as a result of the -- all the work that was done by the INC and the consensus recommendations that were developed, it has really allowed the FDA to require neonatal studies for anti-epileptics on a case-by-case basis.

Next slide, please.

So moving on to global collaborations, one that I would like to mention is the International Council for Harmonization or the ICH, which stands as an example of concerted efforts to harmonize regular -- regulatory standards and promote global

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collaboration and cooperation in therapeutics development.

The ICH fosters alignment among both regulatory authorities and industry experts, and the recent milestone in this collaborative journey is the recent publication of the ICH E11A Guideline, which provides a harmonized global framework for extrapolation of data, both PK efficacy and safety and pediatric drug development.

And this guideline is really grounded in scientific rigor but also provides regulatory harmonization and really exemplifies the synergistic potential inherent in global collaborations when aimed at enhancing therapeutics development for children.

Next slide, please.

There are clearly many international regulatory collaborations. I've just listed a few. Some are solely focused in pediatrics, while others are broader but address pediatric regulatory-related issues.

Initiatives such as the Monthly Pediatric Cluster Conference, which was established in

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2007, for example, facilitate ongoing dialogue and information exchange among regulatory agencies. This one particularly includes FDA, EMA, PMDA, Health Canada, and TGA.

So these collaborative forums really serve as catalysts for sharing scientific insights, discussing policy considerations, and addressing pediatric-specific regulatory challenges, ultimately with the goal of ensuring that pediatric drug-development programs are efficient and practical.

Next slide, please.

So really in summary, given all the presentations today and hopefully from some of the information I've shared with you, I hope it's evident that the landscape of pediatric drug development is characterized by significant achievements stemming from collaborative efforts and multidisciplinary approaches.

Collaborative networks that continue to expand globally are instrumental in driving progress, fostering innovation, and addressing challenges inherent in pediatric and neonatal therapeutics

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development.
And as we look towards the future, really continued emphasis of -- on inclusion of voices, such as Betsy's, of patient outcomes, data transparency, regulatory harmonization, and policy development will be paramount in sustaining the momentum of therapeutic innovation for pediatric patients.
Next slide, please.
Again, I would like to thank the organizers for giving me an opportunity to speak today, as well as my colleagues from the FDA at PTN who contributed to these slides; and I look forward to the rest of the presentations and discussions. Thank you so much.
DR. BELEW: Thank you, Dr. Mulugeta.
Next I'd like to introduce our last speaker of the session, Dr. John Concato. Dr. Concato is the associate director for Real-World Evidence Analytics in the Office of Medical Policy at FDA. Dr. Concato will be speaking about real-world data and real-world evidence in drug development.

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Thank you, Dr. Concato.
DR. CONCATO: Thank you.
Hello, everyone.
And next slide, please.
The views and opinions expressed are my own and should not be attributed as official FDA policy. I do not have any conflicts of interest related to this presentation; and when I mention commercial product, it's not an actual or implied endorsement.
Next, please.
I'll be providing a high-level overview, starting with a background on real-world evidence and then moving onto selected aspects of FDA's Real-World Evidence Program, including guidance development and demonstration of research projects, and then moving on to real-world data and real-world-evidence activities related to neonatal healthcare.
Next.
Let's start with the 21st Century Cures Act of 2016 and mandates met. I need to convey that we have established the program, as Congress asked us

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to, to evaluate the potential use of real-world evidence to support a new indication for a drug already approved or to satisfy post-approval study requirements.
We also have issued a draft framework within two years and guidance for industry starting within five years and -- and continuing through just a couple of months ago.
An important note at the bottom of this slide, our standard for substantial evidence to approve drugs and biologic products is unchanged. We owe that to patients, whether they be adults or neonates. We have to be sure that the drugs are safe and effective.
Next, please.
This is a screenshot of our 2018 real-world-evidence framework. I wanted to with this slide mention that what I'll be discussing applies to the Center for Drugs, the Center for Biologics, and the Oncology Center of Excellence.
We coordinate with our Center for Devices and Radiological Health, but they have their

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separate regulations, and they've covered a real-world-evidence program with a lot of cross-communication and cross-specialization.
Back to drugs and biologics, our program can be thought of informally in the taxonomy of: one, internal agency processes, such as providing consultation to review divisions; number two, external stakeholder engagement listed in sections or even today's workshop and tomorrow -- and tomorrow's workshop; number three, demonstration of research projects -- I'll give an example later -- and last but not least, number four, guidance development.
Next, please.
Just to mention, because there is a bit of ambiguity, if not confusion in the -- in the field, in the ecosystem, real-world data are data related to patient-health status or delivery of healthcare routinely collected from a variety of sources.
And then real-world evidence is clinical evidence regarding the benefits and risks of a medical product, defined simply as being derived from analysis of real-world data, regardless of the

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study-design type.
Next, please.
So why all the attention focused on -- let's say "hype" -- on real-world evidence? This is somewhat simplified, but interest in real-world evidence can be attributed at least in part to improved access to -- and the ability to be rapidly analyzed -- information in the era of so-called big data.
In addition, research over the past actually several decades has shown that observational studies -- while they have a more challenging time addressing sources of bias, they can under certain circumstances generate valid results.
Certainly, the 21st Century Cures Act asking the -- the U.S. FDA to evaluate the potential use of real-world evidence for medical-product approvals is relevant.
And then simply and perhaps and sociologically, the popularity of "real-world" as a term and other factors, unfortunately something like the COVID-19 pandemic, which focused attention on

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different methods of evidence generation -- but I do want to point that with -- without invoking the terms "real-world data" or "real-world evidence," we can actually talk about types of data sources and study designs.
And those terms aren't new but are totally sufficient to convey the intended message.
Next slide, please.
Moving forward to more recently from a couple of years ago, a colleague, Jacqueline Corrigan-Curay, and I published on where are we now with regard to real-world evidence; and the main content of the article -- the main issue being addressed -- excuse me -- was that the terms "RWD" and "RWE" were being used inconsistently and interchangeably.
So the content of our article addressed two common misconceptions, provided a conceptual overview of study design, described our guidance and demonstration projects, highlighted a couple of approvals, and offered a path forward. My next two slides will cover the first two of these five content areas.

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Next, please.
Just in case it helps going forward in general, not just limited to neonatal healthcare, one misconception is that RWD and RWE are new concepts. In reality, sources of data and types of study design, as I mentioned, haven't fundamentally changed.
They might evolve, but it's really the electronic access to more detailed clinical data evolution as well as the data becoming more reliable -- relevant and reliable, is what's making a difference.
The second misconception is that there's a simple dichotomy of, quote, "randomized trials versus observational studies," close quote, again, a misconception. In reality, clinical trials are defined by assignment of treatment according to an investigational protocol.
So if you think about it, single-arm trials face challenges similar to those of observational studies in determining whether differences in clinical outcomes -- in that case compared to an external control group -- represent

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actual treatment effects.
Next slide.
These same issues are shown in this figure. I will not go through each word on the page.
But at the upper portion of the box in the middle of this slide, as methodologists, we talk about randomized interventional studies, nonrandomized but still interventional studies, and then nonrandomized and noninterventional studies, a little bit jargon-y; but the next one down is more shoptalk in our line of work.
We've had traditional randomized trials, which might use real-world data to help plan, such as to assess enrollment criteria and assess trial feasibility or select sites. We have trials in practice settings, such as point-of-care trials where the outcome might be pulled from health-record data.
We have externally controlled trials, and then we have observational studies, which is what many people think of when they hear the term "real-world evidence."
But at the bottom of that simple box,

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note that the generation of real-world evidence can start with randomized trials. It certainly includes externally controlled trials; and of course, it includes observational studies.

This is a bit technical, but I think it's relevant, whether we're talking about neonatal medicine or geriatric medicine or anywhere in between.

Next slide, please.

Here is where the guidance that FDA has published is -- is summarized. I know there's a lot of rows in this slide, but we chose a modular approach, a suite of guidance so that it's one-stop shopping when you have a question as a sponsor or any -- or an investigator.

I'll summarize this slide by saying the first two rows are real-world-data sources, Electronic Health Records and Claims, as well as Registry or Data Standards. In the third row, regulations were developed, assuming clinical trials would be the basis of evidence submissions. So we had to account for the real-world-data differences.

"Regulatory Considerations" speaks for

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itself. Our regulations didn't anticipate nonclinical trials; and then the next three, Externally Controlled Trials, Noninterventional Studies, and Trials in Practice Settings, are design-consideration guidances.

Last but not least, we have a Submitting Real-World Evidence guidance, which allows sponsors to help us to help them if they accurately identify what they're doing with regard to real-world data and real-world evidence.

The link at the bottom provides all the information you might want in general to see these guidances as well as to see summaries of them.

Next slide, please.

Just to give a little bit of detail on our guidances, this is a screenshot of the Assessing Health Records and Medical Claims or HR Claims guidance that was issued in draft several years back.

Next slide, please.

A little bit more in detail, excerpts from "Real-World Data" on the left: "The process for examining the quality of data is not a one-time assessment. Rather, it's an ongoing process in

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multiple phases of the life cycle of" -- Microsoft changed "EHR" to "HER." I apologize for not spotting that typo.

And the figure on the right basically shows the complexity.

Not to go through this dataset, but unlike clinical trials, where the data come in ready to be analyzed, we don't -- we don't blame the clinicians at the bedside for taking care of the neonatal patient and not necessarily knowing that the electronic health record will be pulled later to do our research analysis.

Next slide, please.

So what does FDA do -- CDER and CBER and OCE in particular -- when evaluating real-world evidence? This is a very high-level overview; but when going to look down, we consider whether the real-world data are fit for use, a major issue.

And by "fit for use," we mean whether they're reliable, accurate, complete, and traceable and whether they're clinically relevant.

We also determine whether the study

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design generated adequate scientific evidence to answer -- help answer the regulatory question; and then last but not least, the study conduct has to meet FDA regulatory requirements to ensure the -- the safety and efficacy of the product.

Next slide, please.

So here is an example actually approved for both adult and -- and pediatric patients based on so-called real-world evidence.

PROGRAF, tacrolimus, had been approved for the prophylaxis of organ rejection in patients receiving liver and later kidney and heart transplants based on traditional randomized control trial evidence; and the drug was used widely in clinical care, including for lung transplantation.

But RCTs were not done or at least not submitted to the agency for approval. Later on a sponsor submitted a supplemental New Drug Application for FDA with an observational real-world-evidence study.

The study data and design were evaluated according to FDA standards. We heard in the

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introductory talk about our 314.126 regulation section that determines what is an adequate and well-controlled investigation.

And in -- in this case, approval for preventing rejection/death in lung transplant, again for both adults and pediatric patients, was granted in 2021.

Next slide, please.

I don't want to leave you all with the idea that working with real-world data is an easy task. These are representative challenges with the real-world data or real-world evidence that cover a wide slot of submissions, and most submissions fall short at least at this time.

It's not always a sponsor's fault. I would say in the first category of real-world-data sources sometimes the data are just not reliable and relevant enough; or again, a clinical trial might have datapoints at certain intervals of weeks or months, whereas in clinical care it's more driven by other factors.

We heard earlier about endpoints. The

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suitable capture of endpoints isn't always feasible in real-world-data sources, and sometimes there's a need for linkage with other data sources. Excuse my voice today, I'm asking.

Certainly, the design and interpretation of nonrandomized studies presents problems, such as confounding. An underappreciated problem is problems with index date or zero time -- I don't have time to get into that -- or the use of an inappropriate comparator.

And then last but not least, in the category of conduct, unlike clinical trials, where everything is done prospectively, in -- in this case, we want to be sure that the analysis was prespecified. If it's not, there could be some cherry-picking going on that makes the drug look better than it actually is.

And then last but not least, we do require access to patient-level data and the ability to inspect real-world-data sources.

Next slide, please.

Part of our footprint includes real-

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world-data and real-world-evidence work on neonates. This is a screenshot from a website that is still on the FDA page, "Advancing Standards and Methodologies to Generate Real-World Evidence from Real-World Data through a Neonatal Pilot Project."

The U01 Award at the top is a cooperative research agreement through Health and Human Services. This was a competitive procedure or process whereby the International Neonatal Consortium, part of the Critical Path Institute, was awarded a project.

Basically, it -- the point is to -- to develop a real-world-data analytics platform, and that has been very successful to date.

Next slide, please.

I won't go into the details. I'll leave that for my C-Path colleagues, but this commentary from 2023 in the Journal of Pediatrics on "Real-World Evidence for Neonatal Drug Development: Challenges and Opportunities" mentioned that the challenges surrounding the use of real-world data are substantial but not insurmountable.

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And real-world-evidence-driven drug development represents an evolution in scientific methodology as well as a renewed commitment to advancing neonatal health on a global scale.

Next slide, please.

I'll wrap up by saying that the FDA remains committed to robust policy development aligned with the 21st Century Cures Act while we maintain our evidentiary standards in honoring our obligation to protect and promote public health.

Focusing on the distinction between interventional studies and noninterventional studies can help us all understand and describe the relevant methodologic issues that might be holding us back; and certainly, getting more experience, including the conduct of rigorous noninterventional studies, will help to advance drug development.

Next slide, please.

So hopefully, I've conveyed these summary points. One is that, in addition to the randomized trial paradigm, not in lieu of it, not to replace it, the availability of big data and passage

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of the 21st Century Cures Act reflect and contributed to the emergency of real-world evidence.

Our Real-World Evidence Program for drugs and biologics is advancing, as we outlined in our 2018 framework, including guidance documents and demonstration projects, as I've given a couple of examples of.

And please, again, appreciate that CDER approves drugs and biological products based on existing evidentiary standards, including when evaluating real-world evidence.

But as the earlier slides have indicated and presentations, we -- we all hope for a better future and the appropriate use of real-world data and real-world evidence can advance neonatal drug development in ways that we're not entirely sure -- sure of yet but that we can look forward to seeing in the future.

Next slide, please.

Thank you very much.

DR. BELEW: Thank you, Dr. Concato.

That concludes the presentations for

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Session 1 of our agenda. We're running a bit behind, but we now have a few minutes to take clarifying questions related to the presentations we have heard this morning.

Panelists, please raise your hand in Zoom if you wish to ask a question.

And, members of the public, you may enter your questions in the Q-and-A box.

Dr. Kimberlin, do you have a question?

DR. KIMBERLIN: I -- I do, and I'm not sure if it will fit with this particular section or not. I was struck by a couple of things with -- across the presentations, which were all really good.

One is the comment about the challenge of placebo and -- and the acceptance of -- of a placebo-controlled trial on the one hand and then the -- the need for some sort of comparator -- a good comparator on the other hand, Point Number 1.

Point Number 2, even with the modeling that we can do from older children and adults with a given antiviral, if it's not being used in babies, we don't know what the ontogeny is going to be. We don't

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know how the drug is going to be metabolized, excreted. We don't know what the concentrations are.

Would it be possible to develop a study that has a range -- simultaneously enrolls a range of -- of doses, some of which are modeled to be therapeutic, not yet proven, some of which are deliberately less than that, subtherapeutic or maybe even homeopathic, in a way that then would be able to -- we'd be able to say: "Look. Everybody gets drugged, but we do have a range of -- we anticipate a range of benefit that could be looked at with an adequate sample size"?

So that -- that -- that's the question. Is that something that FDA could be open to?

DR. BELEW: Dr. Kimberlin, thank you so much for the question. I think your first question about placebo -- I think we'll talk more about this during the panel session. As to your second question, we could also perhaps talk about this during the panel as well, unless Dr. Wu has any comments to make.

DR. WU: Yeah. This is Kunyi. I can -- I can give a try and get started, and I think

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we can discuss more in the panel discussion.

But for modeling simulation, just from a technical perspective, if this drug is repurposed and then we know the PK of the drug, just based on our understanding -- it -- it's case by case of course.

But based on our understanding on the ontogeny, on the enzyme maturation, on the receptor-transporter maturation, we may or may not be able to predict those in the neonatal and infant population; and then, again, it's case by case. So this is a technical challenge and difficulties.

And then for your second question, I think you asked, you know, simultaneously enrolled -- so that's, you know, beyond my knowledge; and then we have to discuss. I'd just defer to other disciplines to answer this question.

DR. VISWANATHAN: Hi, Dr. Kimberlin. This is Prabha Viswanathan again. I -- just to briefly touch on the ethical aspect of your -- of your question, if I heard it correctly, about whether it would be acceptable to enroll subtherapeutic doses and -- we never say "never" in ethics. It's all really

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about context.
But prolonged doses of a -- of a -- or multiple doses of -- of a -- of a drug that's known to not offer that prospect of direct benefit to the participant is something that would need to be justified. So I think that's something that we can dig into, into the panel a little bit more.
DR. BELEW: And, Dr. Abzug, I think you had a clarifying question as well?
DR. ABZUG: Thank you.
And I want -- first of all, want to thank everybody for the excellent presentations that we've heard thus far. I also want to pick up on -- on David's question a little bit about the issue of a placebo.
It seems to me there's a tension between the standard of direct benefit to all participating subjects and having a placebo group, which is the gold standard for a randomized control trial because in most circumstances placebo recipients are not expected to have a direct benefit from the intervention.

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So I -- I'd like to hear a little bit more about how that tension is -- is addressed or should be addressed in -- in study design. Thank you.
DR. BELEW: Thank you, Dr. Abzug. I think that those are really important comments, and we're -- we're hoping to cover that more in the panel.
DR. VISWANATHAN: Yeah. I -- I can just provide a very brief response, and I -- I do think it merits more discussion during the panel. We acknowledge that the placebo control doesn't receive benefit. The -- the trial needs to be designed in such a way that risks are minimized for all patients, regardless of their subject assignment.
Ultimately, it is a complex issue. So I -- I do think it probably deserves a little bit more discussion from all the different contributors a little bit later in the afternoon, but thank you for the question.
DR. BELEW: Great. Thank you all for those questions and to our speakers for providing answers. We're now going to take a break; and we'll reconvene at 11:20 for Session 2, when we will discuss

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enterovirus epidemiology and background.
(Off the record.)
DR. PICA: Welcome back. We will now begin Session 2, which will focus on enterovirus epidemiology and background. We are delighted to have Dr. Amy Rosenfeld, Dr. Miranda Delahoy, and Dr. Mark Abzug here this morning.
Next slide, please.
It is now my pleasure to introduce our first speaker, Dr. Amy Rosenfeld, Principal Investigator in the Division of Viral Products in the Office of Vaccines, Research, and Review at FDA. Dr. Rosenfeld's talk is entitled "Picornaviruses and Neonatal Sepsis."
Thank you, Dr. Rosenfeld.
DR. ROSENFELD: Thank you very much for inviting me to speak to you this morning about picornaviruses and neonatal sepsis.
Next slide.
So picornaviridae is a family of viruses. These are single-stranded positive-sent RNA viruses that are nonenveloped; and the viral family is

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composed of 40 genera; and today we're going to talk about 2 of the genera, which is the enterovirus genus and the parechovirus genus.
And the enterovirus genus is composed of 11 -- of 14 species, plus Rhinoviruses A through C, whereas the parechovirus genus is composed solely of one species, parechovirus, which is then subdivided into A and B.
And we're going to talk about the A -- viruses in A's, which is Parechovirus 1, 3A, and 6, which are associated with neonatal-sepsis infection, as well as members of Species B of the enterovirus genus, which are Echoviruses 11, 30, and Coxsackie A.
Additionally, there are additional coxsackieviruses that also associate with the development of neonatal sepsis.
Next slide, please.
So the picornaviruses all have a similar structure. They're composed of, as I said, a nonenveloped particle, which is composed of three viral capsid proteins. Viral Capsid Proteins 1 through 3 are on the exterior surface of the particle,

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and Viral Capsid Protein VP0 is on the inner surface of the particle.

The difference between parechoviruses and enteroviruses is a maturation cleavage, VP0 into VP2 and 4 for enteros, which occurs after the particle is egressed from the infected cell. So it is a cleavage that is thought to be catalyzed by the ion genome in the particle. That occurs after the virus is released.

So capsid proteins are cotranslationally proteolytically processed and self-assembled, and they self-assemble into pentamers, which are on the right, which are five protomers of each viral protein. This gives rise to an icosahedron particle, which has the signature threefold, fivefold, and twofold axes of symmetry.

And here, if you look at the particle on the side, the pentamer, you can see VP4 in green lines the interior surface. Not all particles form a canyon, which is a crevice that surrounds the fivefold axis of symmetry.

For many enteroviruses, including

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poliovirus and rhinoviruses of the major group, this is a receptor-binding site. However, once again, this canyon is not present on the surface of parechoviruses and many other echo -- and many other enteroviruses.

Next slide.

All of these viral genomes are -- have the same organization. They're all linked to viral genome -- viral-protein-linked genome, which is VPG at the five-prime end. This is removed or -- upon release of the viral genome into the cytoplasm.

So you have a free five-prime end without the seven-methylguanosine cap to regulate translation initiation, but the viral RNA is immediately engaged by the ribosome and is the mRNA of the genome.

And once again, it is a single open meeting frame; and this polypeptide is cotranslationally proteolytically processed by viral-encoded proteases into either the mature or immature proteins through the schematic map that I've described beneath.

Next slide.

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These viruses all replicate within the cytoplasm of the infected cell. So they attach to a cell-surface protein, which is known as the receptor. Many of these receptors have not been identified.

Once the particular attaches to the cell protein, the surface protein, it is internalized in an endosome; and depending upon the enterovirus or even parechovirus, un-coding and release of the viral genome is a pH-dependent process. So it's regulated by the acidification of this endosome.

The RNA is released. It's immediately engaged by ribosomes. It's translated into the polypeptide. The final approach -- the final enzyme of this polypeptide is the RNA-dependent RNA polymerase and -- which regulates and is required for replication, which -- of the viral genome, which goes through a negative-strand intermediate.

Once the viral genome is replicated, it is immediately encapsidated by the viral procapsid precursors. They are -- the virus particle is assembled. It is released; and for enteroviruses, as I said, there's the maturation cleavage of VP0 into

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VP2 and VP4 after egress.

Next slide, please.

So the pathogenesis of picornavirus is very interesting. These viruses are species-specific. They are generally spread from one individual or animal to another in an oral-fecal or respiratory mechanism.

Severe disease does not occur at the primary site of infection. It occurs at the secondary sites of an infection, which can include the central nervous system, the liver, the skin, as well as the heart and thought to pancreas.

The presence of neutralizing antibodies in the sera of infected patients is the best biomarker for protection for the good development of severe disease, and this is done from studies of patients that were infected with poliovirus as well as many different serotypes of human rhinovirus.

Next slide, please.

So in the lab, we measure infectious virus generally by two methodologies. Our lab uses a plaque assay, which is serial tenfold dilutions and we

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-- of the viral stock or -- or sample, and then we ask whether or not we can see a focus of dead cells by staining the monolayer with a dye -- with a dye that looks for cell viability.

You can use -- also use endpoint/terminal dilutions, which are done in these 96-well plates; and again, you score for cytopathic effects, as described in the table below.

Next slide, please.

However, the presence of RNA in the -- so clinically, we don't do this anymore. We generally use an RT-PCR looking for a fragment of the viral genome. This suggests that we're measuring the presence of viral RNA and not infectious virus.

And here you can see from studies done by -- on Zika virus that the detection of viral RNA occurs -- can persist much longer than the generation of the infectious virus.

So there is a discordance between the presence and detection of RNA as from infectious virus, and we're really only concerned about whether or not you are producing and shedding infectious

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virus.

Next slide, please.

One of the important aspects of clinical research or the clinic for enteroviruses was -- is discerning or assessing whether or not you have an active infection, if you have immunity, or if you were priorly exposed to the virus; and for this, we use an ELISA binding assay.

And these are described here in the -- in the schematics, as you have a solid support. You have an antibody. You either look for viral antigen or an antibody against the virus, and then you come in with an indicator.

So these are generally done by lateral flow and commercially available for many viruses, such as we saw for SARS-CoV-2.

And if we want to look at neutralization and say that you have seroconverted and you have a protective immune response, we use a microneutralization assay, which is derived from the endpoint/terminal dilution assay that I just described in the previous slide.

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Next slide.

However, there is a caveat to this; and that is the presence of a cross-reactive enterovirus-antibody response, which my lab has been characterizing for many years now.

So what we did was, we immunized mice with individual enteroviruses, including islets of EV-D68 and coxsackieviruses as well as rhinovirus and polio; and then we collected the polyclonal sera and used plaque assays to determine whether or not the sera was able to protect cells and culture from the infection -- from infectious virus.

And you can see here that when you use polyclonal sera from mice immunized with an Enterovirus D islet -- you can see you're able to protect cells and culture not only from the immunizing virus but as well as from heterologous enteroviruses, including polio as well as different islets of EV-D68 and Rhinovirus 1A.

Next slide, please.

This suggests that when we talk about sera -- results from serosurveys, seroconversions,

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sera -- seropositivity studies, we must keep in fact -- keep in mind that there is a presence of a cross-reactive immune response, which may suggest that these studies' conclusions are misleading.

And we must try to figure out mechanisms or assays which are more virus-specific, which has been difficult because there's tremendous genomic conservation among these viruses.

Next slide, please.

And with that, I will end and be happy to take questions. Thank you for inviting me.

DR. PICA: Thank you, Dr. Rosenfeld. We'll actually wait for questions at the end of all the speakers, but thank you so much.

Next I'd like to introduce Dr. Miranda Delahoy, Senior Epidemiologist in the Acute Flaccid Myelitis and Domestic Polio Team within the Division of Viral Diseases at Centers for Disease Control and Prevention.

Thank you for being with us here today, Dr. Delahoy.

DR. DELAHOY: Thank you.

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Good morning, and thanks for the invitation to present today about epidemiologic data and neonatal enterovirus infections, which is collected through national surveillance.

Next slide, please.

Before presenting national surveillance data on neonatal enterovirus infections, I'll spend a few minutes discussing the surveillance systems that collect these data. Knowing about these systems can help understand data availability as well as limitations of surveillance data.

There are three main national-surveillance systems that collect data on enterovirus infections: the National Enterovirus Surveillance System or NES, the National Respiratory and Enteric Virus Surveillance System or NREVSS, and the New Vaccine Surveillance Network, NVSN.

Next slide, please.

This slide gives an overview about these three systems. NES is a passive laboratory-based surveillance system. Passive surveillance systems rely on voluntary reporting and are likely to

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miss cases but can cover large areas and be useful for observing infection trends.

NES has been collecting reports on enterovirus infections, along with virus-type information, since the 1960s. It covers all age groups, and patient age is reported down to the month. The number of reporting laboratories varies from year to year. In 2022, the CDC lab and labs from four states reported EV-typing data to NES.

Scope is limited partly due to the number of laboratories performing EV typing. The other two surveillance systems that collect information on enterovirus infections provide aggregate non-typed data for rhinovirus and enterovirus positivity.

These include the National Respiratory and Enteric Virus Surveillance System or NREVSS, which is also a passive system collecting data from more than 90 labs nationally, and the New Vaccine Surveillance Network or NVSN, which also collects aggregated rhinovirus and enterovirus data among children presenting to 7 pediatric-health facilities

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across the country.

Because NES has the most granular information on enterovirus types and ages of the patients with infections, most of this presentation will focus on data from NES, although I will intersperse some information from NREVSS and NVSN.

Next slide, please.

I'll now present an analysis of two decades' worth of data from NES. We analyzed data on 10,224 non-polio enterovirus infections reported to NES during 2004 to 2022 to assess types and fatal outcomes of neonatal enterovirus infections. Note that the data presented today are considered preliminary.

Next slide, please.

Among all of the infections, 7 percent occurred among neonates defined in this presentation as being under 1 month old.

Next slide.

Many enterovirus types were identified among the neonatal infections reported to NES. This graph shows the number of neonatal infections reported

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to NES during the past two decades by virus type.

Coxsackievirus B5, Coxsackievirus B3, Echovirus 11, and Coxsackievirus B4 were the virus types most frequently detected among neonates during this time period.

Next slide, please.

We'll now take a look at some temporal trends in the nine most common virus types or those that each represented more than 5 percent of the total number of neonatal infections.

Next slide, please.

This graph shows data from NES on the number of reported neonatal infections by year for the most commonly detected enterovirus types among neonates, with each EV type represented by a different color.

To give an example of how to read this, in 2004, all the way on the left, the orange segment is the largest and goes from 1 to 16 on the Y axis, representing 15 total infections for Echovirus 9 because Echovirus 9 is the one that corresponds to that orange color in the key.

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It's hard to see; but beneath that, there is one Coxsackievirus B5 infection in the dark-blue color; and above, there are four CVB4 infections in gray and so on.

Overall, there was not a single virus type that was most commonly detected and reported each year. Rather, the top virus types among neonates changed over time. Several virus types had peaks in certain years and then periods of low detection between peaks.

For example, Coxsackievirus B5, shown in the blue at the very bottom of the stacked graph, had apparent peaks of detection in 2005, 2010, 2014, and 2017 to 2018, whereas CVB3, in the brown color toward the top of the graph, had a large peak in 2014 but low detection in other years.

Please take caution in interpreting these apparent patterns because of the small numbers of infections represented overall, but I do hope -- hope that this helps to visualize changes in predominant virus types over time.

This can also be used to visualize

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overall trends in infection. You can see here that the most neonatal enterovirus infections were reported during 2014.

Next slide, please.

Overall, some virus types were more frequently detected among neonates, compared with older children and adults. These included Coxsackievirus Types B1, B2, B3, B4, and B5 and Echovirus 11. However, EV-D68 and Echovirus 30 were less common among neonates and more frequently detected among persons aged 1 month or older.

Next slide, please.

We also considered temporal patterns of neonatal enterovirus infections. This graph shows the reported number of neonatal infections reported to NES by month from 2013 to 2022. Enterovirus infections tend to peak in late summer and early fall. Few enterovirus infections were reported during the early COVID-19 pandemic or 2020 and 2021.

Next slide, please.

Looking at months during which infections were reported summed across the years from

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2004 to 2022, the numbers of reported infections were highest during July through October.

Next slide, please.

Turning for a moment to other data sources, similar seasonal patterns of rhinovirus and enterovirus circulation among respiratory specimens were also observed in NREVSS, with percent positivity peaking in September or October of the past five years.

Next slide, please.

Similarly, in NVSN, rhinovirus and enterovirus detection peaked in September or October each -- each year among children with respiratory infections.

Next slide, please.

We'll now turn back to the NES data. Enterovirus infections were detected from a number of specimen types, such as CSF, NP swabs, and stool or rectal swabs.

Compared with older patients, enterovirus infections were more commonly detected among CSF for neonatal patients, whereas among persons

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aged 1 month or older infections were more commonly detected by throat or NP swabs.

Next slide, please.

In NES data, only 10 percent of neonates had a known outcome, that is, whether they died.

Next slide, please.

Among the 35 neonatal patients who had known outcome in NES, 15 -- or 43 percent -- died. It is likely that enterovirus testing and reporting in general as well as reporting of outcome data are biased toward patients with more severe infections.

Next slide, please.

There are a number of limitations in the analyses presented today. A small number of labs perform and report EV typing, and these labs are not nationally representative. Enterovirus typing and reporting is voluntary and not systematic.

It is likely that testing and reporting are biased toward including more severe infections and potential infections among younger patients. In NES, outcome data are often unavailable; and in general,

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national enterovirus-surveillance systems include little -- limited clinical information. Excuse me.

Next slide, please.

To summarize our conclusions, enterovirus types detected among neonates differ from those detected among persons aged 1 month or older. Enterovirus infections display a seasonal pattern, typically peaking in late summer; and enterovirus infections can cause severe disease among neonates that can result in death.

National data on enterovirus infections can be used to observe seasonal trends and detect signals in year-to-year changes and enterovirus infections. They can also be used to analyze circulating virus types by age.

It is our hope that enterovirus surveillance can be strengthened in the United States. Strengthening the capacity for enterovirus typing and surveillance could be beneficial for understanding the burden of disease and clinical manifestations of enterovirus infections and for informing potential treatment options and prevention measures.

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Next slide, please.

Thank you all for your attention today and to my CDC team and those who invited us to speak today. I'm happy to take questions during the clarification session.

DR. PICA: Thank you so much, Dr. Delahoy.

Next I'd like to introduce Dr. Mark Abzug. Dr. Abzug is a professor of pediatrics at the University of Colorado School of Medicine in the Section of Infectious Diseases and Epidemiology and is Vice Chair for Academic Affairs for the Department of Pediatrics.

His title is -- his talk is entitled "Neonatal Enterovirus Infections: Challenges and Opportunities."

Thank you, Dr. Abzug.

DR. ABZUG: Thank you.

And thanks to the organizers for the opportunity to speak with you today. My role is to now present over the next 20 minutes or so a clinical overview of the infections that we're talking about developing therapies for.

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Next slide, please.

I have no relevant financial relationships with commercial interests.

Next slide.

So my goal is to do two things. One is to give you a flavor of the clinical challenges that neonatal enterovirus infections present and why we need therapies for them and then to let you know where we are currently as far as treatment options for these infections.

Next slide, please.

So to give a little bit of broadness to the -- to the -- in context to the discussion, neonatal enterovirus infections are one type of manifestation of a broad canopy of -- of presentations that enteroviruses can -- can produce.

Firstly, most infections are likely asymptomatic. Of those that are symptomatic, most of those cause nonspecific febrile illnesses in children or adults. Many cause rashes. For example, Echo 9, as shown here, is a common cause of rash-associated

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illness.

Coxsackie A Viruses are associated with herpangina, which is shown in the picture just immediately to the left with vesicles -- small vesicles in the posterior oropharynx. This is often a highly febrile illness.

Hand-foot-mouth disease is similar but with slight differences. Here you can see on the right-hand side the ulcerations more commonly in the anterior oropharynx but also involving the peripheral extremities. This is often associated with Coxsackie A16, also with Coxsackie A6, and in the context of pandemics of Enterovirus A71.

Hemorrhagic conjunctivitis can cause -- be caused by a number of serotypes. That also may be neurotropic, and that picture is depicted on the lower left, and in the last decade has emerged respiratory illness associated with Enterovirus D68.

Next slide, please.

Coxsackie B Viruses in particular are important causes of myocarditis and pericarditis and account for up to about a third of cases of viral

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myocarditis with a proven etiology. Enteroviruses cause a range of neurologic syndromes, including meningitis, encephalitis, acute disseminated encephalomyelitis, and Reye's syndrome.

They can cause paralytic disease with polioviruses or acute flaccid myelitis with Enterovirus D68. Enterovirus A71 is a type of enterovirus that's common in cause of pandemics of brain-stem encephalitis, particularly in Asia.

Enteroviruses can cause a number of severe infections in immunocompromised hosts, including chronic CNS infection as well as disseminated infections. We're going to talk more about perinatal and neonatal viral sepsis.

And then I'll also mention that there are some data linking enteroviruses in a persistent or chronic form with a number of chronic conditions, as shown here. Those data are really not that definitive.

Next slide, please.

So for neonatal enteroviruses, as we focus in on them, this slide is really just meant to

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give you an overview of the epidemiology to say that newborn enterovirus infections are common.

Many of them, if not most of them, are asymptomatic; but of the smaller group that are symptomatic, you can see that they're associated with a range of presentations in the newborn: viral sepsis, viral meningitis, myocarditis, or any combination thereof.

But overall, if you look across these different articles in the literature -- literature, you'll see that these viruses are a common cause of disease in the newborn period.

Next slide, please.

The epidemiology of neonatal enterovirus infections mirrors that of enterovirus infections in general that we've just heard about. So we tend to see these infections in the summer and fall in temperate regions; and there's variability year to year and place to place, depending on what types of enteroviruses are circulating locally.

And that was really borne out a year ago when we saw these reports from the United Kingdom

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of severe myocarditis in newborns associated with Coxsackie B3 and B4 infections and, as been mentioned earlier, reports from France and elsewhere in Europe of Echovirus 11 infections causing severe neonatal hepatitis and coagulopathy.

Next slide, please.

Transmission to the newborn of enteroviruses may occur in a minority of cases prenatally, and that's evidenced by retrieval of virus from products of conception or by evidence of clinical illness and/or viremia in the baby as early as within a couple of hours after birth to a couple of days after birth.

But the majority of babies when they acquire an enterovirus acquire it intra- or post-partum most often from the mothers, occasionally from other family contacts; and we know from epidemiologic studies up to a few percentage of mothers during enterovirus season will shed virus either from respiratory or GI secretions at the time of delivery.

If a mother has illness in the week prior to delivery associated with enterovirus, then

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there's a much higher rate of the baby becoming infected; and babies have been shown to be infected following both vaginal or caesarean delivery.

And there's speculation that breastmilk may also transmit virus, at least based on reports of positive culture or positive PCR of breastmilk specimens.

There are also reports of sporadic and epidemic spread of enterovirus infections among staff and babies in nursery settings.

Next slide, please.

The vast majority of newborns who have an enterovirus infection fortunately are asymptomatic infections. Then there's a subset of babies who have -- will have a benign illness often characterized by fever for a few days and some other symptoms for around a week. Sometimes there's a biphasic course.

Meningitis that's uncomplicated may occur in some of these babies, generally associated with a good outcome. Fortunately, the disease that we're most concerned about today in this session, severe disease, is the least common of these outcomes

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but the most worrisome.

Next slide, please.

So when we see a baby who may be infected by an enterovirus, there are a number of features that are evident from the history. Most often these babies, even those who have a severe infection, are born to mothers with a normal pregnancy. The babies are most often full term and have had uncomplicated initial courses.

Prematurity does worsen the outcome overall for neonatal enterovirus infections, but it's a minority of babies who become sick who were premature to start with.

If there has been a viral illness in the mother around the time or preceding delivery, which occurs in about 60 to 70 percent, that may be associated with a variety of symptoms, including fever, respiratory or GI symptoms.

Severe abdominal pain in the perinatal period of the mother also is prominent as a result of this infection, and that may mimic chorioamnionitis or abruption and may actually cause an obstetrician to

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think that delivery might be needed sooner rather than later.

There's often a history of viral symptoms in other family members; and in the baby, the viral-illness onset may occur anywhere from the first day of life out to a month of life; but severe disease most often is associated with onset of illness within the first two weeks of life and especially within the first week of life.

Next slide, please.

This is a listing of symptoms and signs that neonates with an enterovirus infection may present with, and you can see it's rather broad and rather long.

Often these babies present as generically ill newborns with fever or hypothermia, irritability, lethargy. They may have anorexia. They may be hypoperfused. They may be jaundiced, and they may have a variety of rashes, with macular or maculopapular rashes being the most common.

GI involvement is often present, and respiratory symptomology is also a frequent presenting

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set of symptoms.

Next slide, please. Next slide, please.

This slide shows the variety of manifestations that I characterize under the heading of "Severe Disease." The more common are on the left-hand side: meningoencephalitis, myocarditis, pneumonitis, hepatitis, coagulopathy, and sepsis.

Some uncommon complications of neonatal enterovirus disease are listed on the right-hand side; and of note, any of these manifestations may occur in -- in -- together as a constellation. So a baby may have meningoencephalitis and hepatitis. It may have myocarditis and hepatitis and coagulopathy, et cetera.

Next slide, please.

Now, this slide is a busy one; and it -- and it aims to summarize the most common scenarios we see with severe enteroviruses. Meningoencephalitis, myocarditis, pneumonitis, and hepatitis and coagulopathy all just highlight some of the points on this slide.

Meningoencephalitis may be caused by

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echoviruses or Coxsackie B Viruses. It's hallmark is in change in consciousness. Seizures may occur. Motor abnormalities may occur. On imaging, particularly MRI, white-matter injury particularly in the periventricular area is not uncommon.

And these babies have a variable prognosis. The majority of them live through their infection, but their neurologic prognosis depends on how severe their acute-encephalitis picture was.

Myocarditis most often is caused by the Coxsackie B Viruses, and this is often -- often associated with a high mortality rate in the order of 30 to 50 percent, and survivors may either have residual cardiac dysfunction or sometimes may go on to have no evident long-term sequalae.

Pneumonitis is a less common presenter of severe enterovirus disease. When it occurs, it's most often associated with echoviruses, occasionally with Coxsackie B Viruses. It may be a primary manifestation, or it may be associated with any of these other manifestations. It tends to be rapid and severe and associated with a very high mortality rate.

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Hepatitis and coagulopathy for years now have been recognized as primarily associated with echoviruses, with Echo 11 being the prototype; but in more recent reports, Coxsackie B Viruses have also been shown to cause severe hepatitis.

And in its most severe form, this syndrome will present as acute hepatic necrosis with acute liver failure with an associated coagulopathy noted by thrombocytopenia and prolonged clotting times and often -- sometimes grave clinical bleeding, including intracranial bleeding.

There's a broad range of mortality reported from anywhere from 24 percent to into the 80-percent range. Of survivors, some will have persistent hepatic dysfunction; but because of the regenerative capacity of the liver, many survivors will eventually develop normal liver function once again.

Next slide, please.

It is hard to give you the answer of what is the mortality rate with neonatal enterovirus disease because we don't have good population-based

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prospective data. Mostly, what we have are case series in the literature that use a variety of different conclusion criteria.

And Dave Byron from AntiVirus Therapeutics put together this graph on the left, which plots out some of the different reported mortality rates in different series in the literature; and you can see that they're really all over the place, reflecting different inclusion criteria used in the different series.

But many of the series show quite high mortality rates; and in this plot, somewhere around 40 to 50 percent was sort of the average if you take all these reports together.

A few years ago we did a query of the PHIS database of 45 children's hospitals; and using diagnostic codes for neonatal enterovirus hepatitis, coagulopathy, or myocarditis, we came up with a 24-percent mortality rate in this database.

And then a recent literature review that spanned 20 years identified a mortality rate of 30 percent. So that at least gives you some

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representative examples.

Next slide, please.

What we do have from the literature are a number of risk factors or markers that help us identify which babies are the ones most likely to have severe disease.

Onset of illness within the first seven days of life -- and especially within the first few days of life -- is a key marker, as is absence of neutralizing antibody in the baby to the serotype of enterovirus that he or she is dealing with.

And that likely is also tied to the next risk factor of maternal illness with offset just before or at delivery, meaning mother has had enough time to transmit a lot of virus to baby but not enough time to develop antibody that will be passably transmitted to the baby.

As I mentioned earlier, prematurity is not the prototype on presentation; but when babies who are premature develop severe neonatal disease, they tend to do worse, as do males; and babies who have multisystem disease, such as hepatitis plus

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myocarditis, tend to do worse.

Severe hepatitis that's caused necrosis and acute liver failure, also a poorer prognosis; and a few lab markers, a positive serum viral culture has been shown to correlate with mortality; and certain serotypes, including Echovirus 11 and some of the Coxsackie B Viruses, are also associated with worse disease.

Next slide, please.

This is a nice graph because I just think it -- it really exemplifies the importance of timing of onset. This is a review over 10 years from China from now almost more than 20 years ago.

But this looked at neonatal enterovirus disease characterized in three different presentations: in the dark bars, nonspecific febrile illness; in the white bars, uncomplicated viral meningitis; and in the bar graph -- or not the bar graph but the -- the line, the solid line, hepatic-necrosis cases.

And you can see that the benign presentations, febrile illness and meningitis, really

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were pretty much scattered over the first month of life, as shown on the X axis.

But if you look at hepatic necrosis, that line has a really strong peak within the first seven days of life, making the point that it's the babies who present earliest who are generally the ones more likely to develop severe disease.

Next slide.

And in my last few minutes with you, I just want to tell you about the current state of therapy and things that are on the horizon for neonatal enterovirus infections. Standard treatment right now includes when a baby presents and is being worked up with the symptomology and the disease manifestations I've shown you.

They typically are given empiric antibacterial treatment until bacterial infection is ruled out. Likewise, specimens are sent for herpes simplex virus, which can often very much mimic the presentation of neonatal enterovirus disease; and usually, an empiric treatment of aciclovir is given until herpes has been ruled out.

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And then after those two specific interventions, we're really left with supportive care, supporting the respiratory symptoms, the cardiovascular symptoms, admitting -- administering blood -- blood products when needed, supporting kidney function.

Some babies go on to need ECMO and even left-ventricular-assist devices in the acute setting, and then occasionally transplant of liver or heart is needed if there's been failure of either of those organs.

Next slide.

We often talk about immunoglobulin therapy in the context of neonatal enterovirus disease, and there are a number of reasons for that. As has -- has been mentioned, enteroviruses -- a key immune defense against enteroviruses in general is the antibody response.

We know for the newborn that a lack of neutralizing antibody increases risk of severe disease for that infecting serotype, and we know that in IVIG there is neutralizing antibody to many different

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enteroviruses, although in variable amounts based on serotype and the specific IVIG lot being addressed.

So for that reason, this therapy, immunoglobulin, has been used in the newborn setting. Mostly, we have anecdotal or retrospective reports of using either IVIG or maternal convalescent plasma that is hopefully enriched with antibody to the serotype that's infected the mother and her baby.

And IVIG or plasma has been used both in the treatment setting as well as for prophylaxis. There has been one small randomized study -- really a pilot study that we and others did many years ago now that looked at newborns in the first two weeks of life with neonatal enterovirus disease.

They were randomized to receive this dose of IVIG or no treatment, and this was a study that was not intended to look at clinical benefit but really to look to see whether there was virologic suggestion that this might be a valid therapy.

And what we were able to show was that in babies who received an IVIG product that had a neutralizing titer of 1 to 800 or greater to that

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baby's own infecting serotype there was faster cessation of viremia and viruria, so at least giving biological plausibility to this therapy.

And then more recently, we have a retrospective study of babies with hepatitis and coagulopathy due to enterovirus infection; and they showed that IVIG administration within three days of illness onset, as compared to receipt of IVIG more than three days beyond illness onset, was associated with a lower mortality.

Next slide, please.

As far as more specific antiviral therapy, I'll mention the capsid-binder approach. These are drugs that inhibit attachment and un-coding. There are three that are in clinical development.

Pleconaril, that has been evaluated for neonatal enterovirus disease in particular both by reports of individual cases and a randomized control trial that I'll tell you more about.

Pocapavir is a poliovirus antiviral that's being developed as part of the poliovirus eradication effort. It has variable activity against

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non-polioviruses but has been used on -- in an expanded-access basis for some neonatal cases of enterovirus disease.

And vapendavir is another capsid binder that's in clinical development, primarily thus far being looked at for rhinovirus infections in adults with obstructive pulmonary disease.

Next slide, please.

So this is the title of the study that a Collaborative Antiviral Study Group did a number of years ago, a randomized double-blind placebo-controlled trial of pleconaril for newborns with enterovirus sepsis.

Next slide.

This baby -- this study looked at babies who were less than 2 weeks of age who presented with presumed enterovirus infection with at least one of hepatitis, coagulopathy, or myocarditis. They were randomized 2 to 1 to receive pleconaril or placebo for 7 days. There were a number of different endpoints, both virological and clinical and other.

We enrolled 61 babies; and you can see

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the 2-to-1 ratio of pleconaril to placebo recipients; and of the babies enrolled, 70 percent were ultimately shown to be enterovirus infected.

Next slide, please.

Amongst the enterovirus-infection group, this graph shows the rate or the time plotted to culture negativity for all cultured sites combined. The dark line is the placebo group. The lighter line is the pleconaril group.

So then you can see that there was a trend of the pleconaril group becoming culture negative overall faster than those who received placebo.

Next slide.

And this shows survival of the patients in the study, the subjects in the study. Again, the light line is the pleconaril group. The darker line is the placebo group.

The top panel is all treated babies in the study, the intend-to-treat group; and you can show that -- or you can see that the overall survival probability was higher in the pleconaril recipients

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than the -- than the placebo recipients, and I show you there on the right-hand side the death rates, and that was significant, with a P-value of 0.02.

The bottom panel looks specifically at the 70 -- the 70 percent who were infected with enteroviruses; and you can see comparable death rates; but here with the smaller numbers, the difference in survival is no longer statistically significant.

Next slide here.

Thank you. So this concludes with what our current treatment status is for severe neonatal enterovirus disease, and that really is supportive care as the mainstay of therapy. Many, if not most, babies these days do receive either IVIG or maternal-convalescent plasma.

As far as antiviral therapy, pleconaril is not FDA-approved. It is not available in the United States. Individual cases may sometimes be able to receive pocapavir via an expanded-access mechanism.

And then I'll just let you know that the Congenital and Perinatal Infections Consortium, which is the next version of the Collaborative

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Antiviral Study Group, is currently conducting a natural-history study to further describe in a prospective manner neonatal enterovirus and parechovirus viral sepsis in newborns to help better define mortality rates in a prospective manner and hopefully identify predictors of morbidity and mortality that will help this -- with the design of clinical trials of antivirals as they become available for study.

I will stop there, and I'm happy to address any questions at this time. Thank you.

DR. PICA: Thank you, Dr. Abzug.

That concludes the presentations for Session 2 of our agenda. We now have a few minutes to take clarifying questions related to the presentations we've just heard; and as a reminder, these questions should be related to the presentation contents specifically. Other topics will be covered during the panel session.

Panelists, please raise your hand in Zoom if you wish to ask a question.

And, members of the public, you may

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enter your questions in the Q-and-A box.
DR. VISWANATHAN: So it looks like we already have a question from Dr. Messacar directed specifically to Dr. Abzug.
Dr. Abzug, the question is: "I am curious on your thoughts about requiring signs of severe enteroviral disease in neonates to enroll them in a treatment trial.
With the risk factors identified, would it be more beneficial to try to enroll and treat neonates identified with enterovirus earlier in the course of disease, who are at high risk for progression?"
So, Dr. Abzug, I'll turn it over to you if you have some preliminary comments you want to make on -- on this; but again, we're really trying to limit this to, you know, just clarification if there's something not clear in a presentation; and then some of these more deeper discussion points we'll delve into in the panel this afternoon.
But, Dr. Abzug, if you have any initial comments, feel free.

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DR. ABZUG: Yeah. Thank you.
And thanks, Kevin. It's a really, really good question on how best to design a study of neonatal enterovirus disease.
The challenge is that a large number of -- well, not a large number but of the -- the number of babies -- larger number of babies who present with enterovirus infections, a modest percentage of them will go on to have severe disease.
The others will have generally a benign outcome, usually with a short hospital stay and usually without identified long-term sequelae. So the value of antiviral therapy in that group is likely to be limited.
So that's why studies have focused on the more severe babies, and we focused on babies who present already -- have presented already with evidence of end-organ disease that predicts a worse outcome.
Kevin's question is: Can we take the universe of babies who present with enterovirus disease in the newborn period, use risk factors to

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predict who will go on to have organ disease that might portend a more severe outcome.
And I think if you look at the -- the list of risk factors, if you subtract out the clinical ones, the ones where there's already hepatitis or already myocarditis or already multisystem disease, the two most predictive risk factors are early onset of illness and lack of neutralizing antibody in the baby to the serotype infecting that child.
I'm not sure that early onset of infection is predictive enough.
If we had a way to rapidly know whether the baby has neutralizing antibody to his or her particular enterovirus and we coupled that with early onset of illness, then I think we may be able to enrich that population enough to know that we're studying the right group of children that will give us the right answer that we want from the study.
DR. PICA: Thank you so much.
Are there other clarifying questions that people would like to ask?
I don't think we can hear you.

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DR. SCHLEISS: Oh, Mark --
DR. PICA: There we go.
DR. SCHLEISS: Can you hear me?
DR. PICA: Yes. We can now.
DR. SCHLEISS: Oh, very good. Yeah. That was a great presentation from the whole panel.
I had a question for Mark about maternal -- maternal strains. I mean, should we be trying to type maternal islets as well in the setting of the neonatal disease.
I -- I'm remembering this interesting case report from some years ago now in which they -- and you cited it briefly in one of your slides or the concept anyway of using maternal plasma, which if it's a perinatally acquired infection, you know, should be highly enriched for neutralizing antibody for that baby's islet.
So maybe this is a question better suited for the later-afternoon session; but anyway, I -- I just wondered. You know, we -- we -- we're in this era now of this great explosion of knowledge about neutralizing antibodies and infectious diseases

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in babies, and I -- I just wondered if you had any thoughts on that -- on that topic.

DR. ABZUG: Yeah. The -- the appeal of convalescent plasma is -- is really strong because that -- that's certainly a better way of knowing that you're giving a baby a high titer of antibody to the relevant virus than by picking a lot of IVIG off a pharmacy shelf.

The challenges are a couple. One is that of timing. We want a mother to have recovered enough clinically that we're confident that she's not viremic and that we're not giving extra virus as we give mothers plasma.

And we want enough time to have elapsed to be confident that there is antibody that's been produced in that and is present in that plasma to give to the baby. So it certainly would be helpful if we had rapid assays to tell us: "Is there still virus in that plasma? Is there a high amount of antibody in that plasma?"

And then we just need the logistics to be able to rapidly plasma freeze and -- and have the

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product to give to baby; and that can be, depending on where -- where a baby is housed, that could be a challenge, depending on the setting.

So it's a -- it's an attractive option; but there are pragmatic obstacles; and if we had some more rapid assays to look at presence of virus, to look at type of virus, and the amount of antibody to it, I think that would put us in -- in better stead for using that therapy more broadly.

DR. PICA: Thank you.

Dr. Vogt, do you have a question related to this?

DR. VOGT: I sure do. I think Mark actually may have already hinted at the answer to it previously.

There are -- but -- but, Dr. Abzug, there are more -- or I guess I should say there are not, like, commercial or readily available ways to do the, you know, measuring of neutralizing antibody titer against a specific virus and/or, you know, identifying the virus.

All that stuff basically happens in

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very slow periods of time when sending things off to reference labs, were a clinician to have a baby in front of them that they suspected had enteroviral sepsis or even had confirmed had enteroviral sepsis.

I guess just to clarify -- are there ways to do that, that you know of? "Quickly," I should say.

DR. ABZUG: Matt, your question is: Are there ways to quickly identify the amount of antibody in a product being given to a baby?

DR. VOGT: Correct. Yeah, for -- for one of these babies with enteroviral sepsis.

DR. ABZUG: Yeah. I do not know of a rapid way that's readily available. I'm open to others who --

DR. VOGT: Yeah.

DR. ABZUG: -- may -- may know -- know more about that.

DR. VOGT: I suspected not, and I'm sure we can talk about it more in the afternoon, but I figured I'd put that out in the clarification time here.

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DR. ABZUG: Well, perhaps there are people like you who can make panels of relevant antibodies.

DR. VOGT: Agreed. Totally agree.

DR. PICA: Dr. Kimberlin, did you have a question as well?

DR. KIMBERLIN: Well, yes.

I'm going to ask Mark if he can to give us some way of thinking about for antivirals, not for -- not for -- for antibody therapies but for antivirals.

How -- how specific do we have to be to say that we need to look for babies infected with Coxsackie B5 and, "Does this antiviral work against that; or does it work against, you know, one of the enteroviruses or, you know, the echoviruses?"

Do we have to get virus specific, or can we look at things more across the -- the totality of -- of virus subtypes that -- that infect these babies?

DR. ABZUG: Good question, and I'd say it depends a little bit on both the -- the virus and

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the drug.
So there are some enteroviruses like poliovirus that seem to have their own particular susceptibility to -- to an agent with pocapavir being a good example of that being a good polio drug but not being as good or at least being more variable against other enterovirus serotypes.
Now, there are other medications, pleconaril, which has relatively broad anti-enterovirus activity but isn't enriched against the polioviruses; and within the spectrum of nonpolio enteroviruses, pleconaril may have more or less activity against some versus the others.
But overall, at least for the ones that infect newborns primarily, there's reasonably good activity.
Then you have some specialized enteroviruses like Enterovirus A71, Enterovirus D68, both of which are not major players in the newborn period but cause their own severe disease in -- in childhood, that seem less susceptible to pocapavir and pleconaril.

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But there are other agents that are in development, particularly protease inhibitors, which tend to have a -- can be against those as well as really having a broad range of invitro activity.
So it's hard to generalize, David. I think it depends a little bit on the group of enterovirus you're talking about and the type of agent, some being more selective and some of the agents being broader in their spectrum.
DR. ROSENFELD: Could I just add into that?
DR. ABZUG: Please.
DR. ROSENFELD: So in fact, actually it goes a little bit even more specific than what Mark said. So for instance, if you look at EV-D68, some particles have canyons and have pocket factors; and other particles do not.
So you really want to have as much information about the actual virus that is infecting the baby that is possible because, for instance, the capsid inhibitor from Rossman's data works against Furman, which is the prototype EV-D68 islet, but does

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not really work against more current circulating islets like islets like nine -- eighteen four nine forty-seven, which was isolated from a case in 2014, because it doesn't really have a canyon and stuff.
So you have to have as much knowledge as possible, unless you're going to target a nonstructural protein like the protease or a 2C, which is a -- which is another protease or a helicase of the virus, and even that has caveats.
DR. PICA: Thank you very much, Dr. Rosenfeld and Dr. Abzug.
I think we have time briefly for one last question, and we have a Q-and-A from an attendee. So the question is: Do you believe that IVIG and pleconaril is synergistic? Is there any data suggesting synergistic effect?
So Dr. Abzug, are you -- are you aware of any data regarding potential synergy between IVIG and -- and pleconaril?
DR. ABZUG: Good question. I am not aware of invitro data that specifically looked at that question, not to say that it doesn't exist, and -- and

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maybe some of our pharmaceutical partners who are with us today know the answer to that.
As far as clinical data, I'll mention that the randomized study that I showed you some graphs from earlier, we included in that a graph that looks at -- looked at pleconaril plus IVIG, pleconaril without IVIG, placebo with IVIG, and placebo without IVIG and plotted the survival in the four groups.
Keep in mind that although the pleconaril and placebo was a randomized intervention, IVIG were not -- was not randomized.
That was up to the individual provider to make that decision; but with all those caveats, we did show that the survival was highest in the pleconaril-IVIG recipients and then sequentially lower, with the lowest group being the placebo, no-IVIG group, so suggesting at least the potential that there might be some clinical synergy, not -- not true antiviral synergy per se but clinical synergy between IVIG and an antiviral.
The results in that plot were not statistically significant but at least interesting in

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terms of hypothesis generation.
DR. PICA: Thank you, everyone, for these questions and to our speakers for providing answers. We will now take a lunch break, and we'll resume at 1 p.m. for our panel discussion on enterovirus trial-design challenges. Thank you all so much.
(Off the record.)
DR. PICA: Hello, everyone. Welcome back. We will now start our panel discussion on enterovirus trial-design challenges. As discussed this morning, there are many challenges related to the development of pediatric therapeutics, including ethical, scientific, clinical, regulatory, and logistical considerations.
There are also additional challenges specific to the development of treatments for severe enterovirus infection. We're looking forward to discussing these themes and important topics this afternoon.
Next slide, please. Next slide.
We welcome -- welcome back our speakers

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from this morning and thank them for participating in our panel this afternoon.
I would also like to welcome some additional panelists: Dr. David Byron, Head of Research and Development at AntiVirus Therapeutics; Dr. Jeffrey Hincks, cofounder and President of ViroDefense; Dr. David Kimberlin, professor and Vice Chair of Clinical and Translational Research as well as Codirector of the Division of Pediatric Infectious Diseases at the University of Alabama at Birmingham; Dr. Steve Oberste, Acting Director of the Division of Viral Diseases at Centers for Diseases Control and Prevention; Dr. Matthew Vogt, Assistant Professor of Pediatrics in Microbiology and Immunology at UNC at Chapel Hill School of Medicine; and Dr. Kevin Messacar, Associate Professor of Pediatrics at University of Colorado.
As a reminder, panelists, please raise your hand in Zoom if you wish to make a comment.
Members of the public may enter questions in the Q-and-A box.
Next slide, please.

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We will start by asking our panelists to discuss the key challenges in antiviral drug development for the treatment of enterovirus infection in infants and neonates.
Please comment on what additional nonclinical or basic-science work may be needed to help drive therapeutic development of treatment of enterovirus infection in infants and neonates.
Dr. Oberste, do you want to turn on your camera and make a comment?
DR. OBERSTE: Yes. Thanks.
I think one of the big challenges at least from kind of where I sit on CDC and from the laboratory perspective is that there are so many different enteroviruses. There's over 100 different types. They use 7 different receptors.
And so, as you heard earlier from -- from Amy, you know, some -- they're even within a type. There are some that have different kind of surface properties that may affect the efficacy of -- of things like capsid-binding drugs; and certainly, you know, other targets could be affected similarly.

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And, you know, one of the issues is that, while there are, you know, certain enteroviruses that seem to be more highly associated with severe disease in neonates, in fact probably most of them can cause severe disease at some level.
You saw the -- the graph that Miranda showed with even a fairly small number of cases, and there's a long tail of lots of other enterovirus types. So that's -- that's, I think, one of the biggest challenge -- challenges, and -- and the other one is something that Matt brought up this morning about rapid ways to -- to type the viruses.
It's -- it's very difficult. It requires sequencing. At least, that's the current state-of-the-art test.
And -- and even though that's much, much faster than the old ways of antigenic typing, going back, you know, decades, it still takes a lot of time; and it's not -- it's not really possible to turn that around in a clinically relevant time frame.
So to me, those are -- those are two of the biggest challenges that we have in -- in getting

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some of the basic information that's needed to -- to drive either drug development or in fact, you know, clinical treatments. Thank you.

DR. VISWANATHAN: Yes. And --

DR. PICA: Dr. -- Dr. Abzug, did you want to comment?

DR. ABZUG: Yeah. I'll just add to the list that -- that Steve has started us with. I want to put the obvious out there, which is, we're dealing with a relatively rare condition that's devastating but fortunately rare in numbers.

And so the incentivization for developing antiviral drugs particularly targeting this population is -- is not presently there and -- and is a major challenge; and with the rarity of the condition, it also means doing the studies of candidate drugs is challenging.

And, as was discussed this morning, this is a prime condition where it -- where network studies are really the only way to evaluate new agents.

But those network studies have to be

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set up over a large number of sites because of the rarity condition -- of conditions that represent a rare -- a broad range of geography since what's happening in one community on a given enterovirus season may not be what's happening in another community.

And those studies need to be done over time; and by "over time," I mean usually several to -- to more than several years because of the year-to-year variability and unpredictability of which enteroviruses are circulating at any given time.

DR. PICA: Yeah. I think that's an excellent point. Dr. Kimberlin, do you have something else to add?

DR. KIMBERLIN: Yeah. I would -- I would add to what Mark just said and -- and say that in addition to wanting to do this over several seasons because of variability of -- of circulating strains or types of -- of enteroviruses, it's just by necessity to get enough subjects. They are so few and far between.

And -- and so you have to have sites

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prepared to enroll at any time, primarily during the summer and fall but not always. We're seeing some circulation even in, you know, January and February, when we wouldn't used to have seen that before.

Climate change is impacting so many ways that infectious diseases circulate or -- or pathogens circulate. So you've got to -- you've got to have sites ready. That means they've got to have warm funding. It's expensive.

And -- and I would suggest more expensive than many times we really legitimately compensate them for in -- in terms of being ready to enroll and maybe not getting anybody not for lack of effort but just because -- because the -- the patients were not coming in, which can be a good thing from the standpoint of the -- of the babies but -- but not so good from the standpoint of trying to get to the end of the study.

So the rarity of the -- of the disease -- the severe-disease manifestations itself, I think, is -- is one of the very biggest challenges. Another would be -- and this is true for so many diseases

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where it's -- it's -- you know, the baby has been healthy and then all of a sudden is -- is not.

It's pretty overwhelming to -- to families; and when they hear things about experimental treatments, many of them just shut down and say: "Nope. I'm not doing that for my baby." And that -- that -- that's not unique to neonatal enteroviral sepsis, but it is a challenge.

DR. PICA: Dr. Vogt?

DR. VOGT: I think this point that I'm going to make also builds off all of the previous points that were made, which is that for this rare disease that is also caused by, as was pointed out, over 100 different viruses that all seem to have the ability to at least cause some of these forms of disease and with all these different disease manifestations like myocarditis or hepatitis or things like that it also becomes hard to just decide, like, what level of preclinical work is needed to advance something into actual clinical trials.

So do you need to show evidence against, you know, one just Echovirus 11 -- let's say

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-- or one -- or Coxsackie B3; or do you need to see, you know, evidence against five clinical syndromes or ten clinical syndromes in preclinical models, with the caveat that all the preclinical models are also models and not humans?

So a complication that I think comes even before we get the chance to think about all the other complications that come with the human studies that follow.

DR. PICA: Dr. Rosenfeld, do you have a comment?

DR. ROSENFELD: I do. As the basic scientist, the basic entero-virologist representative to the panel, I think we -- these are all, I agree, very serious points and concerns. We need to take a step back and say, "Do we actually have models for these diseases?" And we really don't have immune-competent animal models for enteroviruses.

And even -- I mean, I was trained by somebody who generated the first model of a human pathogen. He generated the mouse model for poliovirus infection and paralytic disease, but he will also

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acknowledge the fact that it's not true to real disease.

Like, you cannot orally infect those mice and have the -- the polio replicate and go through the entire neuroinvasion process. We cheat. We immunize the animals IP, IM.

So there is -- we take advantage of the known viremic phase, and that's all based on a lot of autopsies and data generated in the 1930s through the '50s by seminal clinicians like Dorothy Horstmann and David Bodain for polio.

We really don't have any of that information for any other entero, and so we need to start off just asking very simple questions and how to develop a model that we can actually test and say, "This is somewhat related to the human disease" with the understanding that the animals are not humans.

And that has not been well-funded because these are not considered diseases where people die; and so that leads to the incentivization that Mark was talking about; and that really starts off with, "Can you get the NIH and other granting agencies

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to understand the importance of enteroviruses?" And that seems to be very difficult.

DR. PICA: Excellent points.

Dr. Abzug, did you want to respond?

DR. ABZUG: Yeah. I just wanted to build on a couple of the previous points.

You know, I think that the question of incentivization is key; and this really gets to the second bullet that we're supposed to address in this session, which is the collaboration.

And this really needs to be an effort -- there really needs to be an effort -- a collaborative effort amongst industry and academia, as -- as mentioned in that bullet, as well as funding agencies to make this a priority.

I mean, this is a -- this is a group of viruses which -- although they cause adult morbidity and sometimes mortality, they truly are more pediatric-threatening; and the younger the child, the more threatening they are.

And so we're really talking then to a young pediatric population, which is not the kind of

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market that -- that industry thrives on, and it's not necessarily the kind -- type of disease that funding agencies are targeting.

But there really needs to be a collaborative effort to try to raise the -- the visibility of these agents and the need for -- for the funding to develop the drugs -- develop drugs with different roots of administration applicable to the children we're talking about, developing the -- the models that Amy is referring to, and then developing the -- the means -- the networks to do these studies.

It -- it's really a major, major undertaking.

I just want to add a couple other challenges that are -- are at least tangentially related to some that we've mentioned.

Kevin Messacar's question earlier mentioned predictors. We have some predictors of who is going to do badly, but they're not so honed down that we can really apply them yet, I think, to the clinical setting or the clinical-trial setting.

And if we had real-time laboratory

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diagnostics that give us serotype, antibody level, that sort of thing, that might help us do that better.

And then one other thing just to mention is that within a given newborn with severe enterovirus disease, the disease course can be very variable; and variability makes defining endpoints harder.

And it makes having the -- the appropriate end in your study more challenging, and it also makes it harder to predict -- to predict which of the babies you're seeing in front of you are the best candidates for a therapeutic trial. I'll stop there.

DR. PICA: Thank you.

Well, I think Dr. Schleiss had his hand up.

DR. SCHLEISS: Oh, hi, thank you. Yeah. This is a great discussion. I just wanted to ask the panel what their thoughts might be about wastewater surveillance and polio. You know, obviously, that's an enterovirus 'cause it's caused a lot of mortality.

And we had that infamous case in New

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York State a couple years ago now, I guess; and I -- I think the CDC had actually expanded some of the wastewater surveillance in response to that event.

And is there some way to tie in, you know, the kinds of messaging and awareness that Mark was just talking about to vaccine-preventable diseases and sort of package that polio story? Heaven help us if we need therapeutics for -- for wild-type polio. I -- I don't think we're going to get back to that point.

But the antivaccine movement, you know, has kind of forced our hand on this issue. So I -- just a sort of general question to the panel, thoughts about wastewater surveillance, as it might relate to enterovirus surveillance and tying the whole topic into polio because that will certainly capture some public attention.

DR. PICA: Yeah. Thank you, Dr. Schleiss. I know Dr. Rosenfeld and Betsy had their hands up, but I -- before we hear from them, I welcome the panel -- anyone from the panel to -- to answer Dr. Schleiss' question.

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DR. OBERSTE: Yeah. Thanks. I can take that one on since we've been directly involved in the wastewater testing for polio that followed the -- the New York case, and one of the issues for -- in doing wastewater testing for enteroviruses is that they're -- is that they're ubiquitous. There's probably 30 to 50 million cases or infections a year.

So if you pick sewage from any -- basically a city, you know, a wastewater-treatment system, it's going to be positive for enterovirus; and so it's not terribly helpful in that way.

You would have to do typing and sequencing, which is possible; but of course, you know, it's not just a few people depositing viruses into that sewage system. It's probably many thousands, if not, you know, 100,000 or more; and so sorting out all the different enteroviruses that are there is going to be a huge challenge.

And then, again, the vast majority of infections are asymptomatic or very mild; and so which ones actually matter? And so while it's certainly an interesting thought, I think it would be hard to get

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any actionable data out of it.

You know, we had talked to a number of states about doing some wastewater testing for polio specifically and especially in states that -- that had -- states or cities that had known low-vaccine coverage for polio, where we thought there were at-risk populations.

And again, there's a lot involved in setting that up. Even though, you know, there were samples being collected for SARS-CoV-2 testing, it was very different than what we do for polio globally 'cause of course globally, you know, they don't have sewage systems in the places that we're worried about polio transmission.

You know, the sewage system is a ditch on the side of the road; and so it's environmental sampling, not, quote, "wastewater testing"; and so it's very different.

And when you have very low rates of infection like we had in -- even in New York, even though it was -- the virus was detected for some months, relatively low rates of infection in a large

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catchment -- so some big-city catchments' wastewater can be, you know, over a million people.

So you're really looking for a needle in a haystack -- in a very nasty haystack in fact because it's sewage, and so it -- it has a lot of practical challenges to doing wastewater surveillance, not that we wouldn't do it in certain cases; but I think it's hard to find the -- the correct use case where that would be useful.

DR. ROSENFELD: Can I just follow up with what Steve said? There's a reason why BioFire diagnoses people EV -- entero-positive, rhino-positive. It's because the genomes are also extraordinarily similar.

And it's been very difficult to find virus-specific primers so that you would only amplify out, say, EV-71 versus everything else if that's what you think is circulating.

So just logistically, you can say: "Yeah. You're EV-positive, rhinovirus-positive." But it takes a lot more than a PCR to really discriminate between the genomes because you're just using a very

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small fragment.

The -- if you're multiplexing, the primers all have to be at the appropriate annealing temperature; and there's such genetic similarity between the enteros. Plus, there's a huge amount of recombination among enteros, which leads to new enteros arising -- I don't know -- every year.

So this is a huge undertaking, as Steve said; but it's also more complicated than, "Let's just throw out some primers."

DR. PICA: Okay. That does sound quite challenging. Thank you for that comment.

Dr. Hincks, did you want to make a comment?

DR. HINCKS: Yeah. I -- I guess there -- there are some models out there. Utah State has a couple different ones for D68, one for polio. They were funded by NIH to set them up. So, I mean, there are other models that are specific for EV infection. So, I mean, there are some out there, not too many, but just to comment on that.

DR. PICA: Thank you.

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Dr. Kimberlin?

DR. KIMBERLIN: To -- to focus on the bullet under Number 1, two additional things -- well, I guess -- I guess three things come to mind.

One, biomarker, if we could have a biomarker that, I guess, could predict who is going to develop severe disease, that would really be ideal 'cause then we could get what Kevin Messacar was suggesting earlier built into a protocol where you could -- you could treat earlier for a baby that's at higher risk.

I think that could be very important and then also a biomarker for outcome 'cause that could become an endpoint to a study. We'll talk about that later in the afternoon, I would think.

Secondly, Mark Abzug mentioned partnerships; and he brought in funding agencies. I -- I am delighted that FDA is -- is taking these two days to -- to take a deep dive into these two diseases that so many of us care so much about.

I think FDA, to the extent allowed as -- as the regulatory agency, being part of

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conversations early can be really, really helpful to -- to the overall process.

And then finally -- and this is broad. This is not just -- it -- it impacts rare diseases, but it impacts everything else too. The -- the OHRP oversight of sights and IRBs, this whole idea of single IRB being a streamlined thing, it is not; and you -- you can ask anybody.

All it has done is added additional layers of complexity of review, of everything that goes into having a study approved at a given site or across sites. So there could be -- it would help this and so many other things. There could be some regulatory adjustments that could make the conduct of clinical research much easier.

DR. PICA: Thank you for that perspective.

Dr. Vogt, I saw your hand come up.

DR. VOGT: Sure thing. Actually, this wasn't my initial intent; but I'm just going to second Dr. Kimberlin on that point about central IRBs not necessarily really making things easier. It does feel

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like it just adds another layer, which is a shame 'cause it would be nice if they were easier, as they were intended to be.

The point that I was going to make was based more on -- a couple different people have talked about -- and me included -- diagnostics and how nice it would be to have a rapid diagnostic both from the standpoint of, you know, "What is the virus that this child has more specifically than just enteroviruses in general" and also, you know, what seropositivity they may or may not have.

I think also the -- the thing is, I don't know that we need that. I would like to have that. So I don't think we should not try to have that.

But I think of things like there -- you know, there are certain clinical syndromes where we will just empirically treat for them when we're worried that a child is very sick, and we might need to treat them.

So -- so in Dr. Abzug's talk, the example of that was, we often give aciclovir for --

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you know, to treat for potential herpes simplex infection in scenarios where herpes simplex is maybe not the most likely thing the child has; but of course, we'll do that; and aciclovir is not without its toxicities.

I think if we can also, you know, try to make sure that our drugs are within a tolerable level of toxicity one way to potential perform these trials is to have a bit more of an inclusive net and then allow that sort of post hoc analysis, which I know some of the studies that Dr. Abzug cited had, where you sort of break out.

"Okay. We -- you know, this was our intention-to-treat group; but then we found out later, you know" -- for example, if we're using a capsid inhibitor, once we type the viruses -- "You know, these were the kids who had viruses that actually have pocket factor that a capsid inhibitor could impair; and these were the kids who didn't have those."

We -- just to -- to really try to not limit the potential benefit to a lot of children because we're waiting around on some diagnostics that

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may not matter all that much if our drugs and our treatments are relatively innocuous to give, that's something to consider when we're doing our trials -- trial designs as well.

DR. BELEW: I had a -- this is Yodit Belew -- a follow-up question to that comment, Dr. Vogt.

Would you be concerned -- and, others, please feel free to chime in -- with respect to empiric treatment and the potential for development of resistance if we are using antivirals broadly for any enteroviral-diagnosed -- diagnosed infection and continuing treatment while we're waiting for subtypes and susceptibility testing?

DR. VOGT: Sure. I -- I think that's always something we need to think about; and, you know, in some -- when you look at the use of small molecules, for example, there's some small molecules that have worked, you know, for decades and then some small molecules that pretty quickly didn't work that well anymore because the viruses mutated against them.

So I think it's hard to predict just

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how that would work, but I -- I think that for enteroviruses -- you know, I think of these as -- a lot of these infections as things that set on pretty quick. They're -- they're kind of a fast burn.

Like, they -- they come on pretty quick; and then, you know, the virus -- the damage of the virus may last weeks or months or years; but really, the viral infection, you know, is actually happening over the course of -- of days or at -- at most weeks before the infection is cleared.

So you don't have quite the amount of cocirculation of -- of virus and -- and small molecules, and I think the other thing is to -- to think about the epidemiology of these infections, is that, as has been pointed out, this is actually a pretty small group of children who -- certainly who have severe outcomes.

But even when you include all the kids without severe outcomes, the amount of children who would receive these empiric drugs is actually pretty small compared to the number of enteroviruses circulating in the world in all adults and children

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and all-comers.
So you'd really be applying that pressure to a pretty small group of people. So I think of this as at least theoretically to me -- so I'll -- I'll really emphasize the "theoretically to me" part of this -- a lower concern for this group of viruses, although I'm sure other people might disagree.
DR. PICA: Yeah. I -- Dr. Rosenfeld, I'm not sure if you have your hand up or if that was from earlier but --
DR. ROSENFELD: No. I have my hand up. So I have --
DR. PICA: Okay. Great.
DR. ROSENFELD: I have several problems with -- or several concerns with certain aspects of this discussion.
So for instance, the idea of looking at seropositivity for antibodies, there's a lot of cross-reactivity against entero -- against enteroviruses, and my lab has described the cross-neutralized -- is beginning to describe the cross-neutralizing antibody

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response.
So just to say you have a neutralizing antibody response is not really sufficient to say you have a neutralizing antibody response against that specific virus, especially when you talk about cross-reactivity because we don't really know whether -- what cross-reactivity means, if it can exacerbate the viral infection and the disease or not because this is just all done in tissue-culture cells.
The animal models that were referred to are all basically immune compromised. They're interferon alpha beta receptor knockout mice, which is problematic in the fact that these viruses are interferon sensitive.
So if you look at work that was done by the Japanese group for polio, they took out the interferon response by removing TLR3; and the virus was now all over in all extra-neural tissue, suggesting that it is the interferon response that constricts the virus to the primary site of infection.
And we're all talking about this as if it's the virus that is the problem. Most likely if

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you take virus from children who develop non-severe disease and severe disease, the virus' genome is the same.
It has to do with host genetics, and we have no understanding of what host genetics -- single polymorphism, SNPs, or whatever -- correlate with the development of severe disease 'cause severe disease is really just a reflection of viral fitness in that particular environment, and viral fitness is not always defined by the virus.
And so I think that we -- if we want to really address this question appropriately then, we need to take into the fact that host genetics really does contribute.
DR. PICA: Thank you, Amy, for that perspective -- or, Dr. Rosenfeld, I should say.
Dr. Kimberlin and Dr. Vogt, I think you have direct responses to this; and then we'll hear from Dr. Abzug.
DR. KIMBERLIN: Yeah. I do. I -- I don't -- I don't discount what Dr. Rosenfeld was saying. I -- I would point out that the neonatal

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population is immunocompromised. I mean, the -- the innate immune response is different in a neonate than it is in a 2-month-old or a 7-month-old or a 2-year-old or whatever it may be.
So -- so I -- I think that it may be more complex than simply saying that: "The virus is not the issue. It's the host's response to the virus." These -- these people are -- these babies are not able to -- to mount the kind of response -- that's the reason HSV is -- is devastating in a neonate, and if a -- if a 7-week-old gets it, they do fine.
It's -- it's not the genes that are different. It's not the virus that is different. It's the innate immune response that has matured over those first weeks of life.
DR. PICA: Dr. Vogt?
And then, Dr. Abzug?
DR. VOGT: Sure. I just want to point out in response to Dr. Rosenfeld's comments about the cross-neutralization of antibodies, you know, I think there's an important distinction to make; and that's between -- the difference between binding and

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neutralization, and I think we've kind of been switching back and forth between those two.

I think with the -- you know, the therapeutic studies, for example, that Dr. Abzug was talking about, where, for example, they took lots of IVIG and then said: "Okay. Does this lot of IVIG have a 1-to-800 titer against a particular virus," those are neutralization titers. I'm almost certain, although I'm happy to be corrected if I'm wrong.

And -- and a lot of these when we're talking about cross-reactivity or when we're talking about -- let's say -- polyclonal sources of antibody usually we are talking about a neutralization readout.

And so I'll totally agree to the fact that I couldn't tell you if that antibody was generated in response to a polio vaccine or to an enterovirus infection of any specific type.

But in this case, I don't think that's really relevant because if the neutralizing -- if the antibodies neutralize the virus, whether they were elicited by an infection to something or an immunization to another thing, the fact is they

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neutralized the virus; and so it doesn't really matter what caused the antibody to be generated.

It's there; and it's doing its neutralization, you know, activity. So I think that's just a sort of clarification I'd like to point out.

DR. PICA: Thanks.

And, Dr. Abzug?

DR. ABZUG: Thank you.

I just want to broaden a little bit in -- in response to the first bullet our thinking. We've been focused on antivirals, as -- as we're -- we're supposed to, and I'm all for that. I just want to make a comment that we also need to think about alternative routes of administration.

The fact is that most of the enterovirus antivirals that are in development are being developed by oral routes; and as was mentioned this morning, that's probably not the best route for a very sick newborn.

And our study -- I didn't have time to show you the pharmacokinetics data, but it bore that out that it took a while for a significant number of

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the enrolled subjects to reach what we think is a target level that's appropriate. So that's the antiviral piece.

But I also think we need to be thinking broadly. We need to be thinking about immunotherapies, be that antibody based or other; and then another whole possibility to think about, which -- which I don't even know if it's in development, are agents that can be either organ protective or organ repairing.

So for example, the heart and the liver, as I showed this morning, are two of the major target organs for enterovirus disease.

Maybe we don't have the right antiviral to give to a baby; but if we had a medication that could protect that target organ or to help that target -- target organ repair better than natural history would predict, that may be a very important category of therapeutics for us to think about as well. Thanks.

DR. PICA: Okay. Thank you all. I'm going to just take one moment now to read one of the

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comments that we got in the Q-and-A box from a general attendee.

This is from Dr. Park, who is a program officer overseeing the picornavirus at NIH -- at NIH, and Dr. Park notes that: "To address the problem of needing to treat enterovirus infections we are interested to find broad-spectrum antivirals.

For that reason, we provide antiviral-screening services against enterovirus using mouse models. Polio, coxsackie, EV-D68, and EV-71 and echovirus model is being developed.

Additionally, picornavirus is one of the members of the prototype pathogens for pandemic preparedness; and NIH has programs for developing antivirals against prototype pathogens via the AViDD program."

So thank you, Dr. Park, for sharing that information with us. Unfortunately, the way that our Zoom platform is set up for these meetings, attendees who -- who are not panelists or speakers do not have capabilities of actually commenting verbally during these.

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So I -- I apologize, but I thought that that was an important point to share with the larger group.

So if anyone has follow-up questions, they can -- you know, if -- if you're an attendee, you can ask those questions via the chat; or a panelist can either raise their hand and ask questions if -- if they have additional follow-on questions or comments regarding Dr. Park's information there in the Q and A.

I think before we go back -- I see that Dr. Kimberlin has his hand raised again; but before we go to Dr. Kimberlin, I wanted to give -- I know that Ms. Pilon from -- from earlier today had her hand raised.

I just wanted to give you the opportunity if you still had comments on your perspectives about these topics for this session. We'd love to hear from you.

MS. PILON: Yeah. Just a really quick comment 'cause I was looking at, you know, additional nonclinical discussion.

And, you know, earlier there was a

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moment where I thought something relevant to bring up would be, you know, obviously the difficulty in identification of a very heterogeneous cohort but that there are many communities like ours and others whose kids and, you know, infants and neonates also are at higher risk for a severe disease course from enteroviruses and others.

And we have that; and we have seen that, you know, time and time again with more severely impacted children.

And so just looking at -- you know, when you're looking at the difficulty of -- of that cohort identification and working with a patient-family basis for this in particular 'cause there's not as much of -- in my -- my quick research of -- of patient community behind it, it certainly would be -- there are communities who are more affected by these in general that you could engage in this process as well.

DR. PICA: Thank you very much. We appreciate hearing your perspectives on this.

I think that Dr. Kimberlin was next. I

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see that he's had his hand up for a while, and then we will turn to Dr. Vogt to respond to one of the other questions in our Q-and-A box.

But, Dr. Kimberlin, I'll -- I'll go to you next.

DR. KIMBERLIN: This -- and this is just circling back to an earlier question about antiviral resistance and -- and antiviral pressure. Yeah.

Of course, it depends on the molecule in terms of what -- the likelihood of -- if a drug is, you know, quick to develop antiviral resistance, obviously that's going to be a less attractive drug than if it's more difficult to develop resistance to it.

I think Matt's point -- Dr. Vogt's point is a good one that it would be used at least -- is envisioned with this neonatal enteroviral sepsis. It would be used in a really small number of -- of people, even preemptively used in a really small number of people.

And so I -- I think my guess is it

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would be unlikely to -- to lead to much in -- in the way of antiviral resistance. I will say though that if we think about -- let's fast-forward 15 years and say, "We've got two or three drugs on the market."

They will be used preemptively just as aciclovir is now when a neonate comes in and there's at least a flash of concern for neonatal HSV. Aciclovir is started along with the antibiotics, and then it's stopped when the diagnostics rule that out, or it's continued.

Same kind of approach clinically is how I envision a successful molecule drug being used to treat neonatal enteroviral sepsis. So there will be a broader application utilization than just the smaller population that ultimately rules in for that severe manifestation of enteroviral disease.

DR. PICA: Thank you, Dr. Kimberlin.

Dr. Vogt, did you want to respond? So let me just quickly read the -- the question that -- that is -- is included in the Q and A here, "So are there any antibodies, even if not neutralizing, that are specific to a particular enterovirus without much

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cross-reactivity?"

And Dr. Vogt had volunteered to address this question for us.

DR. VOGT: Sure. And I think one thing I'll point out in answering this question is there's an important distinction, again, between polyclonal-antibody sources -- so that's like the IVIG that Dr. Abzug mentioned in some of the clinical trials he referenced -- versus monoclonal antibodies, in which case if there was a monoclonal-antibody product, you know, every single antibody within that product would have the sort of same sequence, the same specificity.

And -- and so for monoclonal antibodies, the answer to that is a relatively easy answer, which is to say that there are some monoclonal antibodies that are indeed specific to certain enteroviruses; and then there are other monoclonal antibodies that cross-react between different enteroviruses.

So, you know, before using -- oh, yeah. So as a potential diagnostic -- so yes. So there are definitely, you know, monoclonal antibodies that would

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cross-react between different enteroviruses; and, you know, right now you can, you know, buy those as laboratory reagents, for example, from, like, big companies like Thermo Fisher.

And, you know, we're working on identifying some that come from humans; and they're -- so -- so I think the answer is "yes."

And actually, in such a diagnostic, especially if you put a few, you know -- let's say even two or three -- monoclonal antibodies you might really be able to make sure you've got that cross-reactivity you're looking for in a diagnostic.

And then also, I just wanted to support what Dr. Kimberlin said, which is that -- I agree. I mean, my hope would be long term if we can have multiple options in our toolbox, if we get that lucky.

You know, we would give this to any child that we were worried about enteroviral sepsis before we even eventually hopefully figured that out, you know, one way or the other, exactly the way we treat HSV.

And, you know, as Dr. Abzug pointed

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out, that might be a combination of different types of drugs.

So there might be small molecules and monoclonal antibodies and then maybe something that is organ specific to help repair the organ or maybe something that is anti-inflammatory, you know, if it's a disease process where the immune response is viewed as actually potentially causing damage rather than helping.

So hopefully we get to that point where we have all those tools.

DR. PICA: That would -- that would be great if we could -- if we could get to that point.

Dr. Rosenfeld, did you have a comment?

DR. ROSENFELD: I do.

So I think that there's a little confusion about resistance and how it arises. So there's two mechanisms by which it can arise. It can arise by point mutations that the polymerase introduces, but it can also arise by recombination with circulating enteros.

And we really don't know very much

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about recombination partners. So we know something about recombination partners for polio; and we know something about the polymerase and reversion rates; and in fact, actually the reversion rate for certain alterations in the genome is very quick.

So work done -- if you look at the reversion of the Stem Loop 5 alteration in the Sabin variant of polio, that reversion occurs from the gut selective pressure without 48 hours -- 24 hours of giving the vaccine to the child, and that's work that was done by David Evans and Phil Minor in the 1980s.

And then the majority of viruses that we see circulating that cause -- let's say -- cVDPV2 outbreaks, they're all recombinants in which the three-prime end of the virus has been changed and recombined with an entero that is circulating.

So to say that we wouldn't get resistance against some kind of small molecule may not -- may be ideal, but it's probably not realistic, and we probably also need to sample what is circulating in the environment to understand if there are recombination partners available.

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And that's one reason why you develop combination therapies also, is to prevent that.

And that has been one of the concerns about the development of the antiviral program for polio, is whether or not you really need combination therapy or you can just combine -- let's say -- 2C protease inhibitor with a monoclonal antibody, which has been proposed.

DR. PICA: So I think Dr. Abzug has a response and then Dr. Vogt.

DR. ABZUG: Yeah. A couple of comments to what -- what Amy just said, you know, resistance is always a concern any time you have an anti-infective. We've learned that by history.

I think one feature that is in our favor here is we're talking about a newborn, and newborns unfortunately haven't had much exposure to the environment, particularly in that first week or two of life when -- when the ones we're -- we're most worried about are getting sick.

So it is not impossible but unlikely that that host will be having multiple enteroviruses

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onboard that have the chance for recombination in that narrow population.

Ultimately though, I -- I think the goal will be to have multiple agents that can be used in combination, particularly agents of different mechanisms; and that will further reduce the chance of resistance developing. Thanks.

DR. PICA: And, Dr. Vogt?

DR. VOGT: And I think just to try to -- to put further context on that, similar to what Dr. Abzug was just doing, is -- you know, as he pointed out -- right -- there's, you know, one baby and one hospital and not a lot of exposure to the enteroviruses.

And so while -- when we think about the circulating vaccine-derived polioviruses that, you know, have arisen from recombination, those have arisen in populations where, like, every child has received that vaccine. So you're talking, you know, hundreds of thousands or even millions of people interacting and sharing these things.

So just kind of another sort of point

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of reference when we're thinking about the likelihood of -- of that 'cause I agree that -- can viruses develop resistance? Yeah. These are small -- these -- these are small RNA viruses.

And one of the main features that we all learn about in, like, Viruses 101 in -- in even high school or, if not, college is that those bad boys -- they like to mutate, and that's kind of how they -- how they, you know, succeed.

And so we know they're going to mutate. The question is: Is that mutation that's going to arise be fit enough to actually become a dominant mutation and then also transmit not just from that one infant but to other people and then actually continue to circulate successfully?

And I think that that likelihood is a very different likelihood when you're talking about an infant with neonatal sepsis from an enterovirus versus populations where every single person has received, you know, a vaccine, for example.

DR. PICA: Thank you, Dr. Vogt.

We'll -- we'll let Dr. Oberste make a

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comment, and then we'll read a question that we got in the chat.

DR. OBERSTE: Yeah. I'd like to address a couple things having to do with recombination. First, with the circulating vaccine-derived polioviruses, I'm not sure there's any evidence that recombination actually plays a role in their emergence per se and certainly not in their -- their pathogenesis or pathology.

As Amy pointed out, the -- the attenuation site and the five-prime NTR of -- of entero -- of the Sabin virus reverts extremely quickly, and that in itself is sufficient to confer neurovirulence on what used to be the vaccine.

My other point is that recombination in the context of drugs and drug treatment really only becomes relevant -- it -- it's really dependent on the target. So for example, if you have a capsid-binding drug, you know, the capsid is what defines an enterovirus type.

And while there is going to be some variability or could be some variability within type,

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that doesn't recombine out because that's what tells you which type it is.

Now, if you have a drug that targets another part of a genome that can recombine with -- with other circulating enteroviruses, that could cause some issues. However, the key would be to find broad-specificity drugs -- for example, to target the -- the protease.

And there are some drugs that have been developed over the years or at least taken to certain stages of development over the years that have much broader specificity, and so then you wouldn't worry as much about recombination because it may -- may recombine out one version, and the new one comes -- that comes in is just as susceptible.

So just kind of thinking of that, recombination to me is maybe not a huge concern. I think it's -- it's some of the point mutations that can confer resistance to, you know, all kind of drugs.

And it's -- and it's very similar to the HIV situation -- let's say. They of course -- they've had drugs for decades, and you don't give a

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single drug if you don't have to.

You know, we would expect resistance to occur at some frequency; and that's the way we -- I think we would want to have a combination, you know, down -- down the road when we -- when we do have treatments.

And finally, I'd just like to mention I -- I would second all the calls for having the ability to use some of these drugs empirically. I think it will depend largely on the safety profile of the drugs, especially since we have been discussing how difficult it is to do the studies.

But if you have a drug that's shown to be extremely safe by, you know, every possible test you can run, then I think that you could make an argument that it's -- it's at least reasonable to try.

Obviously, there's lots of caveats that go with that; but I -- I think that -- that would be the first hurdle; and if you have a very safe drug, that maybe lowers the bar just a little bit.

DR. PICA: Thank you.

Just in the absence of, you know,

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broadly effective therapeutics, we've heard a common theme that it's important to really identify the target.

And we do have someone who's typed into the question -- into the Q-and-A box: "How accurate could viral typing be in identifying which virus might respond to a specific drug? Is that something that we think is possible in the context of enterovirus diversity?"

DR. OBERSTE: I can tackle that one, and maybe others want to comment as well. I think in cases where it's well known how the -- the mechanism of action of the drug -- so for example, the capsid-binding drugs, it's pretty well known where they interact.

And there have been efforts to generate -- either generate resistant viruses in the lab or to characterize viruses from, for example, clinical trials; and so it's pretty well-known which parts of the capsid conferred that resistance; and so by -- again, it would be by sequencing, which is not rapid.

But it would be at least accurate if

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you can identify parts of the capsid that have -- have characteristic amino acids that -- that are known to confer resistance.

And presumably, you could do the same thing with things like a protease inhibitor or others, where the mechanism is known; and you could try -- you could look at the active site of the enzyme.

DR. PICA: Thank you so much. This has certainly been a very spirited discussion. In the interest of time, I just want to introduce our second topic for the panelists.

I'm hoping that we can now talk about potential strategies that could be considered to improve collaboration between industry, academia, parents -- and parents and caregivers to facilitate antiviral therapeutic development for the treatment of enterovirus infection in infants and neonates.

I know Dr. Abzug touched upon this briefly earlier in -- in the afternoon, talking about the importance of network studies.

I don't -- Dr. Abzug, do you want to talk more about that?

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Or does anyone else have any other ideas or comments?

DR. ABZUG: I'm going to take your question and change it a little bit because before we can get to network studies we need agents to -- to study in those networks.

So I think it might be useful to hear a little bit more about the industry-academia partnership, and -- and I -- and I include funding agencies as the third partner in that collaboration to even to the point of having agents to bring to a clinical trial's networks.

So I -- I -- I'd -- I'd like -- like to hear from our industry partners as to what they see as what's necessary to move the field along.

DR. PICA: Yeah. I think that would -- it would be great.

Dr. Hincks, do you have any comments or just --

DR. HINCKS: Sure. It is tough to get funding. That's for sure. I mean, we're advancing two drugs, two different molecular mechanisms of

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action; and we're working hard to try to get funding to -- to do a study, a Phase 2 -- well, Phase 2, 3; and it's -- it's been difficult. I guess that's all I can say about that.

DR. PICA: Thank you.

And, Mr. Byron, do you have anything to mention? We're -- we're not able to hear you, if you're -- if you're providing a response.

Well, it -- it does sound like there are substantial challenges for sure beyond -- beyond even getting to a target in which to study. Are there any other -- other comments related to this question?

DR. ABZUG: I was just going to ask whether any of our government partners on -- on the phone or online have any thoughts on the issue.

MR. BYRON: Can you hear me now? Can -- can anybody hear me? This is Dave Byron.

DR. PICA: Oh, yes. Yes. We can hear you now. Thank you.

MR. BYRON: Okay. So sorry for that. It -- I got a technical glitch, I guess. I mean, I'll follow up on Mark's comment; and funding is always --

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is always an issue; and the duration of time it takes to do studies on these rare diseases makes not only funding an issue.

But -- but also for the sponsor, they have to realize that the time -- the time that they will be spending studying sufficient sample sizes is going to be measured not in months or what we would typically do in the industry in terms of months to perhaps years but a limited number of years.

But if the number of years becomes very long because the number of subjects needed to get an adequate sample size requires, as Mark -- as Dr. Abzug had mentioned, requires a significant number of -- of sites -- sites, and each site sometimes only enrolls one to two subjects in a year or less.

It just -- it -- it adds to the complication from an industrial perspective to want to get behind that support because the end is so far away from the current time. So it's -- it's another complication of studying these in -- you know, whatever you might characterize as ultra-rare diseases.

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DR. PICA: Yeah. Excellent points.

And just as a follow-up, Mr. Byron -- and, Dr. Hincks, you may want to chime in here as well.

Do you think there are things that we could do or things that the broader community could do to encourage more industry partners who would be interested in developing treatments for enterovirus?

MR. BYRON: Well, I mean, I'll -- I'll just finish up. I mean, I think -- I think the community -- the medical community and certain -- and certainly Dr. -- Dr. Abzug and Dr. Kimberlin have done quite a bit to -- to, I think, encourage interactions with -- with the industry.

But one of the pieces that is missing is kind of the early-on FDA interactions to -- to be sure that no studies are started for which there will be questions asked later or that the studies started are -- are kind of previewed so -- so that there isn't -- there isn't time spent or money spent or effort spent that will end up with -- with questions asked that -- that then add more time to the process.

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So I guess I'm not saying that maybe it's not just the academic -- the academic institutions, but it's also perhaps the agency in -- in fostering a clearer view of what will be expected that can always not change but would at least give some comfort.

DR. PICA: I think it's -- and point taken. I just want to make the comment that the FDA has a few mechanisms for interaction with the industry, one of which is through the Pre-IND Program, where some of these questions that you're alluding to could -- could potential be answered.

MR. BYRON: Yeah. Thank you. I -- I do know that -- that there are -- there are mechanisms out there.

But again, from an industry perspective, sometimes as we go through the process or as new -- let's say -- new reviewers come onboard during these long programs, new questions come up that were -- that were perhaps -- you know, that were not -- we were not aware of at the beginning because a new -- a new reviewer has new input.

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So it just -- that's not a -- I'm not trying to be -- to express a frustration. I'm trying to just say, you know, "What can we do?" Well, we're not going to change that; and new reviewers are going to be added all the time. It just -- those are the things that -- that cause starts and stops to programs.

MS. HODOWANEC: Thank you, Mr. Byron. No. We -- we certainly appreciate your -- your concerns, and -- and, you know, I think we -- we don't have all of the answers at this point in terms of what is the path to development for products for neonatal enteroviral infections.

And that is why we are, you know, putting the -- the time and energy into this workshop here today, is to help us get a better understanding of -- of what that path might look like; and ultimately, we would love to be able to put out a guidance document and to provide, you know, some of these answers that you're seeking.

MR. BYRON: Thank you.

DR. PICA: Dr. Kimberlin, I'll let you make one more comment before we take another break.

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DR. KIMBERLIN: And this may be a foretaste of the post-break conversation.

In -- in thinking about -- as an outsider looking into what FDA does, it -- it -- I would encourage to the -- encourage all of us to think about what we could be doing to -- to improve our situation with respect to antiviral drug development in -- in these two diseases that we'll be talking about today and tomorrow.

Looking at the data from an -- from an academic standpoint, at least in clinical care, the way I -- the way I approach it is, I kind of look for the trends. I look for the threads. I look for the truth across studies, and -- and sometimes that's with a primary endpoint that hits.

Sometimes it's that another study did not hit the primary endpoint, but there's some secondary endpoints or some other very useful data in -- in the manuscript that I'm -- that I'm reading to make a clinical decision.

And for these rare diseases, that kind

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of -- where is truth? Where is -- across studies, you know, retrospective studies, prospective studies, randomized studies, where is the trend of -- of evidence that a particular molecule might be helping with the outcome?

And I think -- I think greater flexibility for rare diseases where it is so difficult, as -- as Mr. Byron was saying, to do these studies, they just take a decade to do sometimes.

And -- and being willing to have a little bit more flexibility, I think, for these rare diseases is something that -- that I think could move the needle somewhat.

DR. VISWANATHAN: Thank you, Dr. Kimberlin; and I would say that personally the -- I completely agree with you, and I would say that the agency has taken numerous steps specifically for rare diseases.

And so, as mentioned during the morning presentations, this evidentiary standard in terms of substantial evidence of effectiveness is applicable both to rare diseases as well as diseases that are

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more common. So that evidentiary standard does not change between the two types of diseases.

But where the agency has made it clear is that -- and -- and there have been a number of guidances that have been put forth to, again, as you stated, consider some additional flexibility in getting clinical trials up and running for these rare diseases, which, as we have been talking about today, can be quite challenging.

And just echoing Dr. Aimee Hodowanec's point earlier, you know, we all recognize the challenges of drug development in these two disease areas; and that is one of the reasons that, you know, this -- this workshop was organized.

And we are hoping that all the discussions that are happening today will help us inch a little bit forward, you know, both in terms of potential in the future putting out guidances and/or collectively for the community to understand some of the nuances of what it means to -- to have evidence of effectiveness for consideration, what additional nonclinical or scientific work that needs to be

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considered so that the overall evidence in terms of a disease, endpoints, trial designs, et cetera, could be refined and moved forward.

Thank you.

DR. PICA: Thank you. Thank you so much to all the panelists for this excellent discussion. I think it's given us some food for thought, and we'll have a lot more to talk about when we come back from a short break and reconvene at 2:15. Thanks so much.

(Off the record.)

DR. PICA: Hello, everyone. Welcome back from the break. We will now continue our panel discussion, this time turning our focus specifically to clinical-trial design considerations.

I'm hoping during the next hour and 15 minutes we can discuss ideal study populations for enrollment into clinical trials, appropriate clinical-trial endpoints, and comparator-treatment groups. I now open the floor to anyone who would like to make comments.

Dr. Kimberlin, would you like to go

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first?

DR. KIMBERLIN: Yes. Thank you.

Dr. Abzug mentioned this during his talk, I believe. One of the studies that the Congenital and Perinatal -- and Perinatal Infections Consortium or CPIC, the -- the successor to the CASG, is undertaking now is a natural-history study of neonatal enteroviral sepsis.

And we liberalized the enrollment criteria relative to what was used in the prior CASG pleconaril treatment -- Phase 2 treatment study. So we're -- we're -- we are catching -- catching a broader net of -- of babies with -- with potential enterovirus infection. They don't have to have it to -- to enroll in the study.

But -- but of the subset that will test positive for enterovirus, once we're doing those analyses in our research lab, of those, we -- we should have a broader grouping, compared with that -- that tighter more sick patient that we enrolled in the pleconaril study.

Part of the reason of doing this study

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and being a little bit more forgiving with respect to enrollment, these babies still have, you know, elevated transaminases, myocarditis, things like that, just not as -- quite as strict of criteria of how bad it had to be.

Part of the reason of doing that is to try to inform endpoints to -- to help people who are listening on this call as they think about developing a drug. What would that look like?

And -- and perhaps if they were working within a network such as ours, you know, helping us also design what those future treatment studies would look like, Phase 2 or Phase 3 studies would look like.

So -- so only to make the point that there are some data being generated, being gathered now that hopefully will be informative for the future.

DR. PICA: Yes. Thank you. Thank you for that.

We'll hear from Dr. Vogt and then Dr. Abzug.

DR. VOGT: So a question, David, to you about that. For a clinical study like yours where

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you're more information gathering -- right -- this isn't an interventional study. You're trying to define the natural history.

Is there -- I know the answer as the study is constructed now, but is there any room in study design to sort of include patients who aren't at one of the actual study sites?

So, you know, and -- and we talked about this with a particular patient once before. So that's why I know the answer as the study is designed today.

But for something like natural history, it would seem like it's an easier ask to go outside the network to say: "All right. Invest -- you know, you have to identify an investigator at this other hospital or this institution.

So if you can fill out our form, we can include your patient in the study," as opposed to an intervention obviously, which is a far different type of -- of out-of-network question and -- and seems incredibly unlikely.

DR. KIMBERLIN: Hey, your -- your -- I

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love the tenor of your question. The way the regs are, unless I'm totally missing it, we can't do it. I mean, we've got to have everybody at --

DR. VOGT: Okay. It's just a hard "no"?

DR. KIMBERLIN: The number of hoops that you've got to jump through to get a -- to get a site activated, it takes months and -- and all the different documentation, and they've had their -- their training and so on and so forth, and I understand why we do that.

But as we talk about it -- and I sort of finished prebreak, you know, advocating for flexibility. I would love to have that degree of flexibility. I don't see it happening right now.

We had -- we had a little bit more -- David Boulware up in Minnesota did some interesting work during the pandemic, and -- and -- but it -- it -- it's not one that -- that I'm aware of, of a way -- path forward with it. I'm -- I'm -- I'd love to hear more from people that might be smarter with -- than I am with that.

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DR. VOGT: And is that limitation due to the funders, Dr. Kimberlin; and who is that funding source; or, like, where -- where does the limitation come from just to try to identify places where maybe we can try to liberal -- liberalize the -- the way we do these trials a little bit?

DR. KIMBERLIN: Yeah. It's the regulatory oversight of studies. So it's -- it's not really so much the -- the funding source, although they -- they're going to be -- they obviously will be compliant with what -- with the regulatory environment that we work under.

But it's -- it's everything else, and it also involves subcontracting and -- and getting a legal agreement so there is a mechanism by which data can leave one place to go to a --

DR. VOGT: Yeah.

DR. KIMBERLIN: -- centralized database.

DR. VOGT: Sure.

DR. KIMBERLIN: And you add all those things together, things that -- you know, if you and I

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were taking care of a patient, we'd call each other. We'd work through it, and we'd have something taken care of in 15 or 20 minutes.

It -- it would take -- it -- it'd take substantially longer, months to -- to do the same sort of thing within the confines of the research realm.

DR. VOGT: Sure. Thanks for that answer.

DR. KIMBERLIN: And -- and again, if other people have a different way of doing it, I will be taking notes. I would love to hear it, but that's been -- that's been my experience.

DR. PICA: Thank you for those perspectives.

Dr. Abzug, do you have a comment?

DR. ABZUG: Thank you. Yes.

I'd like to make two comments, one in response to Dr. Kimberlin's description of the natural-history study just to add that, as he mentioned, that study will hopefully identify appropriate endpoints for the next treatment trial. It will also help to, as he implied -- help to -- us

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to know more about the appropriate inclusion.
In the pleconaril-treatment study, we picked the sickest of the sick deliberately to try to get meaningful endpoints.
This natural-history study will tell us whether we can be more liberal and have a sick but not the sickest of the sick study population, which will make the study -- the next study a little bit easier to do, or whether we really need to focus on the most sick infants to -- to get to meaningful endpoints.
And then I want to just make an anecdote because we -- we talked this morning about the challenges of enrolling families of -- of very sick newborns into studies.
My anecdotal experience is that for a treatment study like the pleconaril-treatment study, where there's either a 2-to-1 or 2-out-of-3 or 1-out-of-2 chance at a baby who's going to receive what we think is an active drug, it was much easier to convince parents, even those who are really dealing with a dreadful situation in front of them, to participate in that sort of study than it has been to

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convince them to start participation in a natural-history study, where the only potential benefit is future knowledge that hopefully will -- will help other babies but will not help their own because for those, you know, families with a very sick child one more blood draw is one more blood draw too much sometimes.
Thanks.
DR. PICA: Absolutely, well put.
Dr. Vogt?
DR. VOGT: I think I'll try to build off what Dr. Abzug was just saying in the -- you know, how do we pick what children to target; right? The sickest of the sick versus, you know, intervening a little bit early, I think when you think about it from a virologic standpoint, the earlier we give these drugs, the better.
I mean, you know, if we give the drug -- if we give the virus more time to infect more cells or to maybe get father in a life cycle within a cell, it makes sense to me at least to think that that -- that drug now has a harder hill to climb to show

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some efficacy.
But at the same point then, the challenge with the rare outcomes is of course -- how do you know -- how do you select the kids enough in advance that your end could be high enough to actually point out that there were some kids who never actually got that sick at all but otherwise would have gotten that sick?
I think most folks on this call with at the FDA have probably had to think about that a million times. So maybe I'm just sort of speaking into an echo chamber here, but I think that for a lot of these antiviral drugs definitely earlier is the better.
And we -- we've seen this in animal models; but, you know, animal models are one thing; and -- and humans are another with -- with all the different challenges that have been mentioned before.
DR. PICA: Dr. Abzug?
DR. ABZUG: Thanks. And I can comment on a couple of the bullets that -- that you -- you have up there -- virtual connectivity interruption --

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study looking at pleconaril for infants with meningitis. So these were outside the newborn grade, and they were not as sick as the kind of sick newborns we're talking about.
And the challenge there is that fortunately those babies -- those children are just not as ill, and they generally do quite well.
And we actually aborted the study because it was clear that we were not going to have enough meaningful endpoints to get to say whether the treatment was beneficial or not because most of the children in the study had short hospitalizations and really did not suffer at least in the near term significant morbidity and mortality.
So that's why we have chosen to start really focusing on the sickest babies, those being the newborns.
DR. PICA: Dr. Massaro?
DR. MASSARO: Thanks. I just wanted to piggyback on some of the comments that have been made from the neonatology perspective. You know, I -- I think everybody is homing in on this point that the

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studies -- and I mentioned also during my introductory comments these studies -- studies are so incredibly challenging.

And I -- I hope after I speak that if -- if Betsy is still on she can speak to this as well.

But we do have a lot of experience in the NICU and in the neonatal space and in trials that -- that really do have some of the same issues that have all been mentioned, you know, time sensitivity, critical illness, the HIE population, which Betsy talked about her experience there as a prime example of that where, you know, we enrolled in -- in acute trials with a therapeutic window of six hours in a really, really, really sick population as well.

So I think the keys that we've learned from those experiences, the leveraging of networks, that's been mentioned. Involvement of parents really early in the process -- and we've even learned from, you know, our early successes in that hypothermia for hypoxic ischemic encephalopathy space is -- we're -- we're still learning, and we're still improving.

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So we had mentioned the International Neonatal Consortium; and Lily mentioned the, you know, development of -- of seizure-trial guidelines through that group; and even still, we've struggled with some neonatal-seizure trials, which is another area where, you know, this -- that faces some of these similar challenges.

And we've worked on -- in meeting with parent groups, and -- and there have been publications, as Betsy mentioned, from the erythropoietin and -- and HIE trial from family and patient experiences to try to kind of identify some of those best practices.

So that may be an area to kind of look at some of those publications and resources that may help in this space as well.

So, you know, one of the things we identified in the seizure-trial network is -- is, you know, the use of -- of, you know, the investigators, who are consenting and -- and not having the -- using, you know, even the well-trained clinical research assistant to come and talk to some of these families, who really have complex illnesses.

So there's, you know, the ethical issues of -- of therapeutic misconception and making sure that if it's a treating physician or a clinician that can answer questions for families.

But -- but, you know, the -- the families just really -- I think we have pretty high consent rates in some of our trials where, you know, one of the investigators was really somebody who could answer questions for the family about the disease process and -- and answer questions about the study.

So there's some benefit or -- or -- you know, to the consent process, as we've discussed, in the information that's conveyed to families through that process. So I think that -- and there's, you know, tools and -- and things that are being developed that help with that consent -- that consent process.

So I'll -- I'll just put a plug in to kind of look at some of those resources and some of those trials in other spaces in neonatology that may be helpful for the discussion here; and I see Betsy's hand up, which I'm glad about 'cause I'm sure she has things to add here as well.

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DR. PICA: Yes.

Betsy, please?

MS. PILON: Yeah. So I just wanted to, you know, dovetail off of that a little bit; and obviously, there's a lot of work that's been -- that's been going on, as An mentioned, and lots of resources out there.

You know, some of the things that we found partnering on -- on these trials as they're underway now is the real-time problem-solving of looking at, you know, if there's consenting issues or even bias and things that -- that we're, you know, observing or, you know, questioned.

As patient families involved, we've done a lot of PCORI work; and there's a lot of great PCORI work out there as well, especially the neonatal seizure research network; and there's a lot of resources that have come out of that as well.

So just, you know, some things to consider because, you know, there are lots of cohorts like ours and -- and the -- the -- you know, the

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relevance here, just looking at what that is and -- and that consenting process, again, to An's point, you know, what they tell you, it is very short.

But that doesn't necessarily mean that -- you know, that this can't be done; but it certainly -- you know, there's -- there's things that are learning -- that we're learning and -- and can bring those perspectives and other patient-family involvement that I think, you know, kind of allows for these -- these challenges that -- that are brought up.

You know, and -- and I hear this again from the patient-family perspective of -- I -- you know, these are very sick babies we're talking about; and there's a perception of not wanting to overburden families.

But also, if you're not bringing things to the bedside that their babies and kids can benefit from and you're, you know, making that decision for them of not even approaching families, that also, you know, can be problematic, especially for a lot of, you know, therapeutic interventions and potential, you know, that needs the good enrollment data and

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longitudinal follow-up, you know, to get -- get an actual sizable amount of data for these.

Thank you.

DR. PICA: Excellent point. Thank you so much.

So I -- I think we could just maybe tackle some of these questions a little bit more directly. I'm -- I'm interested in this concept of infection severity. You know, what -- what do we gain, or what do we lose by focusing on severe infection or disease versus mild symptomatic infection, for example?

Dr. Kimberlin?

And then, Dr. Vogt?

DR. KIMBERLIN: Yeah.

In conversations over -- over the years, Dr. Abzug, I think, has shifted my opinion on this to some degree and -- and convinced me that it's really -- it is the sickest ones that -- that are probably most appropriate to study because some of those that are less sick are never, as Dr. Vogt said just a moment ago -- are never going to progress to

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being more severely sick, and these babies are still -- are so few and far between that if we -- if we blend populations too much we won't have the power to be able to see those differences 'cause there just aren't enough to enroll.

So I think it's good and -- and maybe -- I hope anyway the natural-history study that we're conducting now can be informative for the sub -- well, across the spectrum but including the subsets that are -- that are most severely ill in terms of what their outcomes are with their mortality, for example, at 1 month or at 3 months.

But maybe as well, it might, since it's a noninterventional study, allow us to identify those predictors of which ones start out more mild and stay mild versus those that start out more mild and get more severe.

If we could find that, then I would liberalize and go with an -- enroll across the spectrum. If we don't know that, I think I would stay focused on the sickest of the sick.

DR. PICA: Thank --

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DR. VOGT: So, Dr. Kimberlin, I think you -- you teed up my question well and maybe even partially answered it. Unfortunately, I don't have the benefit of the years of discussion between -- between you guys to frame my thinking on this.

But, you know, I was thinking -- so whoever -- I forget whose slide it was; but someone had their unicorn slide about, you know, what's the ideal clinical study; and -- and, you know, they presented it as a unicorn 'cause obviously it's hard, if not impossible, to get your ideal study.

But if I were to dream up an ideal study, you know, I -- I was told when we were planning for this, this isn't a meeting about prevention. This is a meeting about treatment, but that also kind of exists on a spectrum, and I think that's what this bullet point about infection severity is pointing out.

You know, infection just means you have virus in you; and then disease, as Dr. Abzug pointed out in his talk, there's a -- there's a wide range of disease.

So at what point, you know, does

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something become prevention of maybe not infection so much 'cause the infection has already happened but prevention of progression to severe illness versus treatment of a mild illness; and -- and is it even -- is it important that we distinguish that?

It seems the FDA thinks it's important because there's a bullet point right there about it. So to get back to that unicorn study, I would love to see no kids get any severe disease.

And so, you know, I think we lose a little something by only focusing on the children with the most severe disease because the cat is already out of the bag. The horse is out of the barn, whatever you want to use.

So my question -- maybe to frame it as a real question to either Dr. Kimberlin or Dr. Abzug, who've probably thought about this much more than me, would your end needed to find that -- you know, that actual statistical endpoint change if you could prevent every instance of severe disease, every instance?

So we had a drug that's very safe. In

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my unicorn world, this drug is very safe. So we don't feel bad about giving it to basically -- let's say -- any child who is either born to a mother who tests positive for enterovirus or tests positive themselves for enterovirus. So you're just screening kids and screening moms as they come in and give birth.

So now you've identified your sort of overall cohort as just enterovirus-positive, you know, mother-infant dyad. We give all those babies drug, and yeah. Probably only a very, very, very small part of that population was going to progress to any sort of illness.

But if you see a flat line, you don't really need a ton of severe disease -- right -- to get statistical significance when one of your lines is flat. Is that -- let's say again that dollars are not an issue in our unicorn world. Could you do a study like that, Dr. Kimberlin or Abzug; or is that, like, completely impossible to -- to dream of?

DR. PICA: Feel free, Dr. Abzug, to respond.

DR. ABZUG: I -- I can give the first

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response, and Dr. Kimberlin can give the second. I'm -- you know, first of all -- virtual connectivity interruption -- actually, I'm sorry. Are you hearing me? Can you hear better as I lean closer to my laptop?

THE REPORTER: Yes.

DR. PICA: I think it might be something with your connectivity, but it is better when you lean a little bit closer.

DR. ABZUG: Okay. I will try to speak up and lean into my laptop. I think in the real world medications aren't available to be used in the way Dr. Vogt is describing. Could one do a clinical trial in that way? I think that depends on resources. It would have to be quite a large study with quite a large budget.

And that hasn't been the situation to date, which is why we have focused on a sicker population likely to give clinically meaningful endpoints more -- more quickly.

DR. PICA: So, you know, I think just thinking a little bit more about what Dr. Vogt had

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said, you are enrolling mild symptomatic population and want to prevent severe disease; or you're -- you're enrolling individuals who already have severe disease.

You know, what do you think the appropriate trial endpoints would be? Would it be mortality? Would it be time to hospital discharge? What are kind of the key things? And -- and maybe this is informed by your clinical practice, but -- but what would be the -- the endpoints that you think would be the most important to focus on?

And -- and I -- I also want to give Dr. Hincks the -- the opportunity to address some of these comments as well.

DR. VOGT: Yeah. Was that --

DR. ABZUG: I'll just --

DR. VOGT: Yeah. Go ahead.

DR. ABZUG: Go ahead, Matt.

DR. VOGT: Yeah. I don't know if that was directed at anyone specifically.

DR. PICA: Dr. Vogt, I was thinking in the context of your unicorn study and -- and also what

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Dr. Kimberlin had mentioned before. So if you -- if you want to, respond; but then -- then we can turn it over to Dr. Hincks.

DR. VOGT: And it sounds like Dr. Abzug probably has an idea there. I mean, to me, it would just be progression to, you know, severe disease with a broad definition of that 'cause I think that gets back to the one slide that Dr. Abzug had, which was, like, myocarditis, hepatitis, coagulopathy.

These are all bad things, mortality certainly; but -- but all of those are bad things; and I think if we intervene early we actually have a chance to prevent all of those things if we have drugs that are broadly enough acting.

And I do think you'd probably want to have some kind of, you know, post hoc analysis where you have -- again, if, it's, like, a capsid-inhibiting drug, you know, you identify the -- the -- you know, eventually you get to the point where you can identify the specific virus the child; and you can see if there was a match to be made or not.

Or for me, you know, I -- I think about

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antibodies; and so, you know, we know the antibody is only going to react to certain viruses. Did we actually have one of those viruses or not? Hopefully that maybe gets a little bit at your question, and maybe Dr. Abzug has some more thoughts to add.

DR. ABZUG: I agree.

DR. PICA: And -- and, Dr. Hincks, your perspective?

DR. HINCKS: I think doing a trial on everybody that comes in, if they have enteroviral or not, is difficult 'cause we would be treating babies that may not need treatment at all.

So I -- I think there has to be some endpoint that's already detected, whether it's myocarditis, hepatitis, encephalitis; but something is going on that would warrant treatment in the baby.

And I -- I think taking all-comers -- again, it might -- might impact the end; but I think going after the severe disease, you're asking a lot of the antiviral because, again, once the organ is damaged far enough it's not going to recover.

So I don't know. I -- I think it would

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be best to take all severe and minor effects of the disease and then look at the data they generate.

DR. PICA: Dr. Kimberlin?

DR. KIMBERLIN: I really like what Dr. Hincks just said at the very end, "Look at the data that you generate."

If we set mortality as the primary endpoint and we have a number of different things, hospital discharge, including virologic endpoints as secondary or tertiary, and then we don't hit mortality and so it's just tossed out because the primary endpoint wasn't achieved, that would be a real shame.

I think we've got to -- this is a point I was advocating for earlier as well.

I think you've got to look at the totality of the data, whatever the population, whether it's just the sickest of the sick or whether it's, you know, a more broad spectrum, and -- and really look and see what the story that is -- is there that's being told and -- and being -- being willing to -- to think more about the art of it than the science of it, at least as a component, as you would if you're

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reading a book.

What is the storyline that we're seeing, and is it strong enough to -- to get a product to the finish line in terms of the licensure kind of a result for the NDA?

DR. PICA: Dr. Rosenfeld?

And then, Dr. Hincks, again?

DR. ROSENFELD: Yeah. I'm a little confused if -- if we absolutely know that severe disease and replicating virus are concordant. Like, that -- when you see severe disease, you can detect replicating virus rather than the severe disease is due to the body responding to the viral infection; and the virus has already been cleared.

So if you're targeting the virus only and there's no virus, then I'm not clear what we're -- what we're looking at. I understand about, like, IVIG working because it can dampen the viruses that are surrounding and stuff that may contribute to the development of severe disease.

But if you're -- if the actual -- if the actual virus that you think is causing the disease

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is gone, then I don't know what we're -- we're targeting. So I think we need to understand whether or not virus is really replicating in present at that time that severe -- we detect severe disease, and I don't think we have that data.

DR. PICA: Yeah. I think that's an excellent point, Dr. Rosenfeld.

Dr. Hincks?

Then, Dr. Abzug?

Then, Dr. Kimberlin?

DR. HINCKS: Yeah. I mean, we have quite a bit of data from our Capacity Use Program; and, I mean, the -- the way they approach us, PIs will approach us and say, "We have this check -- this neonate, and they're PCR-positive," which -- no -- that might not be culturable or -- or replicating virus.

But they're PCR-positive for enterovirus and typically rhino, entero; and they're presenting with these diagnoses or these effects: myocarditis, hepatitis, things like that; and you put the two together, and you think they have -- have a

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condition of, you know, enteroviral infection with severe disease. So then we treat with pocapavir.

So I don't think it's just one or the other, and -- and I think in -- in a trial you'd be doing the same thing; right? You -- you'd get a patient that would come in. They're positive for PCR entero, and you go ahead and have other conditions that would predict its enteroviral infection with severe disease.

That severity depends on how far the organ has been damaged; right? So you -- you don't go in with one or the other. You kind of -- you need both pieces of information.

DR. PICA: Okay. And even the information is somewhat incomplete because you may be PCR-positive for enterovirus or rhino, entero for that matter; and you don't know, you know, in fact what is -- what is the infecting agent.

Dr. Abzug?

And then, Dr. Kimberlin?

DR. ABZUG: We do have data from the pre-PCR era that shows that -- that these very sick

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babies are viremic at the time that they're presenting and showing organ disease. So I don't think there's doubt that there's a component of active viral infection.

But I -- I will add that pathology studies of babies who've died suggest there's both a component of cytolysis, cell breakdown due to direct viral infection, as well as an inflammatory response of the host, the baby, that may be contributing to the ultimate pathology.

DR. BELEW: Thank you, Dr. Abzug.

This is Yodit Belew. Before we go to Dr. Kimberlin, I just had a follow-up question to both Dr. Kimberlin and Dr. Abzug, considering your long history of -- of taking care of these babies with enteroviral infection and sepsis.

So considering other viral diseases and the effectiveness of antivirals having been established to be generally the earlier you give it, the better they're effective, I wanted to go back to Dr. Kimberlin's earlier point about the natural history and identifying potential baseline

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characteristics and/or biomarkers.

So from the preexisting literature, are there reasonable characteristics that we could rely on if we were to consider therapeutics where you're treating to prevent severe disease, including death? Thank you.

Yes. Dr. Kimberlin, please?

DR. KIMBERLIN: I was hoping that Mark would jump in on that one. I don't know the answer to that. To my -- to my knowledge, we don't have that well defined a biomarker yet. Either -- either that, or I'm -- or I'm flat on my feet in terms of thinking about it.

I -- I would -- my hand up was -- was up in response to the -- the conversation just before that, which might actually be informative to this too about whether it's replicating virus or -- or not.

And the -- and the -- the graphic that popped in my head was what Dr. Abzug showed from our pleconaril study, where there was more rapid clearance of virus among the -- or at least a trend toward that, a P-value, I think, of 0.08, with -- with respect to

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the group getting active drug versus the group getting placebo, which, you know, either was erroneous.

Or it's because there's actively replicating virus; and the antiviral drug is slowing that down. Now, whether we have enough to -- to call viral load the kind of biomarker that -- that your question is getting at, I -- I don't know.

Or is this a rare enough and unusual enough disease, and we want enough flexibility to -- to simply accept virologic endpoints and say that -- that that's good enough for where we are right now?

And maybe post licensure, we could do some of the additional work because then it is -- you don't have to jump through all the different complexities of having a site and being positioned right in the hospital where that particular woman delivers the baby or brings the baby back when the baby gets sick.

Instead, you could do more real-world, to use the -- the catchy phrase, follow-up and -- and learn more about the use of the drug that in -- in this hypothetical is -- has been licensed based upon

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virologic endpoints.

DR. BELEW: Thank you, Dr. Abzug. I was -- I was thinking more along the lines of elevated white count; anemia; maternal status; young age, I think, in Dr. Abzug's presentation being less than 7 years of age, so using those, I guess, characteristics that have been described for a number of years as a way of identifying infants who are likely to have a higher risk of progressing to severe disease to allow identifying an enrollment of these neonates into a potential clinical trial.

Dr. Abzug, please?

DR. ABZUG: Thank you. And I'm leaving my video off just so hopefully you can hear me better. For the demographic predictors like illness within the first seven days of life, I think we need still to learn how predictive that is. I mean, it -- it's clearly a predictor; but what it's positive predictive value is, I think, still needs to -- to be defined.

Things like white count and hematocrit and that sort of thing haven't really been shown to be terrific predictors, but one lab predictor that can be

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useful is a positive serum viral culture at the time the child presents, but nobody does viral cultures, and nor are they rapid.

So I don't think that's particularly useful to pick out that child from the start who's going to have a higher likelihood of an adverse outcome.

And I also just want to clarify in case there's a misconception. It's not like these babies who are the sickest -- it's not like they sit around for three, four, five days with a mild infection and then deteriorate five, six, seven days later.

These sickest babies present and within either -- either on presentation or within 24 to 48 hours are -- are really telling you, "I'm one of the sick ones." So it's not like anyone is sitting around for days thinking, "Hmm, antiviral or not?" That -- that really isn't the clinical reality.

DR. BELEW: Thank you, Dr. Abzug.

Dr. Hincks?

DR. HINCKS: You're -- you're asking me for a comment?

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DR. PICA: Your hand is up. So we just want to --

DR. HINCKS: Oh, thank you. Okay. That was a while ago, but just commenting on what -- what Mark just said, I -- I agree. Some of these cases present very quickly; or they've been seen at one hospital; and they're transferred to another; and within a couple days after that, they become very ill.

So it -- it -- again, it depends on each individual, I would have to say. So I agree with what Mark said.

DR. PICA: Dr. Kimberlin, we'll give you an opportunity to respond; and then we have a different question.

DR. KIMBERLIN: Well, it -- it's -- it's really kind of a question for Dr. Abzug to see if my memory is accurate. Way back in the '90s when the pleconaril study -- when we developed it and we had to define what severe hepatitis was, what severe DIC was, what severe myocarditis was, my recollection is that we kind of made it up.

I mean, we kind of -- we kind of used a

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threshold that we thought would define a severe -- a severe baby; but it wasn't based upon a prior study that showed that, you know, 3.5 fold over baseline is -- is really bad versus 3.4 over baseline being not so bad.

So there was -- as we look at what has been in the literature, I think we have to have some grace with respect to -- there -- there could be some variability. It's not written in stone simply because that's the way it was defined once that that's the way severe disease has to be defined going forward.

Mark, do I -- do I have a faulty memory on that?

DR. ABZUG: No, 'cause your memory is better than mine. But -- but I'll -- I'll add that there's -- there were some preexisting data. We and others have written case -- had written case series where we described our sick population, and these were the kinds of lab findings or parameters that -- that describe them.

But -- but there isn't in the literature that finer gradation to say that 2X normal

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LFT is different from 3X normal LFT. We just picked the ones that had been described, but -- but not -- but there had not been a full analysis of different gradations of those abnormalities, if that makes sense.

DR. VISWANATHAN: This is Prabha Viswanathan. I have a question to our clinical experts in the room, and this is tying together comments from -- from many people. One question for Amy Rosenfeld though is -- is: What can we ask of an antiviral?

So it is clear that the disease course is heterogeneous. The rate of clinical deterioration is heterogeneous, but is there a point that we reach where we think that an antiviral really is not likely to help a child?

So if we have a child who has myocarditis with heart failure, a child with liver -- like, full liver failure, are these groups of patients that you feel like are -- are too severe to include in your clinical trial and may impact your ability to have a successful primary endpoint?

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DR. ABZUG: This is Mark. I'll start. Well, if -- if you believe the study from the -- the pleconaril study that we talked about earlier this morning, I believe we showed a mortality benefit. It didn't meet all of the rigor that we would have liked and that the FDA would have liked.

But I think at least as proof of concept it did show that treating those sickest babies was beneficial, and I -- as far as I know, pleconaril's activity is purely as an antiviral. So that suggests to me that antiviral therapy at that stage of illness can be effective.

DR. BELEW: Thank you for that --

DR. ABZUG: I welcome other opinions.

DR. BELEW: It sounds like you have the final word on the -- on the question, Dr. Abzug.

DR. PICA: Just as a follow-up, maybe looping back to the comment that Dr. Kimberlin had made earlier, what -- what questions do you think could be answered from larger natural-history studies with -- in regard to understanding appropriate populations and trial endpoints?

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Do you think that the disease is so heterogeneous that the data will be hard to interpret, or -- or are there goals for these natural-history studies in the context of -- of designing clinical trials?

DR. ABZUG: Dr. Kimberlin, do you want to start with that one?

DR. KIMBERLIN: Yeah. I'd be happy to. I -- I think we can always learn more, and I think more information, more data are better than -- than less. I -- I think that we -- that -- that many of the good points raised about, you know, is -- is a particular, you know, coxsackievirus worse in neonates than another, you know, echovirus is?

To -- to some extent, I -- I appreciate it, but if we -- if we stay in that rabbit hole, we don't ever have the opportunity to move into a clinical trial to see if an antiviral works.

And I remember with the pleconaril trial design back in the '90s there -- there was one very smart person who was advocating strongly that, "100 different enteroviruses, we can't do this --

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can't do it."
And -- and maybe that's the right answer; but ultimately, I -- I kind of agree with Mark that we did show a benefit, albeit in a Phase 2 study that was never in -- you know, intended to be a licensure trial.
Nevertheless, the data -- I think the story told would, to me anyway, suggest that -- that it works for that particular drug in -- in that population.
So -- so I -- I think that we -- we don't have to -- what is the phrase? You know, you don't -- don't let the -- the good be the enemy, the perfect -- or whatever it is. You know what? Let -- let's -- let's kind of get our -- roll up our sleeves and -- and move forward with what we have.
And if -- if additional information comes out through natural-history studies and others down the road, that's fine; and we can make modifications as needed; but let's not just sit back and wait for it if we have a drug that has the potential that really could move forward and move the

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field.
DR. ABZUG: And I'll add that -- that I'm -- I'm really very hopeful, 'cause I'm an optimist, that the current natural-history study will tell us something about the value of quantitative PCR in this disease. I come from a background of treating children with HIV; and as we all know, that marker has proved incredibly useful.
So whether it's as -- useful as a predictor of babies who are destined to have worse outcomes, which then helps us identify who should be treated and who shouldn't be treated, or whether it's value as an endpoint of -- of treatment because it has predictive value of outcome, I don't know; and maybe -- maybe it'll help with both.
But if we can identify something like that through natural-history studies that then make mortality -- while obviously an important endpoint, not the only endpoint that we need to strive for and -- and hopefully an -- an easier-to-achieve endpoint, then I think that will be a major gain.
DR. PICA: Dr. Hincks, did you have a

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comment?
DR. HINCKS: Yeah. I guess it comes to the next point that we might be talking about, but what about using the natural-history study as the comparator arm to an active trial?
That was for Mark, David.
DR. PICA: If no one has anything to add right at the moment, you know, I think that your question will be a great segue into our final question for this panel discussion; but we did have a couple Q-and-As from online that we wanted to get to regarding the -- the topic that -- that we've already covered.
So maybe I'll go to those first, and then we can -- can move on altogether then and -- and go into that last discussion topic. So we -- I promise we will come back to you, Dr. Hincks.
But going to the -- the Q-and-A briefly here, so we had several comments in here -- and apologies. We will not be able to address all of -- of the comments, but I wanted to -- I wanted to read out one comment, not really a question but, I think, an -- an important comment to share with the group.

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So we had an attendee who says: "I think it is important to separate the idea of trials to license a drug from trials to optimize treatment. A company wants one thing from a trial for licensure, which is a license within a reasonable time.
It is utterly unrealistic to expect an industry-supported trial to look more -- to look at more complex endpoints that will take more patients, read higher costs, and take more time to license a drug."
And I think these are all very fair points; and, you know, the focus of today is really to talk about that licensure issue; but -- but you're right. There are two different objectives there.
And then another question that came in that we've somewhat touched on here but just wanted to -- to close the loop on, so we have a question: "Have any studies looked into risk-based scoring models to predict severe illness? Perhaps a composite of different risk factors?"
I know we've been talking about how this would be really advantageous if we had such

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predictors to identify those at risk for more severe illness, but does anybody have anything else to add on that line of -- of thinking?

Anything from the real world or from the natural-history studies that are -- that are ongoing that could be used to further look into this? And I will stop there.

DR. ABZUG: You know, as I showed earlier in my -- my talk, people have identified some predictors; but I have not seen a composite-scoring model to specifically look at the risk of severe neonatal enterovirus disease.

That is a potential outcome from the -- from the ongoing natural-history study. We're collecting a lot of clinical and laboratory data. So we certainly can look to see if something like that is able to be derived from the dataset.

DR. PICA: Thank you. Does anyone have any other comments on the population discussion before we move on?

DR. VOGT: I mean, I guess just so that my silence isn't, you know, seen as opposition, I

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mean, I think that makes a lot of sense. We have a rare disease. It's really hard to get that comparator population.

And maybe Dr. Kimberlin is working on that comparator population right now. I think it seems pretty reasonable, just to support what Dr. Hincks had said.

DR. PICA: Great. So I think in the remaining minutes we could maybe try to discuss the most appropriate comparator-treatment groups, and I -- I open the floor to either Dr. Hincks or Dr. Kimberlin to start us off.

DR. KIMBERLIN: I'd be happy to, and -- and I -- I guess the -- the theme I would -- I would advocate for, if possible, is to find a creative study design that would not require a placebo.

Enrolling even a 2-to-1 randomization or a 3-to-1 randomization on a placebo-controlled trial when a family's 7- or 8-day-old baby is critically ill is -- it -- it can be done, especially if the drug is not available otherwise, through compassionate use or something along those lines.

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But it's a -- it's a lot easier to sit down and say, "Your baby will get the drug either because everybody is getting treated at the same dose"; and -- and maybe there's natural history or comparators, as -- as Dr. Hincks was suggesting. Maybe the natural-history study could provide -- or I -- I come back to what I said before.

If a drug has not been studied in babies and we have modeling data and we -- you know, we think we know what dose to use but it hasn't been studied, that's the reason we're doing the trial. Maybe something -- this is a new concept to me, and I'm -- I'm developing it as I'm saying it out loud.

But multiple doses of the active drug, some of which are the sweet spot, based upon -- that we anticipate based upon the modeling data, but also a little bit above and some below that too, some of which may be based upon modeling data, are -- are anticipated to be subtherapeutic.

If they're subtherapeutic, they're not going to work. That's your placebo. That's your comparator, or you look across the spectrum of the

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amount of drug exposure you're achieving and correlate that with viral load, or you correlate that with outcome of some kind or a series of outcomes.

Something creative like that would -- would help, I think, with getting a study that not only reads well but actually implements well and has a chance of enrolling.

DR. HINCKS: I -- I definitely agree that designing a study without a true placebo control would enroll a lot faster, and I just think -- I mean, I hate using that "unethical" word; but it -- it seems unethical, similar to oncology studies where all -- all, you know, patients get treated.

But again, it's -- it's -- what is that comparator arm, is the key; and would FDA accept a non-placebo comparator?

DR. PICA: Dr. Vogt?

DR. VOGT: I mean, I think we're already doing this -- right -- this non-placebo controlled trial with pocapavir; and we just call it expanded access or, you know, compassionate use; and I don't say that to be inflammatory or anything like

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that; but that's kind of how it's done; right?
So, you know, Dr. Kimberlin or I have a baby in front of us that we're very concerned about and enterovirus-positive and that sort of thing; and, you know, we call them up and say, "Hey, man, let's -- let's give them this drug, please"; and so we do it.
There's no placebo in that, but there's also no -- there's no real rigorous trial design to that either; right? It's just the whim of particular investigators who take it upon themselves to, you know, call up the company and say, "Hey, Dr. Hincks, can we have your drug?"
So I think we're already doing it. It makes a lot of sense to me to try to do it a little bit more prospectively with a little bit more design behind it. I think when we think of it that way -- again, I'm kind of thinking this out loud just the way that Dr. Kimberlin was -- was thinking out loud earlier.
But it sure makes sense to me that I would rather see a non-placebo-controlled trial that has been prospectively designed and implemented rather

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than compassionate use, which is kind of the same thing but just way more willy-nilly 'cause I do worry that when we do that compassionate-use stuff that, as has been raised before, just the -- the organ damage is just so far gone by the time we give the drug.
I worry that we're going to miss -- that we're going to miss potential benefits that we otherwise might see if we weren't just, you know -- 'cause it takes -- it's -- it's not an instant thing. We don't just call the drug company, and they send the drug that day.
I mean, it's -- I will give them credit. I've had colleagues who've done this, and it seems pretty well streamlined compared to maybe some other expanded-access stuff I've been exposed to. So that's not a knock. It's just the way it is. It's -- it's a very hard thing to do, a lot of paperwork and stuff.
And -- and I'd love to hear from anyone, especially Dr. Hincks on the company side, his perspective on that.
DR. VISWANATHAN: Hi, this is --

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apologies for that. This is Prabha Viswanathan again from FDA. There's a lot to unpack here; but clearly, there are hesitations about placebo control.
And I would like to hear more about what -- whether the hesitation is -- is parental -- it's a concern of parental refusal for enrollment, whether this is really on the provider side, feeling that it's infeasible or unacceptable from a scientific perspective.
And then I want to remind everyone that we -- we have an obligation to the patients and the families who enroll in these clinical trials to conduct trials that are -- that are interpretable, that in the end when we enroll children and expose them to investigational product there needs to be a real end there that we can -- we know what to do with the data that we have.
And without a comparator, it's very hard to know whether these drugs really work. So we certainly want to dialogue with you about -- about different solutions for how we get interpretable data; and I think part of that is, it's important to

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understand what are the real factors limiting enrollment.
Is it the concern that my child is not going to get something that works? We -- we only do trials when there is clinical equipoise about whether the trial -- whether the drug really will impact the endpoint that we're studying. Otherwise, we wouldn't do the trial. We would already know the answer; and in this case, we don't.
So for anybody who cares to respond, I'd like to go back to that a little bit and talk about what are the factors that are -- that are keeping us from doing placebo-controlled trials.
DR. KIMBERLIN: Well, I might -- I might start with that. My impression or experience is that the bigger barrier is -- is with the parents. Think about it.
If, you know, your 10-day-old is -- is critically ill and somebody comes to you and says: "I can -- you can enroll on this study that's placebo controlled. There's a three-to-one chance you're going to get active drug. We're going to take all

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this blood. We're going to do all these things, or I could call Company X and get it compassionate use, and -- and we'll get it tomorrow. What do you want to do," a different drug probably, although sometimes this is -- if there is a compassionate-use program, that can -- with -- with the same drug, that can be -- that can be a disincentive as well.

And they're going to generally -- not generally, but a lot of times they will take the -- the path of: "I want the real thing. I want what has a chance of working."

I do fully appreciate what you're saying about the ethics of -- of the -- of -- of enrolling and exposing -- enrolling babies, exposing them to a -- to an investigational product when there's -- when there's a chance that we won't know how to interpret the data.

But again, I come back to this idea that -- what if we do a range of exposure, and you see a range of response so that the worst outcomes are when there's very little or subtherapeutic exposure? Best outcomes is when you get really good drug

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exposure.

That in and of itself within one single treatment study could provide its own comparator that would be placebo-ish, if you will.

DR. VISWANATHAN: I'd like to just briefly respond to that, and then I'll hand it over to Dr. Vogt. I -- I just am not sure what the difference is practically from having a micro subtherapeutic dose versus a placebo. Is it just telling the -- the family that you're getting something?

But if it's something that you don't think is actually going to work, isn't that just a placebo that also exposes a baby to potential toxicity?

MR. KIRSCH: That -- that's certainly an argument; but the point is, we don't know the dose. If we did -- if we knew the dose and we knew that it worked, then yes. That would be -- that -- that would be a problem, but we don't know that.

There is a -- at -- at least with -- with the kind of point in drug development that I'm -- that I'm envisioning as I make this argument.

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And so, you know, it's possible that 100 milligrams of the drug and 20 milligrams of the drug in a baby, because of the difference in the way it's metabolized, the 20 milligrams is as good as 100 milligrams. We don't know that.

And if we only come in with 100 versus placebo, we'll never know that; but if we give a range of exposure, including some that's on the very low side, I think it's -- it's an ethically sound thing to do, as I'm just kind of developing the concept or -- you know, in -- in midstream here, and I -- I think it definitely is easier for the family.

I mean, if the family says: "Yeah. You're going to be getting the drug" -- or you say to the family: "You're going to be getting the drug. We don't know the dose you're going to be getting, but you will be getting the drug," that is a much easier thing to -- a much easier discussion to have.

DR. VISWANATHAN: I'll just add -- we -- we definitely endorse dose-ranging trials, and it is possible that we -- we end up with doses that have enough similar activity, or you can cap out at

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your -- at your therapeutic dose.

But you may not be able to appreciate the difference between treatment arms, but we certainly do endorse trials that investigate multiple doses for potentially multiple durations so that we arrive at that -- at that correct dose.

I know that there are a number of people who are waiting to speak, and I believe Dr. Vogt is next.

DR. VOGT: I think I'm -- I'm in agreement. I -- I don't know the difference between the homeopathic dose and just a straight-on placebo dose other than to be able to say something to the family that, you know, there's medicine in here.

And personally, I actually kind of find that a bit troubling to try to, you know, convince them there might be some -- some benefit when you actually kind of know that it's -- it's more or less a homeopathic dose.

But I -- I see where you're going, David. Like, you know, again, this is -- this is -- it's an awkward forum because it's online, and we're

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sort of taking turns on our camera.
I'd like to think in real life we'd probably be, like, you know, chatting this out, you know, one -- going -- going around the table pretty quickly, working through these ideas because I -- I do like the idea that -- I guess to clarify what I had said earlier about, you know, wanting to have a not-placebo-controlled trial, I think I meant that more just in direction opposition to having the availability of -- of something by compassionate use at the same time.
To me, it feels like there should be one or the other.
And if I'm given the choice, I'd rather have a prospectively -- prospectively designed no-placebo trial than compassionate use 'cause at least I have -- I think I have a better chance at interpreting the data that comes out of the prospectively designed trial than just us again just sort of based on the whim.
It's -- it's -- it gets -- it's -- so as a -- maybe as a comparator, when earlier we were

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talking about the epidemiology of enteroviruses this morning, you know, there's those passive systems where we get some data; and there's good data there. It's not like that's useless data. There's absolutely good data there.
And then there's the prospective systems, and maybe that data gives us a little bit higher quality or a little bit more precision for certain other types of questions. I think when it comes to rare diseases, I mean, this is that -- this is why we're having a whole two-day symposium on it, as this is tough.
But I do think that trying to interpret compassionate use is tougher than it would be if we had, you know, a trial that was no placebo.
That said, I'm going to talk about the unicorn, which I said before I'd rather us hit a lot of kids before they get super-duper sick and prevent them from ever getting super-duper sick; but that's maybe derailing this conversation too far. So maybe forget I said that.
DR. BELEW: This is Yodit Belew. We

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have a number of hands up; but before we jump in, I just wanted to follow up on the comments that Dr. Vogt and Dr. Viswanathan made. So with -- with respect to the -- the looking at various doses, that is a very typical drug development in many disease therapeutic areas, including viral diseases.
But the difference, I would say, is, you wouldn't intentionally study a dose that is a microdose or lower than what you -- at least based on invitro or cell contra-activity that you think is lower than the minimal effective dose, at least based on the nonclinical data.
And so the -- the dose finding is a very reasonable Phase 2 looking at optimal-dose selection; and I think that would be a reasonable consideration, again, provided that ultimately we do have a comparator arm in order to establish the treatment benefit from the antiviral.
With -- with respect to the compassionate use, the availability of compassionate-use programs at the same time as when you're trying to enroll patients into placebo-controlled clinical

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trials, just to kind of put this out there for the group to discuss and consider is, you know, going back to the ideal population and potentially the severity of the illness at the time of enrollment.
What would you think about if, for example, compassionate use would be limited to those who are severely ill and don't meet eligibility criteria to enroll into the clinical trial and the clinical trial perhaps would focus on populations that may be less critically ill?
And I don't know who had their hands up first; but just going from left to right, Dr. Abzug?
DR. ABZUG: Thank you. I'm -- I'm not sure which question I'm responding to now, but I'll say a couple of things.
One additional flaw with the low-medium-high trial design where all the arms are active is if the outcomes are the same amongst the three groups. You don't know if everybody derived benefit or no one derived benefit. So that's -- that's a problem.
Dr. Hincks mentioned, I think, whether

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the natural-history study could be an appropriate comparator, if you will, of historical control but at least a contemporary-era historical control. I -- I think that's a possibility, except that we would have to subtract out those subjects who received a compassionate-use agent.

And then now -- now remind me of the most recent question that you posed. Oh, people who don't meet inclusion criteria and get the compassionate use but others can't. I think that's a valid approach.

I'll -- I'll tell you that when the pleconaril randomized study was going on we had it opened at one tertiary-care center in our city; but it wasn't opened at another tertiary-care center, which is a different hospital system in our same city.

And before compassionate use would have been available, that baby might have been transferred to our hospital for the study; but when an alternate mechanism of having 100-percent access to the study drug was available, that removed the incentive for transferring the baby to the -- the center with the

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active study.

So it -- it even gets murky when you try to define who meets or doesn't meet inclusion criteria because usually inclusion criteria for a study means being at a center where that study is available and open. Thanks.

DR. PICA: Thank you very much for that. So I -- I -- we are running out of time; but given all of this robust discussion regarding use of natural-history data, we would like to give our real-world-evidence expert, Dr. Concato, an opportunity to comment.

But before I turn it over to Dr. Concato, I did want to just read one of the comments in the Q-and-A from an attendee that I think is a nice segue for this.

So the comment states: "Regarding the conversation about using the natural-history study as a comparison group, it seems like there would be an inherent bias because parents might be more likely to enroll in a new investigational drug trial if their child was sick and the current management wasn't

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working well, whereas many more patients' parents might agree to participate in a natural-history/observational study.

It seems like it would bias towards underestimating the benefit of the treatment being studied." And so I think this highlights some of the many inherent challenges with natural-history data; and with that, I will turn it over to Dr. Concato to see what -- what comments he would like to make.

DR. CONCATO: Thank you, and I'll -- I'll leave my camera off as well due to connectivity issues, and yes. That was indeed a nice segue. I was already raising my hand to make a comment about the possible use of a comparator arm for a single-arm trial, whether it's the natural-history study that was mentioned or other sources of data.

And unfortunately, I know no pleasure in saying this. The challenges are pretty -- pretty common. You know, oncology was mentioned; but the endpoint for oncology tumors don't tend to shrink.

I'm an internist, not a pediatrician or a neonatologist; but listening to the earlier

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presentations the heterogeneity both within an organ system and across organ systems, CNS, heart, liver, lung, this is quite challenging to imagine how comparability is going to be assured, which is the crux of the matter for an externally controlled child.

I will refer to an externally controlled child guidance that CDER, CBER, or OCE published last year for our -- our current thinking in this regard; and in particular, I don't have it open on my other monitor; but what comes to mind is the table of comparability.

There's more than one way to -- to organize one's thinking; but I believe we settled on ten different domains; and just off the top of my head, again, deferring to the clinical division about whether this makes clinical sense or not.

But even if it doesn't matter which enterovirus, at least even with a small child, you tend to get balance; but we believe we know which -- which viruses were involved, would they be the same; but more -- more fundamentally, prognosis, as I mentioned, would be very -- very heterogeneric --

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heterogeneous.
Even something as straightforward as the outcome, what is the endpoint; and is it measured the same in the single-arm trial versus the natural-history study? Supportive therapy could vary.
And I think the -- I didn't see the question in the chat. I was getting -- preparing myself to -- to make a more general comment, but I think the commenter also had another concern.
So again, our bar is -- is singular. Our evidentiary threshold is the same. We have regulatory flexibility, but it would take an awful lot of things to go well for an externally controlled trial to work out.
That doesn't mean we shouldn't explore the possibility; but again, a -- sometimes a small randomized trial is better than a larger externally controlled trial because it conserves for bias. Thank you.
DR. PICA: Thanks so much for that.
Dr. Hincks, I -- I think you've had your hand up for quite a bit.

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DR. HINCKS: Sure. So again, there's several questions that have been raised. The -- the one regarding compassionate use, Mark mentioned the issues that he had with pleconaril. We ended up shutting that down because it was an issue.
We were getting a lot of calls for compassionate use because they didn't want to deal with the clinical trial. So I don't think that could continue if there's a clinical trial ongoing.
As far as the various doses, there's a lot of variable already, as we mentioned: disease state, virus, viral load. Adding multiple doses on top of that, I think, would just dilute out any effects that we're trying to look for. My opinion is, you go in with your highest, safest dose to show effect. I think that was it for now. Responses?
DR. CONCATO: As a nonclinical trialist -- this is Dr. Concato again -- I'll just say that I -- I agree that coming in with the dose that you think works.
And also, a problem with the giving homeopathic doses, I think others have mentioned

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there's an ethical quandary there because if we really don't think it works and we're telling the patients -- or we -- we think we'll get better enrollment because, you know, they -- they think it works, that's -- that -- that would be viewed as deceiving the patients.
I mean, it's not only equipoise. It's also the standard of care. The drug could actually do more harm than good, which unfortunately sometimes is the case. So I'll -- I'll defer to the clinical trialists, but.
DR. KIMBERLIN: And if I could respond to it, I -- I -- as I was developing the concept in real time, I guess one caveat, which may not sway people, this would not be a Phase 3 study I'm talking about. This wouldn't be where the drug had been -- the dose had been determined in Phase 1.
You've done a Phase 2 for, you know, feasibility and whether or not there's enough clinical evidence to move forward; and then you go to Phase 3. This would be more of a Phase 2A-ish level where you're still working on what the dose is, and you're trying to get with one trial enough information --

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DR. CONCATO: Then -- then it works.
DR. KIMBERLIN: -- to get a drug --
DR. CONCATO: Yeah.
DR. KIMBERLIN: -- across the finish line.
DR. CONCATO: Yeah. Thank you. And by the way, I hit the wrong button. My apologies. I was trying to type in an answer to the propensity-score question.
So in fairness to the person who asked, propensity scores are indeed how externally controlled trials and observational studies would be done; but it's not a magic bullet.
So the -- the data either do or do not support the comparability issue, and -- and we -- we can't wave a magic wand and have propensity scores provide comparability if it's not there to begin with. Thank you. Sorry for not typing it in the chat -- in the Q-and-A, I should say.
DR. PICA: Thank you. Thank you for that answer.
Wow, this has just been such robust

discussion. Thank you to all of our speakers and panelists for your participation, and many thanks to our meeting organizers and AV team for providing support today.

We look forward to welcoming you all back tomorrow for Day 2 of the workshop tomorrow at 9 a.m. Thanks so much.

(Whereupon, the meeting concluded at 3:30 p.m.)

CERTIFICATE

I, ALEXANDRA HOBRECHT, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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