THE DEVELOPMENT AND EVALUATION OF

HUMAN CYTOMEGALOVIRUS VACCINES WORKSHOP

Tuesday, January 10, 2012

Lister Hill Center Auditorium
National Institutes of Health
Building 38A
9000 Rockville Pike
Bethesda, Maryland 20892

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Reported by: Natasha Kornilova
Capital Reporting Company

"This transcript has not been edited or corrected, but appears as received from the commerical transcribing service. Accordingly, the Food and Drug Administration makes no representation to its accuracy."

 © 2012

C O N T E N T S

PAGE

SESSION I - BACKGROUND: EPIDEMIOLOGY & DIAGNOSIS

INTRODUCTION & GOALS OF MEETING
PHILLIP KRAUSE, FDA/CBER/OVRR 5

CLINICAL HALLMARKS OF FETAL INFECTION AND DISEASE & EPIDEMIOLOGY OF FETAL INFECTION - U.S., Europe and the Rest of the World
KAREN FOWLER, University of Alabama, Birmingham 14

DIAGNOSIS OF INFECTION IN ADULTS (PREGNANT WOMEN), FETUSES AND NEWBORNS
TIZIANA LAZZAROTTO, University of Bologna, Italy 40

DISCUSSION 50

HUMAN OBSERVATIONAL STUDIES & CORRELATES OF PROTECTION FROM INFECTION/DISEASE (INCLUDING VIRAL ANTIGENS) THAT PLAY A ROLE IN PROTECTION
ED MOCARSKI, JR., Emory University, Atlanta 75

SUPERINFECTION OF SEROPOSITIVE WOMEN
WILLIAM BRITT, University of Alabama, Birmingham 101

ROLE OF ANTIBODIES & CMI IN PREVENTING CONGENTIAL CMV
MARIA GRAZIA REVELLO, IRCCS Policlinico San Matteo, Pavia, Italy 118

WHAT HAVE WE LEARNED FROM PRIOR VACCINE TRIALS?
STANLEY PLOTKIN, Vaccine Consultant, Philadelphia, Pennsylvania 133

DISCUSSION 145

C O N T E N T S (C O N T 'D)

PAGE

SESSION II - MANUFACTUERERS AND REGULATORS
PERSPECTIVE & GOALS

REGULATORY CONSIDERATIONS (U.S.)
PHILIP KRAUSE 177

REGULATORY CONSIDERATIONS (EUROPE)
PIETER NEELS, EMA 191

MANUFACTURER'S ROUNDTABLE
MARK FEINBERG, Merck 201
SALLY MOSSMAN, GSK 207
PHIL DORMITZER, Novartis 212
RAFAELA DUMAS, Sanofi Pasteur 215
RICHARD KENNEY, Vical 220

SESSION III - TARGET POPULATIONS FOR A CMV
VACCINE FOR NON-TRANSPLANT INDICATIONS

CONSIDERATIONS AND PARAMETERS OF INTEREST FOR
ACIP RECOMMENDATION OF IMMUNIZATION
OF VARIOUS POPULATIONS
LARRY PICKERING, CDC 244

ADOLESCENT FEMALES & ADULT WOMEN
GAIL DREMMLER, Baylor College of Medicine,
Houston, Texas 259
CHILDREN
PAUL GRIFFITHS, University College London,
United Kingdom 279

MODELING CMV TRANSMISSION & DISEASE
TATIANA LANZIERI, CDC 295

PERSPECTIVES ON MATERNAL IMMUNIZATION STRATEGIES
JEFFREY ROBERTS, FDA/CBER/OVRR 308

LESSON LEARNED FROM OTHER VACCINES
JANE SEWARD, CDC 322

ROUND TABLE DISCUSSION 336

P R O C E E D I N G S

DR. KRAUSE: FDA, National Institute of Allergy and Infectious Diseases, CDC, and the National Vaccine Program Office, I would like to welcome you to the "Development and Evaluation of Human Cytomegalovirus Vaccines" I think there is a mistake on the sign out front, which is being corrected also known as the "CMV Vaccines Workshop."

We're really excited to have this workshop today and I hope the discussions really make a difference in helping to pave the way for the availability of a safe and effective cytomegalovirus vaccine.

So all of you know that cytomegalovirus causes significant disease in the United States and around the world. In healthy individuals, it causes infectious mononucleosis, it causes congenital disease, it causes severe disease in transplant recipients, and, of course, there are other possible sequelae of long-term infection that are perhaps to be worked out a little bit more, including potential immunosenescence, vascular disease, and possibly others.

CMV has also long been recognized an important vaccine target, and, of course, it goes well back to before the 1985 Institute of Medicine "Vaccine Prioritization" report, which discussed the importance of CMV. The "2000 IOM Vaccines for the 21st Century" report pointed out that CMV vaccine, if it were administered at age 12, would save both money and quality-adjusted life years, and was among a fairly short list of vaccines for which that would be the case. And in October 2000, there was a National Vaccine Program Office-sponsored meeting in the Atlanta area on cytomegalovirus vaccines.

At that meeting in 2000, there was a very nice report published in 2004 that summarized the meeting, and I went through that report to just identify the gaps that were identified at that time, what needed to be done to pave the way for a CMV vaccine, and the questions were really in the realm of what we still need to learn about the basic knowledge about disease. What factors alter the outcome of CMV infection? How much protection is afforded by prior infection, and what immune arms effect it? And what's

the importance of strain heterogeneity?

A number of clinical questions came up as well, including definition of clinical trial endpoints and the need to do that, identification of sites and populations appropriate to whatever endpoints are chosen, standardization and validation of methods to detect infection, and overall raising consciousness regarding the risks, and developing improved diagnostic methods for CMV.

And a couple other things were discussed as well, including a need for improved understanding of the epidemiology and natural history of CMV, and NIH support for clinical trials, especially in Phase I and II was very gratefully acknowledged by the participants in the meeting in the hope that that would continue, and, if appropriate, then NIH support for Phase III trials was hoped for.

So today and tomorrow we hopefully will be able to go through and ask the question, which of these gaps have been filled? which have yet to be filled? where do we really stand? and what has yet to be accomplished to get us to where we would like to be in

the context of a CMV vaccine?

When one thinks about CMV, I think it's useful or people frequently bring up the case of rubella as well because rubella also causes serious congenital disease. Although congenital rubella syndrome was first recognized in 1941, rubella, the virus, was first cultured in 1962. Fortuitously, from the perspective of having developed the culture test, a worldwide epidemic came up from 1963 to 1965. In the '64 to '65 season, we were around 20,000 cases of congenital rubella syndrome in the United States, and it was really during this epidemic that the availability of the culture tests allowed additional characterization, well, first, diagnosis of the syndrome, as well as additional characterization of the nature of congenital rubella.

And amazingly, for a virus, it was first cultured in 1962. By 1969, there were four vaccine candidates, and three of them were licensed initially in the U.S., and the fourth one, the RA27/3 strain, developed by Stanley Plotkin, is now the one that is used throughout the world, and so this really shows

what the scientific community was able to accomplish with a concerted effort in what amounted to a public health emergency.

So why has CMV vaccine development been so difficult? Well, these are my perspectives. I think it's a very complex virus which itself contains many immune evasion functions. There is uncertainty regarding the mechanisms of protection and the basis for predicting protection, and there is lack of clarity regarding development pathways in the likely market. And so hopefully we'll be able to update ourselves on these topics as well during this meeting.

So what are the meeting goals? Well, we would like to summarize the current state of knowledge about cytomegalovirus as it relates to vaccine development. We would like to identify the remaining challenges and gaps that, if addressed, could facilitate the availability of a CMV vaccine.

So the agenda is designed to accomplish those goals. Today we'll be going through Sessions 1, 2, and 3. We'll be going through the background necessary to have a discussion about CMV vaccines, including

epidemiology and diagnosis and immunology and virology. In the second session, we'll have manufacturers and regulators perspectives and goals. In the third session, we'll discuss target populations for CMV vaccine for non-transplant indications. In the fourth session, which will begin tomorrow morning at 8:00 a.m., we'll discuss Phase III trial design for congenital CMV; in the fifth session, transplant Phase III clinical trial issues; and in the sixth session, various organizations, including the sponsors, will discuss their plans for the future. In the seventh session then, we'll have a roundtable discussion to come to our conclusions and identify the next steps from this meeting.

So this is a very ambitious agenda, and we have a very tight schedule, and so the speakers absolutely must keep to time. If any speaker is over time, the session chair will need to ask them to sit down. There is certainly nothing personal about that, but if talks go over time, we will not have time for the very important roundtable discussions which will be occurring at the end of each of the sessions, and the

meeting is not going to meet its objectives. So I ask each of the speakers to do everything they can to keep to time.

In addition, from the perspective of time, there is a fairly tight time available for breaks, and unfortunately, because of the scandal over the $16 muffins, we're not allowed to provide coffee during the breaks, so in order to get coffee, you'll have to go down to the cafeteria, which then may lead to some difficulty getting everything done during the breaks that you would like to get done, but I ask you to please find your way back to the meeting room, if anything, a few minutes before the break is over so that we can really keep the meeting on time.

We do value discussion, however, and I think this is a great facility for that. Each one of these seats has a microphone, and so we hope to hear really from everybody and get their perspectives and achieve a high level of audience participation.

I would really like to close by thanking the organizing committee. There are four U.S. Government sponsors of this meeting: representative from NIAID is Catherine

Laughlin; from the Centers for Disease Control and Prevention is Stephanie Bialek; and from the National Vaccine Program Office is Jennifer Read. And then we have program committee members as well who have devoted a huge amount of effort to putting this program together: Suresh Boppana, Paul Griffiths, Ed Mocarski, Robert Pass, Stanley Plotkin, and Mark Schleiss. And so we're very hopeful that this meeting will achieve its objectives.

And I've been asked to make one other announcement, which you saw before I started, but the Lister Hill facility is very serious about not bringing food or drink into the auditorium, so I would like to make sure that you all adhere to that because we are their guests here.

And with that, I would like to introduce Suresh Boppana, who is going to be the chair of the first session of the meeting.

One more thing with respect to time that I would like to ask is that so each of the speakers will be giving their talks we would like the questions at the end of each talk to be mostly clarifying questions.

There will be time for discussion afterwards, but when the previous speaker is starting to answer questions, I would like to ask the next speaker to already make their way down to the front of the auditorium so that we can make the transitions between speakers as seamless as possible.

So, Suresh, why don't you kick off the scientific portion of the meeting? Thank you.

DR. BOPPANA: Good morning.Thank you very much, Phil. I would like to thank Phil for putting so much effort and making this happen. He is the chief organizer of the meeting. The Session 1 is focused on giving background information and epidemiology of disease burden and the diagnosis of CMV infection in various settings with the focus on identifying gaps in knowledge as it relates to clinical trials of vaccines.

The first talk will be given by Karen Fowler from the University of Alabama at Birmingham. Karen is one of the few card-carrying epidemiologists who has done so much work on congenital CMV epidemiology and defining the disease burden, especially the sensorineural hearing loss. Karen will be talking

about clinical hallmarks of fetal infection and disease and epidemiology of fetal infection in the U.S., Europe, and the rest of the world.

DR. FOWLER: Good morning. Okay. Congenital CMV infection is found worldwide and contributes to thousands of children each year born with or developing permanent disability, such as hearing loss, vision loss, cerebral palsy, and cognitive impairment. In the United States, Canada, Western Europe, and Australia, congenital CMV infection occurs is about .5 to .7 percent of all live births. In other parts of the world, such as Latin America, Africa, and most countries in Asia, congenital CMV infection is higher, occurring in about 1 to 2 percent of all births.

To put these percentages into numbers of births annually, about twenty to thirty thousand newborns in the United States each year will be born with congenital CMV infection. In Brazil, approximately 35,000 newborns will be born each year with congenital CMV infection. And if you think of the population and birth rate of India, if 1 percent of infants are born with congenital CMV infection rates,

about 240,000 infants will be infected with CMV annually in India. These numbers demonstrate that congenital CMV infection and the infection's subsequent sequelae are a global problem.

Infants with congenital CMV infection may present at birth with disseminated disease and also with CNS abnormalities. About 10 percent of these infants with congenital CMV infection will have these symptoms present at birth. The vast majority, though 90 percent will have no clinical manifestations present during the newborn period, although some of these infants will have sequelae associated with the disease.

About 40 to 60 percent of symptomatic infants will have permanent sequelae observed, with sensorineural hearing loss the most common, at 40 to 50 percent. Twenty to 50 percent will have cognitive impairment or mental retardation. And these infants may also have retinitis and cerebral palsy. The variable and wide range of CMV-related disabilities is due to the range of reports from the literature describing selected and enriched groups of symptomatic infants seen in clinics around the globe, making it

difficult to choose a precise estimate.

Asymptomatics are not without risk of CMV-related disabilities. Although few of these infants will have permanent problems due to CMV, about 10 to 15 percent will, and it's primarily sensorineural hearing loss that occurs. Although cognitive impairment and retinitis have been observed, it's unclear whether this is at a higher rate than would be observed in a general population of young children. Since asymptomatic infants are not detected in the newborn nursery without CMV screening, it's hard to know the number of infants who go undetected, and it's also difficult to obtain an unbiased estimate of permanent sequelae for these infants. Also, since most infants born with CMV are asymptomatic, these 10 to 15 percent infants with CMV-related disabilities are not a trivial number.

Congenital CMV-related disabilities are as common, if not more so, among infants and children as other disease such as Down syndrome, fetal alcohol syndrome, or spina bifida, as seen on this slide of data gathered by Mike Cannon in 2009.

Congenital CMV infection contributes

significantly to childhood hearing loss, with CMV-related hearing loss being second to genetic causes both at birth and in the early years of life. These data here are based on extrapolation of a few studies. So it may be that CMV's role in childhood hearing loss is underestimated since usually when late-onset hearing loss appears, it is too late to make a retrospective diagnosis that identifies CMV as the etiology.

So let's talk about the CMV seroprevalence. CMV seroprevalence in women of reproductive age varies greatly based on geographic and socioeconomic backgrounds of the study populations.

As seen in this slide, Canada and the U.S. have midranges of CMV seroprevalence from 40 to 60 percent. Studies in Western Europe show a similar trend, with CMV seroprevalences varying from 30 percent to 70 percent, depending on the country and the delivery population selected.

The few studies from the Middle East and Africa find that pregnant women in these countries have high CMV seroprevalence, greater than 70 percent, and in many areas, greater than 90 percent.

Australia has a very similar pattern as the U.S., Canada, and Western Europe, with Japan and other Asian countries identifying high CMV seroprevalence in pregnant women studied.

Finally, in Latin America, high CMV seroprevalence in pregnant women are also found. Brazil highlights what we see in any large country. The CMV seroprevalence rates may vary depending on the area of the country, the socioeconomic conditions, and the age of the delivery population.

These data from Bate et al. and the NHANES data show that CMV seroprevalence is always changing, the CMV seroprevalence increasing generally with age, however, even with the increasing CMV seroprevalence observed in these three racial and ethnic groups here, their underlying CMV seroprevalence is very different during their reproductive years, and increases in their CMV seropositivity are occurring at different times during these women's childbearing years.

Obviously, age is associated with CMV seropositivity. In low to moderate seroprevalence countries, CMV seroprevalence rises steadily from

childhood through 60-plus years of age. As seen in the U.S. and also in Australia, CMV seroprevalence increases with increasing age. Unlike the high seroprevalence countries, where CMV is nearly universal in early childhood, acquisition of CMV in low to mid seroprevalence countries begins in early childhood but is not widespread.

In high seroprevalence countries, CMV acquisition seems to occur early in the perinatal period and childhood, so most women enter their reproductive years with high CMV seropositivity.

Higher seroprevalences are associated with Blacks and Hispanics in the United States, but, similarly, high seropositivity has been observed in other countries with respect to non-White race. Even children as young as 3 years of age in New Zealand have very different CMV seroprevalence rates depending on the ethnic and racial group they are from.

Other factors that have been associated with CMV seropositivity are female sex, increasing parity, and lower socioeconomic status. Both sexual activity and exposure to young children have been behaviors

associated with CMV seropositivity.

Studies in STD clinics among teens in contraceptive clinics and pregnant women have shown that sexual activity and markers and factors associated with sexual activity are associated with increasing the seropositivity. Young age of sexual debut, the number of lifetime partners, new sexual partners, and other sexually transmitted infections are all associated with an increased risk of CMV acquisition.

Studies in day care centers among parents and families and day care workers have shown that young children shed virus in saliva and urine, creating exposure opportunities for virus transmission to other children, to their parents, day care, or nursery workers.

We've seen from these studies higher excretion rates in children attending day cares versus those that do not, with the highest excretion rates being in toddlers and young children. They've been able to follow children and document CMV shedding in children who were previously uninfected at enrollment, isolation of CMV from toys and other objects in the day

care setting, identification of similar strains with CMV within day care centers, and higher CMV seroconversion rates of parents of children attending day care, and also the isolation of day care CMV strains in the mothers of children in day care.

Work by Stuart Adler and others have shown the importance in the role of children in transmitting CMV to other children, their families, and pregnant women.

In addition to sociodemographic factors, sexual activity, and young children, both breastfeeding and exposure to persons known to be infected with CMV, such as siblings or mothers, likely account for the primary modes of infection in the early years of life seen in high seroprevalence countries.

So we know what factors contribute to CMV acquisition for women of childbearing age; however, we do not know which women will deliver a newborn with congenital CMV infection. Some women will have primary infections during pregnancy delivering a newborn with congenital CMV infection, and other women who are seroimmune prior to pregnancy will also deliver a

newborn with congenital CMV infection. Does the burden of disease differ if the infection follows a primary or non-primary maternal infection?

In our study done in 1992 at UAB, we found that infants following a primary maternal infection had greater disability; however, preconceptual immunity was not completely protective, and even infants of non-primary maternal infections had some sequelae, although less severe than those following primary infections.

Shannon Ross, in 2006, at UAB, looked further at primary and non-primary infections and found that symptomatic infection was similar between infants whether their mother had a primary or non-primary infection. Sensorineural hearing loss was also similar between infants of mothers with primary infections and infants of mothers with non-primary infections, although infants whose mothers had primary infections were more likely to have bilateral hearing loss and more progressive or late-onset hearing loss.

Investigators in Brussels in a population that had a 59-percent CMV seroprevalence rate found that although CMV-positive infants of maternal primary

infections had more sensorineural hearing loss, both primary and non-primary groups had similar rates of bilateral sensorineural hearing loss.

Our colleagues in Brazil demonstrated that in a Brazilian delivery population where there is almost universal immunity to CMV, that 10 percent of CMV-positive infants were symptomatic and 9.8 percent had hearing loss with 50 percent of the loss being bilateral in nature. They were able to document that 60 percent, or six out of ten infants with sensorineural hearing loss were born to mothers with non-primary CMV infection. Four of these infants had moderate to severe unilateral loss, and two infants had moderate to profound bilateral sensorineural hearing loss. These studies and data indicate that even in non-primary infections, that CMV may cause damage to the fetus, and considering the high CMV seroprevalence rates of Asia, Africa, and Latin America, the disease burden due to CMV may be underestimated.

What are the factors associated with acquisition of CMV in newborns whether following a primary or non-primary maternal infection?

Interestingly, the incidence of congenital CMV infection is higher in populations where the underlying CMV seroprevalence or preexisting immunity is higher in the mothers. So high CMV seroprevalence with non-primary infections also occurring is an important factor for delivering a newborn with congenital CMV infection.

Similarly, maternal and sociodemographic factors have been associated with delivering an infant with congenital CMV infection in studies of different populations. Consistently, young maternal age has been observed. In Birmingham, young teen mothers, whether Black or White, had significantly higher congenital infection rates, as high as 2 to 4 percent as compared to the .5 to .7 percent reported in the United States.

In the UAB delivery population of young women in a case-controlled study, factors associated with women who had primary infections during pregnancy and delivered a CMV-positive baby were young maternal age, less than 18 years of age, and caring for young children in the year before pregnancy. In the same study, factors associated with women who had non-

primary infection during pregnancy and delivered a baby with congenital CMV infection were both caring for young children in the year before pregnancy and having sexually transmitted infections during pregnancy as a marker of sexual activity along with the pregnancy.

So although we do not know if there is a different pattern of exposures that leads to primary and non-primary infection, it is likely that young children are important, and also in some populations, sexual activity, whether it is a first exposure to CMV or a reinfection after multiple exposures to CMV.

So finally, I would like to briefly summarize our most recent data from the CHIMES study. It provides us with the most up-to-date congenital CMV prevalence rates for a large screen population of healthy newborns. Over 96 percent of the newborns at our cohort resided in well-baby clinics or nurseries.

The study population between 2007 and 2010 was 66,452 infants enrolled at the seven sites listed on the slide. The study population was equally divided between White non-Hispanic, Black non-Hispanic, and White Hispanic infants. We had about 5 percent Asian

infants and less than 3 percent multi-race infants in the cohort.

The overall prevalence of congenital CMV infection in this cohort is .5 percent with 9.4 percent of these infants having symptomatic infection. And just to give you a definition, we did not include in our definition of symptomatic infection hearing loss at birth.

As seen in this graph, the South had the highest prevalence of congenital CMV infection, a reflection of their underlying delivery population. And the red bar that I put across here is at the .5 percent, which was our overall estimate.

Black non-Hispanic infants had over twice the congenital CMV infection rate of the overall group and were significantly higher than White non-Hispanic, White Hispanic, and Asian infants.

Offspring of women less than 25 years of age had significantly higher congenital CMV infection rates than infants of older women, with the highest rates being seen in newborns of teen mothers where the prevalence of congenital CMV infection was greater than

1 percent.

Overall, hearing loss at birth in CMV-infected infants is 9 percent, although newborn hearing screening only identified 5 percent of these positive infants with hearing loss at birth.

So far, the CHIMES study has identified 5.7 percent of asymptomatic infants with sensorineural hearing loss at birth, whereas, not surprisingly, 41.9 percent of symptomatic infants were found to have sensorineural hearing loss at birth.

And, finally, we estimate that hearing loss due to congenital CMV infection in this birth cohort is somewhere between 20 and 38 percent, indicating the importance of identifying CMV infection so children may be properly followed for hearing evaluations in determination of their hearing status.

So my final slides are, what are the knowledge gaps for vaccine development in relation to epidemiology? And I do not see that any of these bulleted listed here on the slide as insurmountable issues, but only where we lack detailed information about the epidemiology of maternal and congenital CMV

infection.

First, I think that the CMV seroprevalence data in pregnant women are decades old, and uncertain if prevalence rates have remained the same. Not so much, I think CMV has been very stable. If you look at the data over time, it changes, but I think that it's more the migrations in populations, the subpopulations that will impact the numbers of primary and non-primary infections in a population.

In fact, a study, I think by Knowles in 2005, in Irish women found that 30 percent of the Irish women were CMV seroprevalence, but because they had had so much migration into Ireland, that they had very different rates for Asian women at like 93 percent, and African women who resided in Ireland had 97 percent CMV seropositivity. So the changing numbers in migration and delivery populations will affect that.

And then also, although sources of infection are known for infants and young children, the rates of infection are not well known for young children, and differences based on racial and ethnic backgrounds and exposures breastfeeding, day care, and family would be

expected.

And then although some adolescent pregnancy data and adolescent STD clinic and contraceptive clinic data are available, it is not known if these teens are representative of the general population of adolescents.

And then also we have outcome and sequelae data for asymptomatics that is very sparse due to the lack of CMV screening to identify asymptomatic infants and provide long-term follow-up data to measure the true burden of disease. It is possible that the true burden of disease due to CMV infection is underestimated since 90 percent of infections are asymptomatic birth and usually go unnoticed.

Finally, little is known about outcome and sequelae following CMV infection in high seroprevalence countries where most maternal infections will be non-primary infections. Unfortunately, we've had our Brazilian colleagues and Marisa will comment a little bit further who have done some work to show us that the burden of CMV does occur in high seroprevalence countries and needs to considered.

So that's all I have. Thank you. Open for questions.

(Applause.)

DR. FOWLER: I went short, so we'll have time for discussion.

DR. BOPPANA: Karen, thank you so much. That's a very good comprehensive review. We have time for questions, so please identify yourself, and just your name and where you're from, affiliation, before asking questions. Thank you.

DR. PASS: Bob Pass, from the University of Alabama at Birmingham. Karen, there is one point I wanted to ask clarification on. The last slide on the CHIMES study, the 28-percent hearing loss in that birth cohort. Was that 28 percent of congenital CMV or congenital accounted for 28 percent of the hearing loss?

DR. FOWLER: It accounted for 28 percent of the hearing loss, and the reason I gave the broad range is we're obviously not through with the study, and anybody that's worked with newborn hearing screening data knows it's very difficult to get the etiologies of

the loss. So it's an estimate right now.

Yes?

DR. FEINBERG: Thank you for your very helpful summary. My name is Mark Feinberg, I'm from Merck. I was wondering if you could comment on what's known from an epidemiologic perspective about what predicts which children will develop disease after congenital infection and which will not.

DR. FOWLER: That's a challenge. I think, you know, we've looked at virus burden, and I'm not sure that that has been consistent, and we say that if they have a higher virus burden at birth, that they're more likely to have sequelae, but then there are other studies that have said, no, that didn't matter. And that's been really a challenge to say which children.

I mean, we obviously know symptomatic children are going to have a worse outcome than asymptomatic, but other than that, once you start to try to separate out characteristics of asymptomatic children, it's very difficult to know, and that's always the challenge when you deal with parents who say, "Well, what's the risk of my child having hearing

loss?" and we say, "Oh, 10 or 15 percent." "Well, how will I know?"I don't know.Someone else can comment. Maybe other people have. But I think we haven't had clear we don't know the answer, I guess. I don't know the answer. Maybe someone can share that does.

Yes?

DR. SPECTOR: DR. SPECTOR. You mentioned that there is the higher seroprevalence in the woman. Is there a similar higher or distribution of seroprevalence if you look in the day care centers, or are they approximately equivalent in terms of gender?

DR. FOWLER: Are you meaning just a I'm sorry.

DR. SPECTOR: Boys and girls. How does it

DR. FOWLER: Yeah, I don't know how it compares in the day care centers. As the population ages, women have a slightly higher

DR. SPECTOR: No, I'm talking about the children.

DR. FOWLER: For the children, I don't know that that would be different. I don't see why that would be different, it's just the opportunity for

acquisition. Yeah, so I wouldn't think that difference. And I think the argument would be, which we just it's a good argument, but we don't necessarily approve, is that women of reproductive age care for young children and have those opportunities. So that might be the slight difference.

I'm sorry.

DR. MALDONADO: Yes, Bonnie Maldonado, with Stanford and AAP. The data on racial differences has been shown in the past, but the CHIMES data, again, it really highlights that geographic distribution, and I wonder if that data has been adjusted for by I mean, have you looked at that in a multivariate fashion as well in terms of the racial distribution? Are there other cofactors that actually may be cofounders?

DR. FOWLER: Right. I just presented an overview of what we have, but when you adjust the two factors, even when you adjust for maternal age and socioeconomic status, race, Black race, remains significantly higher than White non-Hispanic and White Hispanic in our population, and one you adjust for maternal age, basically the socioeconomic factors don't

I mean, when you look at socioeconomic status in this cohort, it appears that it's related, but once you adjust for age and race, it's not any longer related.

DR. MOCARSKI: That was exactly my question, really how much does the social/racial reflect the age

DR. FOWLER: Right.

DR. MOCARSKI:and that's important, I guess.

DR. FOWLER: I think really the factor that's the strongest is young maternal age, which is possibly, you know, we could say it's because they're having primary infections or reinfections.

DR. MOCARSKI: And I'm Ed Mocarski, from Emory.

Just one follow-up to Mark Feinberg's question. If you look in the CHIMES study and ask, is it more likely to have detected CMV DNA, let's say, in blood versus saliva, is there any way to differentiate those two sources in terms of symptomatic kids?

DR. FOWLER: Well, I don't know if everybody knows, we're ongoing with our study, and I presented the 66,000, we're right at 100,000 right now, so we haven't really yet answered that question, but

definitely

DR. MOCARSKI: So that's important, yeah, that will be an important contribution.

DR. FOWLER: Yeah. So far I don't think we have we don't have the answer right now.

DR. BOPPANA: At least right now there's not

FEMALE SPEAKER:Microphone, please.

DR. MOCARSKI: Use your microphone.

DR. BOPPANA: I'm not sure there is a difference right now, but as Karen said, the data is still being collected and analyzed, so it's not final yet.

DR. FOWLER: Yes.

DR. HARPAZ: Rafael Harpaz, CDC. In countries with very high seroprevalence, what are the risk factors for transmission, i.e., amongst women who are infected? What do we know about risk factors for transmission?

DR. FOWLER: We don't know that much. I think the best data we have is from Brazil, and I think Marisa, would you comment any or you want I'll comment, but Marisa is going to be up here in a minute and we'll

let her comment further. But they've seen also, I think, sexual transmission as well as young children. I think, didn't you do a case control?

DR. MUSSI-PINHATA: Yes. Mothers who transmit are younger, younger age at sexual debut, less schooling in this very high rate of seroprevalence rate, for instance, from 12 years old they are seroprevalent, but the pregnant women. So I think it's the same risk factors. Also exposure to young children.

DR. FOWLER: Right. I think when I went to the literature, to say, "Okay, is there a difference between the high seroprevalence countries and the low or mid seroprevalence?" I couldn't find that there was a difference, that there was anything, but then, you know, I don't think we've done exhaustive studies. But whether it's because it's a primary infection or it could be a reinfection, you know, that's the question.

Yes?

DR. SCHODEL: Florian Schodel. Does the level viremia change with age?

DR. FOWLER: I'm going to defer that to

someone else. Would you say it I mean who's more experienced? I don't have the answer.

DR. BOPPANA: I'm not sure we have really good data in terms of age-specific viremia data.

DR. FOWLER: Yeah.

DR. BOPPANA: Maybe there is, but you may want to comment. I don't know if you have any data, Maria Grazia?

DR. REVELLO: No, I don't have any special data, but, rather, what I wanted to do was a point with respect to how dated are our seroprevalence data because, for example, for Italy, it reported 68 percent seroprevalence. Right now it's hardly 50 percent. So these data are really changing, and, of course, there is another variable, that is the assay that they used in order to determine the seroprevalence in a given population, and that could also makes a big difference. That has been experience as far as rubella is concerned with the advent is very sensitive assay, for example, the seroprevalence or the seropositivity to rubella has dramatically increased, but we don't know whether it's actually increased or it increased because the assay,

better sensitivity.

DR. FOWLER: Right.

DR. BENEDICT: Just to follow up to that Chris Benedict, from La Jolla that comment. So would you say that you think it's going to drop, that we have more false positives in the historical literature? And you said because the data was shown as 68 percent for Italy was that right? and you're saying it's 50?

DR. REVELLO: No, simply what I am saying is that I don't know the year of that reference, but it was at least 20 years ago more or less. The

DR. BENEDICT: So as the assays get better, you would say we're cleaning out false positives or not?

DR. REVELLO: No, it's not a matter there are two, let's say, two things to be kept separate. One is a true lowering in the seroprevalence given that rise in conditions, given the fact that women do not breastfed their babies or a number of things, and this one reason for having a lower seroprevalence, but at the same time, one has to keep in mind that the assay that you use in order to discriminate whether a person

is seropositive or seronegative might have influence on the results, and so it's something that one has to keep in mind when looking at seroprevalence as a whole.

DR. BENEDICT: Great. Thanks.

DR. BOPPANA: I think we have to move on. I'm sorry.

DR. FOWLER: To follow up, one second. Also, too, because there are so many studies in Europe and the United States, I just took some of the studies, and, you know, obviously I want to say that it's not you know, and that's the point. If you take one study in one area, it's not the same in another part of the country or the overall country, and it's reflective of the underlying delivery population. So to be clear, it wasn't like I thought this was all of Italy; it was just an example of how you had the ranges. Okay? Thanks.

DR. BOPPANA: Thank you, Karen.

So the next talk is going to be by Tiziana Lazzarotto, from Bologna. She is going to be talking about diagnosis of infection in adults, mostly pregnant women, fetuses, and newborn infants.

DR. LAZZAROTTO: Thank you. Good morning. And thank you to the organizing committee for the honor to present at this lecture. And the topics of my presentation: the first are the diagnosis of maternal infection; the second are the diagnosis of fetal infection; and the last is the diagnosis of infection in newborns.

And the first topic is the diagnosis of primary CMV infection in pregnant women when we are testing the pregnant women at the early prenatal visit. And the diagnosis of primary is made up of three parts: clinical, serological, and virological diagnosis.

With the clinical diagnosis, in a part, there are no symptoms in pregnant women, and when we have symptoms, they are not specific for CMV infection. This is the reason that the clinical diagnosis in pregnant women is unreliable.

And with serological diagnosis, we try to detect CMV-specific antibodies, IgG and IgM. And there are some four possible results.

The first, when we obtain IgG negative and IgM negative, this result is indicative of a non-immune

woman, and this woman is at the risk of acquiring primary infection. In this case, it is mandatory to offer primary prevention, and the pregnant woman must be informed of hygiene and behavior measures in order to reduce the chance of infection.

The second results that we obtain, IgG positive and IgM negative. When we obtain these results before the pregnancy or at the early prenatal visit, it is indicative of a past infection.

So the third results, IgG negative and IgM positive, and these results could be indicative of acute phase of primary infection or IgM false positive results. In this case, it's mandatory to offer to pregnant women the second serological testing performed in the same lab after 10 to 15 days. After this time, if we obtain negative results for IgG, it is indicative of false IgM positive results. When we obtain with the second testing positive results for IgG, it is indicative of a seroconversion.

The last. The last, when we obtain IgG positive and IgM positive, and when we obtain the results at the early prenatal visit, and we don't know

which is the serostatus of the pregnant woman before the pregnancy, these results could be indicative of a primary infection. And in this case, it's mandatory to offer advanced diagnosis.

And then the possibility to offer the avidity test. And what is the avidity? Avidity is the (indiscernible) which with multivalent antibody binds multivalent antigen, and the degree of antibody avidity increases progressively and slowly, reflecting the maturation of the immunoresponse. During CMV infection, IgG maturation occurs approximately at the 18 to 20 weeks, and if we can use this test, the avidity test, in the first part of the pregnancy, for the first time, and this test, the sensitivity of this test, to identify pregnant women at the risk of transmitting the virus to the fetus is very high, it is 100 percent, especially when we use this test before 16 to 18 week gestation. But if you use this test, in the second part of the pregnancy, for the first time, the sensitivity reduced to 60 percent to identify pregnant women at the risk of transmitting the virus to the fetus.

So the sensitivity of the avidity IgG test to detect a recent primary infection during the first 12 to 16 week gestation ranges from 92.8 to 100 percent. And the specificity to exclude, indeed, the same period during the first 12-16 week gestation, a recent primary infection ranges from 84.7 to 100 percent.

Be aware, interpreting test results of IgG avidity is very important because serological tests vary from one laboratory to another; therefore, the method used and its reference values must be careful assessed. The value of IgG avidity helps to interpret a positive result for CMV IgM, and the limits are that the kinetics of IgG avidity depend on the kit used, and with some of these kits the results may depend upon CMV IgG concentration. Moreover, dating the infection may be difficult in cases for which the IgG avidity index is reported as moderate or intermediate or grey zone.

In our experience in Bologna, using Radim IgG assay, and the moderate avidity index combined with IgM positive results is a marker of primary CMV infection.

I would like to show you the results that we obtained with a comparison of anti-CMV IgG avidity in

381 serum samples of primary infection, and we compared the results in relation to congenital CMV infection. As you can see here, the serum sample were made up of four groups. The first group, we considered all serum samples that we obtained before 12 week gestation when we had the serological diagnosis of primary CMV infection. And as you can see here, 70 samples had low avidity, and 29 samples had moderate avidity. The rate of congenital infection in low avidity sample was at 23 percent and moderate at 3.4 percent. As you can see, the second group we test a sample that we obtained between 13-16 week gestation.As you can see here, 113 had low avidity, and the rate for congenital CMV infection was 26.5 percent. Twenty-two had moderate avidity and the rate of congenital infection in this group was 27.3 percent. We obtained similar data in the other groups.

So in conclusion, the diagnosis of primary CMV infection in pregnant women before 16 week gestation is reliable, and in particular, the combination of IgM positivity and low and moderate in some cases depends on the kit used, avidity index had

the same diagnostic values as seroconversion.

Virological diagnosis. Virological is very often unreliable. We can detect the DNA, the virus, in blood during the primary and non-primary infection, and we can detect the DNA for about 6 months during the primary infection after onset, and in non-primary infection, we can detect the DNA, but the viral load is very low, and the presence of DNA in blood in pregnant women is intermittent.

So which is the percentages of sensitivity for DNAemia in primary and non-primary infection, and we found a percentage of 33.3 percent for DNAemia in primary infected pregnant women, and Arora and colleagues found a percentage of 24 percent for DNAemia in seropositive women.

In pregnancy, during both primary and non-primary infection, CMV may be present in body fluids, but the presence of virus in blood or urine or cervical secretion is a poor indicator of the risk of intrauterine transmission and the severity of fetal/neonatal damage. It is the reason that the virological diagnosis is very often unreliable.

Virological tests play a secondary role in the diagnosis of primary CMV infection in seronegative women and can only support serological diagnosis, and also plays, virological tests, a role in the diagnosis of non-primary CMV infection in seropositive women.

In conclusion, serological diagnosis is reliable when we screen the pregnant women before 12-week gestation and when we use the advanced diagnosis before 16-week gestation, and it is very important to complete the serological diagnosis with counseling. Be aware, the clinical diagnosis and virological diagnosis.

And the diagnosis of non-primary CMV infection in pregnant women is more challenging, and this is a possible approach to diagnose of non-primary CMV infection. When we obtain positive results for IgG and IgM combined with high avidity before 16-week gestation, these results could be indicative of a high risk of non-primary infection. And another possibility is to study the increase of CMV-specific IgG antibodies or the presence of CMV in blood, urine, and saliva, at the moment, but no optimal diagnostic method is

available.

The second topic of my presentation is the diagnosis of fetal infection. And we offer prenatal diagnosis. And in prenatal diagnosis we consider invasive prenatal diagnosis, amniocentesis, noninvasive prenatal diagnosis, ultrasound examination, and the counseling. When we offer, after 6, 8 weeks from the onset of maternal infection and after 20 weeks of gestation. We offer in Bologna, in Italy, we offer the prenatal diagnosis during 20 to 21 week gestation to maternal primary infection. When we have maternal primary infection, the first half of gestation, and when we observe ultrasound abnormalities. Which test we use, amniotic fluid, the virus isolation, and the viral DNA by real time PCR.

I report here the results that we obtained in Bologna, with the virus isolation and the real time PCR in 772 samples of amniotic fluid of primary infected women. As you can see here, PCR is more sensitive than the virus isolation, and the specificity of the two tests is the same. We obtained very good positive predictive value. The percentage is 100 percent; and a

very good negative predictive value, the percentage is 93.8 percent.

So the prenatal diagnosis is reliable because negative PCR in amniotic fluid excludes, in most cases, congenital CMV infection. The negative predictive value is approximately 94 percent or symptomatic congenital infection because in 6 percent we have infected fetuses, but there are at birth asymptomatic and asymptomatic during subsequent monitoring. The positive PCR in amniotic fluid identifies infected fetuses; the positive predictive value is 100 percent.

So for the prognosis, fetal blood could be used for the prognosis, but at the moment further studies in a larger number of symptomatic cases should be performed to verify the prognostic efficacy of determination of different parameters in fetal blood.

So the last topic is the diagnosis infection in newborns, and the detection of CMV-specific IgM in blood of newborns is not sensitive. As you can see here, the moderate sensitivity, whichever the assay used, ranges from 44 to 70 percent, the specificity is 100 percent.

The gold standard for congenital CMV infection in newborns is the CMV isolation urine and/or saliva performed during the first 2, 3 weeks of life. But should we consider urine/saliva real time PCR testing as an additional and reliable assay for the diagnosis of congenital CMV infection?

And we tested 199 urine with real time PCR and virus isolation. As you can see here, we obtained 100 percent on specificity and 100 percent on sensitivity. Similar data was published by Boppana in 2011, and the group obtained a very good specificity and very good sensitivity with the real time PCR in saliva.

So in conclusion, for the diagnosis of congenital CMV infection, the best samples are urine and/or saliva. The best form of testing, virus isolation and real-time PCR. For the screening, the best sample is saliva and virus isolation real-time PCR testing.

A note for retrospective diagnosis, and probably the best sample only in this case is the dried blood spots with real-time PCR.

So I would like to thank all my colleagues from my lab, from the Department of Obstetrics and Gynecology, and from the Department of Pediatrics, and thank you for your attention.

(Applause.)

DR. BOPPANA: Thank you, Tiziana.

We have a couple of minutes for questions. Just only a few questions, please.

DR. PLOTKIN: Stanley Plotkin, University of Pennsylvania. Tiziana, in the context of a vaccine study, there will be a specimen, a serologic specimen, taken from the woman before pregnancy starts, so you have a zero specimen. Now, would I be correct in is your opinion that the subsequent specimens should be, let's say at 16 weeks IgM and avidity and would you recommend second specimen, let's say, at 30 weeks and urine at birth? I mean, what specimens would you suggest for a vaccine study to indicate maternal infection?

DR. LAZZAROTTO: For me, the best sample is the blood and the serological testing are the best tests to follow up the

DR. PLOTKIN: But when?

DR. LAZZAROTTO: When? Before the 16-week gestation and then if the pregnant women is negative, to continue the follow-up for 4 weeks, to take a sample each 4 weeks, and to continue during the pregnancy.

DR. PLOTKIN: Well, that's not going to be practical probably, so what would be the next screening specimen?

DR. LAZZAROTTO: Yes, in Italy, when we have a negative pregnant woman in the pregnancy, we test each 4 weeks for only the first part of the pregnancy until 24-week gestation. And we test, the last time, the pregnant women, only at the end of the pregnancy. This is our we don't have guidelines, but I think this is a good approach to follow all the pregnancy because it's very important to recognize the primary infection in the first part of the pregnancy because the pregnant is very high risk to transmit, to have symptoms in the fetuses and the newborns. And it's very important to recognize the late seroconversion when it is enough to test the pregnant woman at the end of the pregnancy.

DR. BOPPANA: Thank you, Tiziana, that's all

the time we have. We have time for discussion just following this anyway.

So now we move on to the roundtable discussion with speakers Karen Fowler, Tiziana, as well as Marisa Mussi-Pinhata, and Mike Cannon, from CDC, to address some of the important questions that either weren't brought up in their presentations or issues that are thought to be important to be discussed right now.

I guess just to start off, I want to get to questions, but I would want Marisa and Mike to very briefly comment on the burden of disease in different populations, and, Marisa, especially in the highly seropositive population, if you don't mind, very briefly, please.

DR. MUSSI-PINHATA: Yes. I will very briefly summarize our studies, which has been done in the Brazilian population which is 97-percent seropositive. In this population, primary infection takes place way before childbearing age. It's likely that at least 50 percent of babies are early infected through breastfeeding.

In pregnant women, even in their very young age, 12 to 19 years old, the adolescents, they are already 97-percent seroprevalent. And in this population, we have evidence that frequent exposure to CMV, of course, once we found based on new antibody specificities, that about 35 percent of women had evidence of previous or recent infection with more than one CMV strain. And reinfections with new virus were responsible for a significant number of congenital CMV infections.

And if we compare transmitter mothers with those who seroconvert in lower CMV seroprevalence populations, they had a rate of approximately five times higher of reinfection as compared to new infections in lower seroprevalence populations.

And also, as Dr. Fowler showed, we found hearing loss, 10 percent, similarly to low seroprevalence rates population, and also we found occurrence of bilateral and severe profound in babies born to women with non-primary CMV infection.

So we think that taken together these finds reveal that even with several naturally acquired

boosters of CMV infection, CMV is being transmitted from mother to infants and causing disease in infants.

We think that these observations imply that the development of a vaccine might be not only target against primary infection but also against reinfection. Additionally, frequent exposure in these populations to CMV might also limit protective activity of vaccine-induced immunity.

Thank you.

DR. BOPPANA: Thanks, Marisa.

Mike, do you have any comment about the disease burden? Very brief.

DR. CANNON: I don't know that I have much to add beyond what Karen said other than that congenital CMV is, as far as burden of disability, it ranks up with some of the better known conditions such as Down syndrome and spina bifida. And also if you think about newborn screening, the number of children who are detected, in the U.S. anyway, with newborn screening for all other conditions is about equal to the number of children each year who have congenital CMV-related disability. So that's my brief addition.

DR. BOPPANA: Okay. Thank you. I'll open up for questions.

Ed?

DR. MOCARSKI: I sort of want to follow up on what Stan asked about and get us a broader picture of this. If you think about CMV transmission and disease, a lot of literature supports the idea that the first and second trimester are probably the most consequential transmission, the first or second trimester.

Coming back to the question about when you test for CMV, obviously before, sometime before, pregnancy you should test serologically. If you evaluate the woman at delivery for serological status, how much does the third trimester give you a buffer, as it were, to whether you have an ambiguous serological result?

As you've spent a lot of time, Tiziana, going through for us, there is a lot of serological innuendo in terms of IgM positive, IgG and IgM positive, and avidity that might be very complicated to get into.

So my question is, how much does the third

trimester being less of a symptomatic transmission period give you a period where testing before pregnancy and at birth might be a good way to find out those seroconversions that are important?

DR. LAZZAROTTO: Okay. It depends on the seroprevalence of the country because

DR. MOCARSKI: Speaking only of the seronegative or primary infections.

DR. LAZZAROTTO: Seronegative, okay. And the best testing is to have just before the pregnancy and not 3 it depends 2, 3 months just before the pregnancy because 6 months or 1 year is a long time, and sometimes it's a problem, the pregnant woman seroconverted before the pregnancy. And when I tested, I considered negative results when we obtained the results just before the pregnancy. This is the important point. If we test the pregnant women in the first trimester, if you have the results in the first trimester, you have the possibility to understand which is the kind of infection because with avidity test you immediately recognize if the pregnant women has primary or non-primary infection. This is the point, half of

the point, test the pregnant women before 12-week gestation because you have time to follow up, to test the pregnant women, to understand which is.

Another point is the risk to have symptomatic infection in newborns when you have the infection in the late of pregnancy. This is correct; it is the question?

In Bologna, in our experience, but in the literature, in most cases you don't have clinical problems when you have the primary infection in the end of the pregnancy. This is my experience, long-time experience, but my data is in most cases, and this is the reason that we test the seronegative pregnant women until 24/25-week gestation, and then we stop the testing, and we consider the last testing just before the delivery. Yes.

DR. BOPPANA: Stanley?

DR. PLOTKIN: Yes. I would like to ask Dr. Mussi-Pinhata, do you have at this stage any data comparing transmitting women to non-transmitting women with respect either to fibroblast entry antibodies, epithelial cell antibodies, or CTL?

DR. MUSSI-PINHATA: No, we do not have. We are starting a new project that we want to take this to get this data but not so far.

DR. BOPPANA: Yes, Phil.

DR. KRAUSE: So from the perspective of the panel, based on what we've heard, do you think that a vaccine, in order to be useful, and you can vie this among seropositive versus seronegative mothers, would need to achieve better immunity than natural infection does? And I guess a subtext of this question is, to what extent are infections in children born to seropositive mothers due to new strains that perhaps are not adequately controlled because they're presenting different antigens versus simply that the previous immunity associated with the previous natural infection isn't sufficient to control a reinfection?

DR. BOPPANA: Well, actually the speakers of the next two presentations are probably very qualified to address this question, and they're going to be talking about this issue to some extent.

I think one of the difficulties, at least as far as I can understand, is to define the markers of

protective immunity in terms of the transmission to the fetus in this setting. As far as I know, we don't really have that information. So without that information, I'm not really sure how to really think whether you need what kind of immunity do you need by a vaccine?

I know, Maria Grazia, you've done a lot of work in pregnant women and transmission. I don't know. What do you think?

DR. REVELLO: If we had been able to identify some protective markers, then we wouldn't be here probably right now.

(Laughter.)

DR. BOPPANA: Bill?

DR. BRITT: Can I follow up on Phil's question and ask Tiziana a question? Suresh and I did a study many years ago looking at primary infections, looking at transmitters and non-transmitters, and we were looking at avidity, too, with an in-house avidity assay, and when I actually went back and looked at that data prior to this conference, I noticed something that we really didn't talk about in that paper, and that was

the women that transmitted virus they were all primary infections they had a very delayed acquisition of high-avidity IgG antibodies, much greater than the population that were protected from transmitting the virus.

So the question that I have for you is, have you ever looked at similar things in your population? And it may be that natural immunity that we think about is that one shoe doesn't fit everyone, that people are quite different in terms of their ability to generate these responses to this virus.

DR. LAZZAROTTO: Yeah. That I know because the avidity test is a very delicate test because with the avidity test we study the avidity maturation of IgG antibodies, and the problem is which test we use. And I reported the time of maturation for CMV infection in my experience, but this time was published by other groups, and there is Germany and Keros in France, and this author reported the same time of maturation of IgG avidity for CMV. I used the commercial available kits, and probably, and when I discuss this point, every time I said it's very important to know very well the kit

that we use in the lab, it's very, very important.

And the time is not absolute the time but is a medium of the time. And medium, I observed that the maturation occurs in 18/20, but sometime, it's true, sometime I have some patients with a long, long maturation of IgG avidity, it's true, Bill, but is all in most cases because avidity testing is serological. We use for the follow-up of pregnancy.

And it's very important to study all data when we have the first time the IgM positive, which is the results of the avidity. Every time I ask the symptoms because it's very important to combine the results of the testing and the counseling, and I arrive to have the primary infection when all data combined the same time.

DR. BOPPANA: Tiziana, I think what Bill is asking is, did you see a difference in the transmission versus no transmission

DR. LAZZAROTTO: No.

DR. BOPPANA: in terms of the duration of affinity maturation?

Maria Grazia?

DR. REVELLO: Sorry. Well, I read your paper I don't know how many times.

(Laughter.)

DR. BRITT: Yeah, we don't write very clearly.

(Laughter.)

DR. REVELLO: But, anyway, as far as avidity is concerned, I think that I don't remember exactly the kind of assay that you are using in that paper, but it was something

DR. BRITT: It was isothiocynate.

DR. REVELLO: Sorry?

DR. BRITT: It was an isothiocyanate elution. It was a traditional one that they used with rubella and things.

DR. REVELLO: Yeah. But something quite different compared to the avidity assays that are currently used where they work in terms of avidity index. And then, you know, I think that, at least according to our still unpublished data, there might be a correlation between avidity maturation and risk of transmission. This is in general. However, as Tiziana

pointed out, the avidity assay is a tricky one and in a way is a very crude way to look at how this antibody actually function. What we need is to develop more to standardize and to have a more, you know, defined target that should be used in this assay in order to draw some conclusion, but there might be, indeed, some hint in that direction.

DR. LAZZAROTTO: I remember sorry I remember just I studied the avidity results after the delivery in a group of pregnant women with primary infection during the first trimester, but old study, I didn't publish the data, but I didn't found any difference between, I remember.

DR. BERNSTEIN: David Bernstein, Cincinnati. I wonder if anybody would address the problems of making a serological diagnosis in the presence of vaccine-induced antibody. If we're going to do a study, we'll need an assay, obviously, to detect infection in the presence.

(Mumbling.)

DR. BERNSTEIN: I know, and Bob said he may want to comment, and the one we're doing, we're looking

to antibodies other than the single protein that's in the vaccine. It's a little easier if you had, obviously, a live viral vaccine; then it becomes quite difficult, I think.

DR. BOPPANA: Go ahead, in the back.

DR. SCHODEL: Florian Schodel, Philadelphia. I just wanted to speculate and ask whether anybody has data on the correlation between the affinity and the control of virus replication over time, coming back to sort of an idea of an area of exposure occur for other than the presence or absence of the virus.

Tiziana, you may never have found a good correlation simply because presence of virus is not a good correlate, but maybe likelihood of reactivation and the titers that are achieved during reactivation might be. And I was just wondering whether either Bill or you have any data on the correlation between antibodies, on one hand, and how frequently somebody reactivates and what titer they achieve.

DR. BRITT: I certainly don't have any data, but I'm not sure the precision of either assay would allow to make a really meaningful correlation there,

so, but ...

DR. LAZZAROTTO: I do agree.

DR. DA COSTA: Hi, Xavier Da Costa, at Sanofi. I was just wondering about the viruses themselves. I mean, you've looked at a lot of the population characteristics. What about the viruses themselves? Are there differences in the strains genetically where you see high prevalence rates versus low prevalence rates?

DR. BOPPANA: I'm not sure. There is so much genetic heterogeneity amongst circulating CMV strains, I don't really know whether I mean, people have made lots of observations over the years about the prevalence of certain genotypes based on looking at certain genes by using traditional Sanger sequencing and those RFLP and made some observations, but I don't know if we will start using these newer techniques, including next-gen sequencing, whether any of these results will really hold up because of the heterogeneity and the strain variation, the diversity is so great. So I don't know. Is that your question? Or ...

Stuart.

DR. ADLER: Stuart Adler. Two comments. One, in response to Dave Bernstein's question, for the live vaccine, for Towne vaccine studies in terms of a definition of reinfection, we were able to use the development of antibodies that blocked entry into endothelial/epithelial cells, because Towne does that poorly, that worked very well.

Secondly, with regard to avidity, our working assumption is that high-avidity antibodies are protective both against maternal infection and fetal infection, and at least for the Towne vaccine, we studied that quite intensely, and we did not see a variation. All of the subjects developed high-avidity antibodies using two different methods within about 2 to 4 months after immunization. There were no subjects, and there were about several hundred, I think, who had a delayed avidity maturation response to a live virus vaccine.

DR. MOCARSKI: So that really does get back to Phil's question, that I don't think we got an answer or a sense of from you guys. Does a vaccine, now

because of the increasing recognition of transmission in non-primary settings, have to do better than natural infection? What Stuart just said is that Towne vaccine did do the high-avidity business, right? So does a vaccine really have to do better than natural infection? Is that a sense you have from the understanding you have?

DR. BOPPANA: Well, like I said, at first glance it does seem so, but I think what probably may be a better question or a better way to answer some of these questions would be to understand, is there a difference between these seropositive women who transmit compared to most of them who don't? You know, is it immunity? is it viruses? or is it the host? I mean, it could be any of these things, so

DR. MOCARSKI: No, I certainly appreciate that there are scientific questions that need to be addressed, but the fact of the transmission is in front of us I think pretty clearly. So it leads one to a risk-balanced view of whether you think there's a need to do better than natural immunity. We want to know what aspect of immunity to do better at, and that may

come from those studies, but is it predicting that the vaccine is going to have to do better than natural immunity to have an effect on a seropositive population?

DR. BOPPANA: Anybody? Any other panel members?

DR. CANNON: Well, I'll just comment, and maybe Karen and Bob can address this better, but your paper from several years ago suggests that seropositive women were less likely to end up transmitting, so there's that. And then, you know, even though there appears to be hearing loss in these high seroprevalence populations that is presumably due to some sort of non-primary infection, there does seem to be pretty good evidence that at least the severely affected children, you are protected in that sense. So you may have isolated hearing loss. I don't think there's really good data yet to suggest that you're getting these more severe outcomes. So, I mean, I would probably say natural immunity would be pretty good.

DR. MOCARSKI: To achieve.

DR. CANNON: To achieve, yeah.

DR. BOPPANA: Well, I mean, I think I agree with you for the most part, Mike. I think one of the difficulties with determining the severity of the disease in primary versus non-primary is I think a lot of the data, not all of it, but a lot of the data used to select your populations can range from, you know, the way the babies are (indiscernible) is different.

So you need the data from screening studies to be able to address the disease burden issue. So I'm not sure we can really take the data that had populations that were selected for some reason or other to really answer this question.

And the other issue is I understand the issues of the cognitive outcomes, but for a clinical trial or a study standpoint, hearing loss is the outcome that can be easily and objectively measured, and the other outcomes are so hard to really get at, and so I think you really need to keep in mind the hearing loss. Hearing function is ease and should be the primary outcome of any of the efficacy trials or studies in prevention or efficacy.

DR. SCHODEL: Maybe the question is a little

misleading because simply it seems that over time with increasing age, the likelihood of getting infected when you're seropositive is reduced, which might be just a function of age, but it might also be a function of increasing immunity, increasing reexposure, and better natural immunity. So maybe natural immunity eventually does what it should do, it's just not as good at the very first episode, which is also, in my view and I'm sort of an amateur reading literature you know, children shed a lot and very long, and as you go later in age, it seems, although the data aren't that great, that the time of shedding, the time of reactivation may be less. Maybe strains play a role, too.

So maybe natural immunity is fine, but maybe a single episode at a low age is not enough. So immunization should do better than that but not necessarily better than what natural immunity can achieve over time.

MALE SPEAKER: Just one comment. I think natural immunity is a pretty broad spectrum, and there are certainly people with very high levels of antibodies or CMI responses. So how we define natural

immunity is hard to define.

I would just like consensus because I think what our target is, is ill-defined in terms of non-primary infection. Is there a consensus now whether or not disease burden among non-primary infection is due to reactivation or reinfection? Because it's critically important in designing a vaccine, which are you trying to stop?

DR. BOPPANA: I think some of these issues are just beginning to be studied, so I don't think there is a consensus. I mean, I'm sure we have lots of opinions, but, I mean, at least my opinion is not based on any kind of, you know, data.

Bob?

DR. PASS: Yeah. One of the objectives of this meeting that Phil Krause defined at the start of this morning's session was to identify areas where we needed more knowledge. I think David Bernstein hit on one, it would be great to have properly validated serologic assays based on basically viral proteins that one could select and use depending upon the composition of a vaccine. We were very fortunate in our vaccine

study that the vaccine was comprised of only a modified glycoprotein B molecule, so it was easy to develop an assay that would measure antibody to basically everything else. It will be more complicated when you have vaccines that have two or three antigens in them, but we definitely need assays that can do that and that are properly validated.

And the second thing is when you think about primary infection, really avidity doesn't matter if you're doing a vaccine trial. You start with seronegative women, so if they have any serologic evidence or any virologic evidence of CMV infection, that's an endpoint, depending upon how you want to choose to define it in your trial.

We need an assay that will perform similarly well with seropositive women. With seronegative women, if you don't get CMV, you're not going to have a baby with congenital infection, period, end of story. We need an assay that we can do in seropositive women that we could come close to saying the same thing. If the infections are indeed due almost entirely to reinfection, it would be great to have an antibody

assay that we could say, "If you don't convert on this assay, you're not going to transmit CMV to your fetus even though you have had infection in the past."

DR. SPECTOR: DR. SPECTOR. I would like to suggest at this meeting that instead of reiterating what we've been doing and saying, "Let's do it over again, let's do it a little better," that perhaps we might think that we're doing the wrong assays and that perhaps what is much more important is not even a solution neutralization assay but a neutralization assay on cell-to-cell spread, which is what your initial infection is going to be. And it's just a general comment to, can we think of this meeting as really to try to come up with new ideas that might get us new information? To do the same thing over and over again, I'm not sure how much new information you're going to get rather than thinking, are there different ways perhaps you should be doing the assay?

DR. MOCARSKI: So just to add, maybe the point there would be to add, as an action item, that the existing serological banks, now which are huge right? in terms of natural studies of transmission, be

assessed by different antibody as well as other antibody, and mostly antibody-based methods, that would evaluate not just one type of effector, neutralization of cell-free virus, right? That's the general action item that would be reasonable, and that is a reasonable idea, and the serum banks exist to do those correlates directly on any assay. Am I correct?

DR. BOPPANA: Uh-huh, yes.

DR. ADLER: Obviously we're in an area of ignorance here, at least with regard to seropositive women. I would just point out, though, that there may be some analogy to the HIV field where repeated sexual exposure can overcome what may be sort of a natural process in other words, that you have a stochastic effect and in the case of women particularly in populations where exposure is frequent, it may simply be that repeated exposure results in greater superinfection than in populations where exposure is less frequent, but that doesn't mean that in the latter type of population, a vaccine wouldn't be useful in raising immune responses.

DR. BOPPANA: Okay. Thank you. I think we

have to stop and take a break. I think, as Phil pointed out, there is coffee downstairs, I think, at the cafeteria. We can continue our discussions informal. We'll come back at 10:00.

(Break.)

DR. MOCARSKI: So could I get some folks to settle down and we'll continue this because we have to stay on schedule. The center is only available until 5:30, and then we have to stop. I'd like to just be sure that everyone knows to identify themselves and before they make any comment or ask a question so that the transcriber can make sure she understands who is making the comment for the transcript that's being prepared.

And second is, please, there is water now up here for the speakers, I noticed it was a little bit lax, but it has to be kept back here, government regulations.

(Laughter.)

DR. MOCARSKI: But there is water, and so speakers should avail themselves of the water.

I'm Ed Mocarski. I think it's fair to say

that this meeting has a general goal of trying to understand, is there a way to assess the efficacy of CMV vaccine in trials? And as soon as I began thinking about the many, many decades of work that's gone on in CMV, I thought of this well-known American secretary of defense who is prone to point out the obvious, but that there are known knowns and there are things we know that we know, there are unknowns, let's say there are things that we know we don't know, and most people tend to stop there, but there are also unknown unknowns, and I think the one area that we really need to avoid, because CMV is such a complex biological entity, is that last one at this point.

I think there's enough information, there are enough knowns to make some good healthy decisions, that is to say, within the confines of a sort of a risk-based decision of whether to go after a CMV congenital disease as a vaccination target.

My job has been to sort of overview some of the virological and immunological studies. We've already heard that there really aren't any absolutely perfectly informative immunological assays. I'm going

to start with the virological studies and hopefully convince you that there are known knowns that we can depend on.

And I'm going to start with this, a diagram that I don't think I've shown in 30 years, but it just indicates, I think, how much we know and how much we have confirmed expectations of luminaries who came before us.

This is actually a diagram that illustrates primary infection sources in pregnancy and other aspects, reinfection issues, and reactivation from latency. And this big circle here indicates sort of the proportion of individuals you might expect in the population to have either consequences of primary infection or consequences of latent or recurrent reinfection. And, in fact, this diagram illustrates pretty well what's become known for the U.S. population from the larger studies in terms of the contributions of primary and non-primary infection to transplacental transmission.

Now, this is actually an unmodified diagram from Tom Weller's New England Journal series in 1971

where he was just reminiscing on the first 15 years of CMV studies, but even at that point it was very clear, not only that CMV was a cause of congenital disease, that reinfection as well as that is to say, that non-primary as well as primary infection was involved and that there were parameters that could be controlled if an effective vaccine were to be found.

And so what I want to stress in congenital CMV really is that these are confounders to the scientists among us who are continuing their survey and understanding of the biology of the virus, and, in fact, I could throw up a couple hundred reading frames right now and tell you how complicated life really is. I won't do that, but it is definitely fair to say that these complications were identified four decades ago, they remain a challenge at a scientific level, and we've already heard some of that enunciated today.

Now, we've changed the terminology here, and just to be clear, you've already heard "non-primary" used many times, indicating either and really not yet parsed out contribution of the reactivation of latent virus, and it is very clear that humans carry multiple

strains, first identified in AIDS patients, HIV-infected individuals, but now very clearly identified in the general population at transmission or subsequent reinfections results in many of us carrying multiple CMV strains. And reinfection, that is to say, the acquisition of a new strain in time, has been scored, and so it clearly contributes. How much the proportion of non-primary infection is reactivation versus reinfection, still to be established, but I think it could be established within my lifetime.

Okay, I am not going to show a lot of data. I'm going to try to bring some discussion points forward as I interpret what I was assigned to get into. CMV certainly in utero transmission and birth defects, we already have heard a lot about it. I'm trying here to organize surveillance possibilities that might be useful to detect, that is to say, to detect the transmission and disease markers as you get to primary infection of the fetus from either a primary or non-primary infection in a pregnant woman. That's going to happen via the placenta, so I also mention the placenta in this overview.

Viremia, we've already heard about viremia. It's a difficult aspect of transplacental transmission when you consider fetal viremia simply because it's hard to acquire the appropriate amount of newborn blood, and dried blood spots don't seem to give quite enough volume to make it as efficient a way to detect virus as to look in shedding. And, of course, qualitatively to determine whether an infant is infected, shedding is an absolutely wonderful way to go. Urine, a little more sensitive than saliva within 3 weeks of birth to prevent detecting a virus that's acquired at or after birth, but one that was congenitally available.

Disease, of course, we've already heard numbers and pretty much circling around somewhere between 20 and 30 percent of the infants who shed virus, somewhat dependent upon whether the mother was immune or not to CMV, but overall. And the spectrum, of course, hearing deficit, recognized, I think, in Karen's overall, somewhere around 90 percent of individuals that have any of the more complicated consequences of CMV infection. And what's important

is, especially the less severe disease, both hearing loss detectable at birth and as well that develops over the first years of life from progressive damage by the virus in the sensorineural sites. And the most severe congenital CMV well known for decades to be obvious through clinical signs and symptoms but not a good way to screen for the more subtle effects of CMV, hearing loss in particular, which is the most widespread. And, of course, the severe consequences of transmission are supported by ultrasound during pregnancy, particularly in some centers over others. And imaging after birth of the newborn can certainly tell severe central nervous, cranial, and other abnormalities.

But a standard case definition here really becomes challenging. So if there is a standard case definition for CMV congenital disease, it really does become hearing loss for those of you who really want a standard case definition, hearing loss with virus being shed I think is pretty much it, and we can discuss that later maybe if it's a disagreement.

Viremia, of course, is a parameter that in most other settings of CMV pathogenesis is the most

related to disease outcome. It's still a question for the congenital transmission because of the difficulty of collecting the data, of course, and so shedding, the qualitative measure of whether the infant has become infected, is really the most valuable endpoint.

And as I would note and many of you work in areas of solid organ transplant and hematopoietic cell transplant that the higher viremia is the basis of preemptive therapy strategies in those populations, so we would hope to learn something about congenital infection in the near future especially from the CHIMES study and others going around in the world. There are several I don't have it on my slides there are several countries that are systematically testing for CMV now, so it should lead to some additional information outside the efforts in the U.S.

So there are approachable detection methods. Viremia probably needs more study, and I'll have "MS" where more study is needed to really be the bottom line. Of course, a study that included viremia in the infant that was associated with a vaccine trial with a placebo arm would be very informative in this regard,

and shedding certainly is pretty well accepted now, I think, as an indication of infection in the child. So any effort to prevent transplacental transmission of the virus would certainly be well served by measuring viral shedding either in urine, or saliva has become more popular because it's easily acquired. Studies around the world have shown with a little strip of filter paper, a diaper is a pretty good source of CMV in urine, and certainly a cheek swab works.

Detection post-vaccination. Obviously I don't know if you can see that the gold standard we've already heard is virus culture. That was the way it was done in Tom Weller's day and still.As you can hear some centers consider that still the only way to really confirm the transplacental transmission and shedding in urine or saliva, and so that has stimulated an ongoing debate in the congenital infection community, CMV congenital infection over sensitivity and specificity of the surrogates for detecting infectious virus, and I think that point is well-established.

It's also well established that the most

severe CMV disease is accompanied by culture positivity. That's the reason why it was so certain back in 1971 after only 15 years of study of the virus. Peripheral blood is less studied because of the sampling challenge I've already said. Surrogate marker of choice has been CMV DNA presence in a sample. CMV DNA PCR real time are favored these days. And certainly in small volumes of blood I would say higher sensitivity. Some of the other popular methods that are used in transplant, antigenemia, which because it's applicable to all body fluids, and antigenemia is limited to blood samples.

So for shedding in saliva and urine, you have free virus present, not just cell-associated virus, and so you're measuring DNA associated with free virus production and release, the nature of which can spread the infection to other individuals, as we've also already heard.

I'm going to get to how do viral strain diversity and multiple infections influence disease outcome a little bit, but basically there's enough sequence in this virus to find whatever you need to

find for your purposes. If you need a marker of infection that's not in your vaccine, unless it's a completely wild-type virus that contains all the genes of the wild-type parent and it's a live, attenuated, you can find something to screen for immune correlates. And also the issue of strain diversity, which does get attention and I'll point to one study, recent study, regarding greater virulence potential for certain strains doesn't change the general parameters that you would use to get into studying CMV vaccines, although you might want to include that little bit in the study to see what the consequences are on the potentially more virulent strains.

And here I tend to come back to the thought that much of what we're talking about here is it's similar to the times in the HIV pandemic before it was recognized that there were CMV strains that were in effect in retina, cause retinitis in HIV-infected individuals, while they were shedding one strain in semen, another strain in oral secretions, another strain yet in peripheral blood. I mean, there are studies that show that that happens. We always thought

that was the immune status of the HIV-infected individual. Maybe it's not only the immune status of the HIV individual; it may be more the pattern of CMV biology.

Limited work by Tom Kowalik looking at whole genome sequencing in severely infected individuals suggests that there is quite a bit of viral genome heterogeneity within a host, which is a surprise to us DNA virus aficionados, who wouldn't otherwise expect that, but it doesn't change the basic realities of what you might know and have known for decades, I don't think.

Ten to fifteen percent we've already been through this show disease at birth. Another equal proportion develop primary and non-primary, are both important, we've already heard all this. This study that just occurred and was reported, Yamamoto and Britt and the collaboration, really reinforced the fact that there is about 1percent transmission even in a largely seropositive population overall by DNA PCR in the saliva, and that the overall incidence of hearing loss was pretty much spot on with what Ross and the Alabama

folks have seen multiple times over the years.

A sidebar here is, how much does natural infection provide protection? I kind of asked that question in the last session. I think many studies have seen that there's a 30- to 40-percent transmission rate in primary maternal infection. There is clearly less then if 1percent transmission in non-primary infection. Now, that states it in a way that it doesn't typically get stated. The more common way to state it is based on Karen Fowler's work, which looks at populations who are either seropositive or seronegative, and indicates a 69percent protection value of being seropositive.

But as a basic virologist, I like to think about this, we don't know all the pieces of that yet, we don't know all the reasons for that yet, but it is in favor of very strong protection from natural infection in most cases, and, of course, any vaccine doesn't have to be an absolutely effective vaccine to be effective.

As Paul Griffiths I think pointed out first in 2001, and was later pointed out by the Alabama group

in 2006 or 7, you really only have to reach 50 or 60 percent of the population, the human population, to really drive CMV into non-existence. Now, part of me doesn't want that to happen

(Laughter.)

DR. MOCARSKI: but it is a reality that the force of infection of this virus is such that it doesn't need a lot of competition from a vaccine to be wiped down or out.

We need to understand the immune correlates. I mean, that's a scientific need. It would help vaccine studies because of immune correlates of protection in Phase I and Phase II rather than waiting for an efficacy trial, whether it's guided by disease or guided by transplacental transmission as a Phase III.

You've all seen this data, I just put it up here to remind us. This is now a global disease, and it should be evaluated that way. Karen estimated 240,000 infected Indian children a year, something in the neighborhood of worldwide, a couple, a few, hundred thousand is reasonable, that's quite an incidence.

Now, just getting to the maternal and fetal side and I think a lot of us have seen this diagram, and thank you to the Lenore Pereira for providing it and the complexities again that the biology of the virus presents at the maternal-fetal interface. I don't think that they necessarily drive you away from thinking about vaccination. They certainly drive a fascinating area of what is happening with cells that host the virus, cells that control the virus, and immune correlates that carry the virus across this interface from replication on the maternal side, which even in CMV seropositive women, it's not been studied carefully, but could be quite frequent in placenta with viral transmission, we don't know why or how, but certainly there are candidate cells from some of the work that Lenore has done in this site that become infected to congenital CMV infection that can clearly be understood, and many, I think, folks, including Lenore, are trying to look at this in great detail.

I would take away the current understanding of what influences CMV infection and transmission across the placenta, certainly the frequency of

placental infection in the uncontrolled observational studies that have appeared in the literature in California or in Australia and the pretty much universally obtained 1-percent transmission that placental infection seropositives is probably more frequent than transplacental transmission. So there's a barrier there, whether it's an immune barrier, a physical barrier, cell-type barrier, I think we can hope to understand that scientifically in the future.

Certainly somebody needs to evaluate placental infection and virus transmission in parallel in the same set of individuals and same subjects, and not only do they need to do that, they need to attract the immune correlates of that placental infection, because it's not 100 percent, and that transplacental transmission so that we have an understanding of not only maternal control of placental infection but also maternal control of transplacental transmission. Both of those are really critical scientific questions that have really not been addressed.

CMV antigens and DNA can both be detected in maternal vascular endothelial cells, decidual

fibroblasts, cytotrophoblasts, and if you looked at that diagram I showed you, spread to a particular set of cytotrophoblasts in the placenta, it seems pretty reasonable as a hypothesis. It needs to be evaluated further, and I think with more kinetics in mind, that is to say, what happens first? what happens next?

And certainly there are all of the host cells you might hope for in the uteroplacental interface to help control this, but we don't have any idea whether innate control is important, how much it contributes. Certainly, there's a suggestion, humoral or cellular adaptive control is important, but we need to understand more.

So those needs studies, and I put little "MS's" on all those, and I didn't stop to say the MS, again more studies, more studies. There is really a scientific need for information here. That should not prevent anyone from thinking about a vaccine study, which would be a great addition, not only as a scientific thing, but as a way to control this medically important problem.

We've known for 30 years that CD8+ T cell

immune surveillance is important and crucial. Adaptive T cell transfer in the early '90s by actually, it's 20 years by Stan Riddell and colleagues, now done lots of places worldwide.

And a great contribution of CD4+ T cells, whether that's to cellular immunity itself or to antibodies that are generated, but their contribution in all sorts of settings have been seen, and, indeed, in children who eventually control their CMV CD4+ T cells, really over and above CD8+'s seem to play a dominant role. So what's going on there I think we need to understand.

Avid antibody. We've already talked a lot about the avidity of the antibody seems to make a difference as to how well it acts to neutralize or however it controls the virus. We need to understand how it might control the virus, what step is actually blocked by antibody in vivo.

And certainly pre-transplant vaccination works. Stan showed that a long time ago, 1989. And pre-exposure gB vaccine, as Bob Pass's studies recently showed, certainly contributes at least some level of

protection.

Pre-exposure subunit vaccine in transplant, as Paul Griffith showed, is quite useful in transplant.

So immunology of CMV infection. I can't really tell you what goes on at the uteroplacental interface, it really hasn't been studied yet, but you certainly have a great marker for seroprevalence in women distinguishing those susceptible to primary infection from those susceptible to non-primary infection, as it works in transplant as well, it's the same thing.

Strong cellular T cell response in seropositive individuals. I'll just mention one study that's been done recently in pregnancy, but often a remarkably high percentage of the total human T cell response is committed to the recognition of CMV, and the reason I put that up there is it seems to really go up, like in old age, during pregnancy, which is a real mystery for those of us who think about the pathogenesis of CMV disease and its control.

Passive antibody blocks transmission of CMV in some settings. Clearly, we've got the mother's milk

story from long ago, and the more recent studies that have spawned additional larger scale and controlled studies, and whether avidity matters, it will maybe come out of that.

T cell immunity has certainly shown to protect against CMV in many settings in transplants and in AIDS, suppressing the virus. And we really don't know enough about that arm in pregnancy. And immune women with recurrent infection transmit to the fetus much less frequently than non-immune women. I'd give it a twentyfold benefit, or tenfold at least, given the fuzziness of all the data, but there is certainly a great benefit of being seropositive in preventing transplacental transmission.

There were some striking results with hyperimmune globulin, as you're, I think, all fully aware, and we may hear later in the session whether it can be reproduced, I'm not sure.

We've also seen data published from the Pereira lab that those individuals who received gamma globulin had some remarkable pathological recovery signs such that there is something beneficial to that,

it seems, at the maternal-fetal interface.

And we also don't know mechanism, and we won't know mechanism anytime in the near future. Is this antiviral antibody or is it some sort of an Fc receptor-driven regulation at the placental interface? Again, arguments that went on in the hematopoietic cell transplant 30 years ago with gamma globulin will go on in this business as well because the current studies don't dissect that at all.

And so that answer may only come with immunotherapeutic, would a CMV-specific neutralizing antibody actually do well in this setting? Who knows?

What measures are available to follow immune parameters of protection and durability of protection? Well, neutralization assays, and, of course, there are other antibody-based assays and strategies to look at neutralization that need to be appreciated. The most dramatic that's come on the scene in the last 10 years is the difference in entry of the virus into fibroblasts and these epithelial cells that are used as a convenient assay, which comes down to structural envelope glycoproteins encoded by the virus that

something maybe should be included in a vaccine.

So viral targets of neutralizing antibodies include the old favorite gB, it's the major envelope glycoprotein in terms of neutralization response whether measured, I think, either on fibroblasts or on APRE cells. It's a very important function. It actually binds receptors and mediates the fusion step in viral entry.

gH/gL, a partner infusion, but really and also may bind specific receptors in CMV, regulating the fusion step. It's not a fusion protein, but somehow that and all the herpesviruses buddies up with gB to regulate fusion in some way.

There are other modified complexes of gH/gL, and amongst those are one containing gL and ones containing the two or the three other players that have been called the pentameric complex, which enhances entry into these epithelial and endothelial cell types, and may be important, the pathogenesis still to be understood both at the primary site of infection, or pharynx, what have you, in steps that get to the placenta and over into the fetus.

And gM/gN is a major envelope glycoprotein, and it functions probably in egress. The point is and this just comes down to assays if you had a vaccine that doesn't have one of these, you can use any of them as a source of an assay for natural infection. That's the only thing to say here for assays. As long as your vaccine lacks one and even Towne lacks one of these three, and as a consequence, has poor expression of actually some other functions. So there are lots of ways to go with assaying for natural infection in a vaccinated population, even if you have a complex vaccine.

What measures are available to follow immune parameters? Well, obviously, CD4+ and CD8+ T cells are critical, and multiparameter flow has become a workhorse. It's not easy to put in a mass activity in a Phase III trial, though. Interferon-gamma ELISPOTs are more likely to be used throughout clinical development, but there are good ways to use those and I think promising ways, if there are correlates that need to be studied. There are few studies so far in pregnant women and newborns, I already made that point.

I believe Grazia Revello will review this work that's gone on in Pavia.

I was impressed by this recent study in human immunology, which I alluded to earlier, which said basically the same thing happens in pregnancy, only transiently, as happens with this massive CMV response in elderly. You get this massive memory inflation with these revertent memory effector cells that are very different than your I call them "Rafitopes," "Rafi Ahmed topes" but, you know, the idea is there is a very different relationship here, the virus with the host cellular immune response that we don't understand the consequences of. It happens during pregnancy and actually reverses back down to normal after pregnancy. What that has to do with viral control I don't know.

There are prominent viral antigens. And what's nice about the set of CMV antigens that have been studied is they have a very good coverage of the HLA diversity in the world's population, so it's easy to select antigens that can be used as vaccination targets as well as for surveying cellular immunity in naturally infected populations. There is no shortage

of choice in CMV, not a very Republican comment, but it's choice.

(Laughter.)

DR. MOCARSKI: No correlates yet for protection of transmission in the cellular side. They're needed.

What cellular immune parameters are relevant?

DR. KRAUSE: Ed?

DR. MOCARSKI: I tend to think

DR. KRAUSE: Ed

DR. MOCARSKI: I'm done.

DR. KRAUSE: You didn't well, I don't think you used the timer, but you are a little over.

DR. MOCARSKI:I'm done. Okay. I'm done.

DR. KRAUSE: So if you can wrap up, that would be good.

DR. MOCARSKI: Okay. I don't need it, and I'm done.

Strain diversity? You know it happens, I've already said I don't think it's a stopper for and so I'll finish on this, a quote which I think is something that is well thinking about, worth thinking about, for

a virus that has been studied for many, many, many years, you can only send so many fingers to your father when you've been kidnapped to prove that you've been kidnapped, and you can only have so much data that CMV transplacental transmission is a congenital disease, and so you keep sending those fingers, eventually you're out of fingers, but certainly I don't mean to say it's not necessary and very important to continue the studies.

Okay, I'll end there. And thank you, Phil.

(Applause.)

DR. MOCARSKI: Phil, what you're telling me is I should just move on.I will. I will.

DR. KRAUSE: I'm afraid so, but save your questions for Ed for the discussion.

DR. MOCARSKI: That's perfectly fine. And so now we'll have Bill Britt, who is going to follow on the Mac here and show us some of the work that he's actually done. Thanks, Bill.

DR. BRITT: Is it better?

DR. MOCARSKI: Oh, I don't know.

DR. KRAUSE: Oh, and, Ed, there's a timer on

the front table there. I don't know if you want to grab that. There's a timer on that front table which you could grab.

DR. BRITT: Well, I'll start. Mine will be a little faster because some of the slides that I've actually put in this presentation have been presented by Marisa as well as Ed and Karen Fowler. But I was instructed to talk about reinfections or superinfections, and this is a slide that Karen used, and I think it illustrates a peculiarity, the biology of CMV and congenital CMV. As the rates of maternal seroprevalence go up, the rate of congenital infection goes up, which is sort of counterintuitive for most viral diseases.

More importantly is if you look at the ratio of non-primary to primary maternal infections that result in congenital CMV, if you look at data that Sergio Stagno published in the '80s, it's about 4.3 for the low income rate population, about .7 for the middle and upper income population, and more recently, work from the CDC shows overall it's about 3.4. So there are three to four times as many non-primary infections

resulting in congenital infections than there is primary. So it is a significant contribution to congenital CMV.

So what is re-infection or reactivation or recurrence? Well, when I first came to Birmingham, we used the word "recurrence," and that was based on data that Charlie Alford and Clark Huang had generated using restriction enzyme mapping of CMV isolates, and this is actually a figure from the paper in the New England Journal that was published in 1980, I believe, and what they did was they compared the isolates from the mothers and the babies with subsequent pregnancies, and they said the viruses look the same, so they probably were reactivated from the mothers.

But actually if you look kind of closely, there are some bands here that weren't in the same baby, and in fact, this mother right here acquired another band. Charlie and Clark used to talk about these as submolar bands, minor bands, and things like that when they interpreted these gels, they were the best they had at the time, but that leaves it open, some reason, I think for question whether these really

were reactivations or were reinfections or were these the same viruses?

The other problems with these assays, for any of you in the audience that have done them, these are P32-labeled fragments, they grew them in extracellular viruses, so these viruses here, for instance, were passaged up to 25 times in vitro before they ever got enough virus in a supernatant to label them for these assays.

So the question is, does recurrence actually account for non-primary infections reactivation I mean, account for this, I think is still open to question.

So what's the other possibility? Acquisition of a new virus. Well, reinfection was clearly demonstrated in Stanley's vaccine studies, it's been demonstrated in populations in sexually transmitted disease clinics, clearly in the HIV populations, and the transplant populations. So CMVs can reinfect even in immunocompetent individuals.

We started to look at this question for non-primaries Suresh Boppana and I and it was really based on a fortuitous finding that Michael Mach and I came up

with, and this slide is sort of smashed in here, but there is a linear epitope in glycoprotein H, which you can see. This is the 81-69 representation. In Towne, this epitope is not present. This epitope actually is a target for neutralizing antibodies defined both with human sera and with the monoclonal antibody. So we took this and actually asked the question, can we use it as a serologic probe to look at reinfections, much like you would sera type-specific reagents.

We also subsequently have found when Suresh and Zdenek Novak found one in glycoprotein B. This is not a target of neutralizing antibodies, but it varies, and I'm sorry for the slide.

But anyway, by using these two antigens in combination, you can come up with seven different combinations of possibilities of reinfections. The report of this that we published was Suresh's paper, and it showed that if you looked at women with infected infants these were seropositive women that the much higher percentage of them were reinfected based on the serologic assay for gH than mothers of uninfected infants. This was statistically significant.

More importantly, when we looked at these women, they acquired this new in this case, for instance, as an example, they acquired a new antibody specificity to this glycoprotein H AP86 we call it during pregnancy, they delivered an infant, and we took the virus out of the urine of that infant and sequenced it; indeed, they did acquire this new epitope. So in these women, they actually acquired a new reactivity during pregnancy, and we recovered the virus from the infected infant they actually they had that sequence.

So we think we have defined reinfection. We extended that now into Brazil with the help of Marisa and Ulie, who have done tremendous work in their center. And as Marisa mentioned this morning, the seroprevalence in that population is about 97 percent.

So we looked at a group of women with these were approximately I know 140 women that delivered congenitally infected babies, and the reason there are 40 in this study is because this was a serum bank, sera available from a serum bank, that we could actually look at their prenatal sera. And just to go over it quickly, we had a control group, and the rate of

reinfection in that group measured just by the seroconversion during pregnancy, not the presence of other reactivities, was about 4.6 percent versus about 17 percent, annualized, about 23 percent and about 6.1 percent. So we think we demonstrated reinfection in this population, and we believe it may be a major contributor to the non-primary infections.

One point I want to make, and I think actually I would like just to put this out to the audience, if you look in these controls right here, about 4.6 percent of them demonstrated reinfection during pregnancy. Again, realizing this is a minimal estimate, but if that's the rate of reinfection in this population, let's just say, for instance, it is, maybe it's 5 percent, maybe it's 8 percent, if the rate of congenital infection in that population is 1 percent, one could speculate that maybe the transmission rate following non-primary infections is much higher than the 1 percent that we all quote. Again, that's a speculation, but I just put it out there, and these numbers certainly don't support that, but I think it illustrates we don't really know what the rate of

transmission is following non-primary infection because we don't understand the immunologic or the virologic parameters of a non-primary infection.

So are there experimental evidence of reinfection? And the best comes, I think, from the primate studies done in Oregon. This is Louis Picker and Scott Hansen's paper in "Nature Medicine," and what they've done is they've used rhesus CMV as a vaccine platform to generate a vaccine against SIV in rhesus macaques, they've introduced heterologous antigens in there, and all I want to show is that after they put those in there and they detect the presence of these heterologous proteins in the urine, a virus recovered from these animals, and these animals were all seropositive before they received this vaccine, and you can see as far as 644 days out after immunization with these vectors, they were still excreting virus that contained heterologous antigens. So I think that's fairly strong experimental proof that reinfection occurs in these models, these primate models.

So what are the sources of reinfection? Ed mentioned that there is a lot of diversity in viruses,

and that's clear, that's clear from Tim Kowalik's work recently and from work done in immunocompromised patients, less so in immunocompetent patients.

This is a slide that I generated for a grant proposal about 10 years ago, and it was looking at a congenitally infected baby with central nervous system disease, and what I did was I isolated virus from the CSF and virus from the urine, and I sequenced the gN component, UL73, and you can see that there are two different viruses, there is one in the CNS and there is one in the urine.

More recently, Shannon Ross, in our division, has looked at this in a group of babies that were congenitally infected, and here are 13 with congenital infection, looking at different viral genotypes. This is based on UL73 gN, gB, and gH, looking at the conventional nomenclature for the different genotypes, but what I want to show you is that in this baby, for instance, there are two different types of gN: one in the urine, one in blood; there are two different types of gB: one in the urine, one in the saliva; again, another case where there are two.

About 30 percent of these infants showed different viruses in different body compartments, so, again, multiple viruses appear to be transmitted to these infants, and why they settle in these different compartments is clearly not known.

This is from Tim's, this is a slide Tim Kowalik gave me, but just for the people in the audience that don't know this data, deep sequencing of CMV from viruses isolated from babies with congenital infection shows tremendous diversity of the virus, on the order of dengue virus in terms of genetic diversity. So there is almost, as Tim would say, a quasi-species or a swarm of these viruses that can be present in these infants, and according to his more recent data, these expand as these infants age.

So what are the mechanisms of reinfection? Well, one possibility is viral strain variation in targets of antiviral antibodies. This is the study from New England Journal showing reinfection. And just to point out that these women that had evidence of reinfection and transmission to their infants, if you look at their antibody this is antibody neutralization

against an unrelated virus, 8169, there is really not much difference between previous pregnancies and delivery, you can see all the way across, however, if we look at their neutralizing capacity against the baby's virus on the previous pregnancy versus the delivery, we see a boost in the antibody neutralizing titers, suggesting again that they saw a new virus that they hadn't seen in the previous pregnancy and they boosted their neutralizing capacity.

This is, again, an ancient slide looking at glycoprotein B, and this was a really convoluted experiment I did long ago where I used vaccinia-infected fibroblasts to actually absorb and deplete glycoprotein B antibodies from sera.

And this is me right here, I'm seropositive, and this is a patient with congenital infection, a woman who delivered a congenitally infected baby. As you can see, when I used uninfected vaccinia-infected cells that don't express gB and try to absorb out the neutralizing titer, nothing really happens with my sera, across here you can see, nor with the patients here.

However, when I use a vaccinia construct expressing glycoprotein B to infect the fibroblasts and then use that to absorb, you can see with increasing cell numbers I actually drop the titer of the neutralizing activity, and for me, I did it for 8169, which is the parent of the glycoprotein, but I also did it for this virus, which is unrelated, from a patient, and from this virus here, again unrelated from a congenitally infected baby.

So it appears that I have neutralizing antibodies that can take out all of these viruses, sort of group-specific antibodies, if you will.

When I take this patient's sera and I do the same absorption, I'm successful with 8169 and with this unrelated virus, Kaufman, they both take it out, but when I try to neutralize their virus, I can't neutralize their virus by just absorbing out these group-specific determinants. So it's possible that glycoprotein B is inducing both strain-specific and group-specific neutralizing antibodies, and this could be evidence of a sera type-specific neutralizing antibody response.

We've done the same thing with glycoprotein N. This has been a little easier because we've used the 8169 backbone, and now that we have BAC genetics, which I know Ulie is in the audience, and I thank him for that advance, for the field of HCMV. But, anyway, we've replaced the different glycoprotein Ns with the conventional genotypes gN1, gN2, gN3 so we made four different viruses. And this is a group of women, again with non-primary infections to CMV. And this is a sera from 2002, and you can see that this individual did not have antibodies against glycoprotein N2, but then about a year later they developed antibodies, neutralizing antibodies, against this virus.They neutralized all these viruses about the same. So it appears that they picked up a sera type-specific reactivity.

Finally, again to illustrate this, these are the same four viruses that we worked on in Michael Mach's lab showing the differences. This is a sera from a patient KOB showing good neutralizing titers against all four genotypes of these congenic viruses versus this sera right here, which shows very strong activity against glyco gN type 4 versus gN type 1

there's not very much activity. So there clearly appears to be some sera type-specific antibody responses.

What about the role of CD8+ T lymphocytes and CD4+? There's really no evidence on that, but this is a paper again from Oregon, from Klause, who is in the audience, and Scott Hansen, showing that if you try to reinfect a seropositive monkey with a recombinant CMV vector that does not contain the immune evasion functions encoded by US2 through 11 I think is the one that's gone in this virus that you cannot successfully infect those animals. Again, those immune evasion functions seem to be critical for this reinfection, suggesting the ability to evade the CD8+ response is critical for reinfection.

These monkeys could be readily reinfected, as you can see, when you put these different constructs in them, which is a Gag and Naf-expressing viral vaccine, and they started to excrete viruses with these heterologous proteins. So they could be reinfected but not by the viruses lacking these immune evasion functions.

So I'm going to go very quickly on this because this has been touched on by, I think, Mike Cannon and Karen and Marisa.

So what is the outcome of maternal non-primary infections? And really the person that started this was Karin Ahlfors in Sweden. She published data that was not well-received, I think, but clearly she showed that with non-primary infections in her population, she could find a similar prevalence and a similar rate of symptomatic infections and a similar number of patients with neurologic sequelae suggesting there wasn't, and she argued much difference between the type of infection.

More recently, you've seen this data that Karen put up from Shannon Ross reviewing our series from Birmingham, and again just to focus on symptomatic infection, when we looked over the non-primaries versus the primaries, the rate of symptomatic infection was approximately the same.

Suresh looked at this more closely in 1999, looking at non-primary, again symptomatic infection. Looking at non-primaries versus primaries, the numbers

are small, but you can see there is not a lot of difference between these groups.

And, again, the same idea. This is overall, not symptomatic, but this is just outcomes showing there is really not very much difference between these groups except for the possibility of hearing loss.

So one of the things that happened with the publication of that paper, there was some confusion about how this hit with the other data that we had published, and recently we looked at our data, and Shannon and Suresh and I have looked at this data in a different way, but I put this slide up just to illustrate to people in the audience that don't review the literature of congenital CMV very closely, but this is the population from Alabama, and what Shannon has done is gone into this population and pulled the babies out that were identified by screening at our hospital, where most of the babies are born and our screening program is in place, versus those that are referred into this clinic. We used to have a large congenital CMV clinic, so we got a lot of referrals from within the state, within the adjacent states, for babies with

symptomatic infection.

But what I want to show you is there is a huge difference in the findings from these symptomatics in terms of the instance of, for instance, jaundice, petechiae, hepatosplenomegaly, things like this; they're all quite different. These referral populations, much sicker babies than what we saw in our screen population, and it's probably a referral bias.

And if you go down here, you can see the sequelae, again, referred versus screen, much greater with hearing loss, with IQ, and with neurologic abnormalities such as seizures.

So the point being is that for a disease where the incidence is not that high, and particularly the sequelae, the small contamination from a referral population into any populations at study can really change what we think of the epidemiology of this and the natural history of this disease.

So the way to get around that is to do a screening study.

DR. MOCARSKI: Bill?

DR. BRITT: Yes, I'm going to stop right now.

And this is just Marisa's and Ulie's data from Brazil. And you've seen this data, but these babies do have hearing loss and it's very similar to what we see in Alabama.

Finally and I put this in for Mike Cannon because there was an issue of intervention what can we do? I can't speak to the fact whether a vaccine would prevent non-primary infection, but this is an interesting piece of data that I think most of us should be aware of, and it should be incorporated in the vaccine studies. When people counseled women who were seronegative, they dramatically influenced whether they acquired CMV during pregnancy, by about a 50-percent drop. Stuart has been part of one of these studies, the other study came from France.

And I'll stop there. Thank you.

(Applause.)

DR. MOCARSKI: I think we're going to leave all of the discussion to the discussion time and keep going. Maria Grazia Revello has been involved in studying this problem for many years.

DR. REVELLO: I'm not so old.

DR. MOCARSKI: No, she's not so old, but dedicated.

DR. REVELLO: Okay.

DR. MOCARSKI: There you go.

DR. REVELLO: Thank you, Ed.

Okay, I suppose that I've been given the most difficult title in all the program, and I hope this was not done on purpose.

(Laughter.)

DR. REVELLO: Anyway, there is one thing we for sure agree, and that is that immunity provided by natural infection is fairly protective, and at least this is true from the individual point of view of a pregnant woman who, if susceptible and acquire primary CMV infection during pregnancy, has at least 40 percent risk of transmitting the infection compared to only 1 percent more or less risk carried by a pregnant woman with preconception immunity.

Said this, we really know very, very little about the actual role played by humoral or cellular immunity in preventing congenital CMV, and even less we know about the role of single components of the two

arms of the immune response.

In the last 25 years, just a handful of papers have been published, and the great majority of the authors are in the audience, so I don't have to go into many details.

Looking at whether it was possible to define any difference in the antibody response, which is the easiest part to explore as far as the complex immune response in transmitter versus non-transmitter mothers. And as you can see, findings were quite heterogeneous, but this is difficult to compare considering that different antigens were examined with different assays and at different times after the onset of maternal infection.

Anyway, in general, much of the attention was given to the Boppana and Britt paper where reduction in the antibody neutralizing activity as detoured on fibroblasts as well as in the avidity maturation were most likely associated to women who eventually transmitted infection.

However, six years ago, more or less, Professor Nigro and Professor Adler showed that,

indeed, antibodies could make a difference both as far as the virological outcome and the clinical outcome of pregnancy complicated by a primary CMV infection, and what they did was to what they reported was the efficacy of passive antibodies, hyperimmune globulin to CMV, given to two groups of women identified according to the fact of whether they had performed amniocentesis or not. And in the group of women who did not undergo amniocentesis, so they didn't know whether the fetus was infected or not, some of them were given hyperimmune globulin, some not, and at the end there were 37 women treated with hyperimmune globulin and 47 who were not who could be compared because the virologic outcome of birth was available. And this group was called the prevention group.

The other group, which was identified in the group of women who underwent amniocentesis and had positive results, so they knew they were carrying infected fetuses, and some again were treated with hyperimmune globulin, and some were treated and some were not, and in this group, the efficacy of the hyperimmune globulin was assessed as far as the

clinical outcome of these newborns was concerned.

The hyperimmune globulin were given as a ready-to-use immunoglobulin solution manufactured by Biotest Pharma in Germany. The commercial name is Cytotect; they are available in Europe. And the content of this solution, as far as CMV-specific antibody are concerned, is equivalent to 50 units, and the reference standard is Paul-Ehrlich-Institut serum, which serves, as we said, as a reference standard per mL.

In the prevention group, the women received a monthly infusion of 100 units per kilo, and that means 2 mL until delivery. Whereas in the therapy group, all women, 31 women, received at least one infusion with twice as much dosage, and a minority of these women, 9, for the precision, they had additional infusions because of persistence of ultrasound abnormalities.

And the results were absolutely impressive in that in the prevention group, 24-percent reduction was detected. In the transmission rate, since only 16 women out of the 37 treated gave birth to newborns with congenital infection compared to 40 percent of the

women who did not receive the hyperimmune globulin. In the therapy group, the efficacy was even greater.

It was difficult, however, to appreciate the real efficacy of this drug given the fact that the study was not randomized and not controlled. So the authors, in order to explain these positive results, suggested some possible mechanism of actions of hyperimmune globulin, and particularly, high neutralizing activity and avidity in the hyperimmune globulin preparation mainly to justify the effect in the prevention group, whereas in the therapy group, immunomodulatory effect and anti-inflammatory effect were postulated.

As far as the first issue, that is, the role of neutralizing and avidity, neutralizing activity and avidity in reducing the risk of transmission, well, the data that were shown in the paper did not allow to really appreciate how this supposed mechanism really worked because neutralizing antibodies were not detoured in these women, but only ELISA antibodies were detoured, and as far as avidity is concerned, significant differences were reported in the avidity

values at enrollment and at delivery in the three groups the therapy, prevention, and the control group however, no significant difference was reported among these three groups.

And, in addition, by looking at the actual values of avidity reported here, they were rather low altogether considering that for the measurement of avidity, it was used the assay that is shown over there, the Bouty assay, and minus 25 avidity index means low avidity, whereas greater than 45 means high avidity. If you look at the results that have been obtained in this study, one gave the impression that these avidities where not too high anyway irrespective of whether the groups, the two groups, did receive hyperimmune globulin.

One explanation for these results can be the fact that, as already mentioned by Tiziana Lazzarotto, the panorama of avidity assay available on the market is a bit uneven, so to say, as far as performance is concerned, and this is the kit that's been used in the New England paper, and you can see immediately that, according to this assay, it takes quite a long time to

evidentiate an avidity maturation following a primary CMV infection, more than 6 months. So this remark is not a specific criticism to the paper but, rather, a reminder to everybody that commercial assays have different performances, and one has to be aware when they are used, particularly when they are used for research purposes.

Irrespective of the fact that the study given the fact that the results were very astonishing and because there is nothing that really can be offered to a woman with a primary CMV infection, a great effort was put on in setting up controlled studies in order to verify whether the passive antibodies could have been modifying the natural history of primary infection with respect to congenital infection. And three studies were indeed set up. One Italian study that's called the CHIP study was a Phase II randomized double-blind drug versus placebo multicenter study sponsored by the Italian Ministry of Health, and this study has just been completed and the data analysis is ongoing.

A second study, a European study, was organized by Biotest that's the pharmaceutical company

that's an open, controlled multicenter and multinational study. It includes centers in Germany, Hungary, Belgium, Austria, and lately Italy as well.

And then there is a third one, a U.S. study, so things are getting bigger and bigger. It's a Phase III randomized, double-blind drug versus placebo using CytoGam, that's the adult preparation of hyperimmune globulin available in the United States. I think in the audience there are participants to this study, so they can be more aware than what I am as far as the actual status of this study.

I have been authorized by the steering committee of the CHIP study to release the very first preliminary results of this study today. The occasion is an exceptional one, and also because in the audience there is Tiziana Lazzarotto, and I would like to thank her and the Bologna Center because of their active participation in this study. Pavia Center and Bologna Center recruited more than two-thirds of the patients required for this study.

Just to briefly remind the generalities of this study, we had to enroll 120 women with primary

infection in order to show a reduction from 40 percent to 16 percent, that's the one reported in the Nigro study of congenital infection with 80-percent power and 5-percent type I error, and given the 10-percent attrition. The study population we used consisted of pregnant women referred to participating centers because of suspected CMV infection, so women were enrolled once the diagnosis of primacy in the infection was reached. And the drug used was at the same dosage and with the same schedule as already reported in the Nigro study.

The treatment was started, had to be started, within 6 weeks from the presumed onset of the infection, and to be repeated every 4 weeks until 36 weeks of gestation or positive amniocentesis because the primary point was to assess the efficacy of the hyperimmune globulin by compare the number of newborns or fetuses or infected fetuses born to mothers, to treated or untreated mothers. And then there was a number of secondary objectives that now I'm not going through now because of time constrictions.

So the main inclusion criteria was to have

adult pregnant women with primary infection acquired between 5 and 26 weeks gestation that is, first and second trimester in order to have an even distribution and even rate of transmission. And as I said, randomization and treatment had to be started within 6 weeks of presumed onset of infection. This was a very strict criteria and it was based on the consideration that was already anticipated by Tiziana in her talk, that now nobody knows how long that takes indeed to reach the fetus. Prenatal diagnosis experience tell us that after 6 to 8 weeks from the presumed onset of infection, 90 percent of fetuses, infected fetuses, can be reliably diagnosed. So there is not much time that we have in order to intervene if we want to modify the vertical transmission process, and 6 weeks was therefore chosen because it was feasible and at the same time reasonable.

So the study started officially in November 2008 with the signature of the contract between Policlinico of San Matteo that's the hospital in Pavia, Pavia is the coordinating center of the study and the Ministry of Health. They give us 3 years to complete

the active phase of the study. In June '09, 2009, the first patient was enrolled. The last one was enrolled in March 21st this year. Then we had to wait for this last woman to deliver her baby, and this happened on October 29, and so by that date, the study was formally closed because the study did not foresee any kind of follow-up of babies.

So at the end, we had 124 women enrolled, 123 randomized, and 122 available for primary endpoint, that is, women who did receive at least one treatment, and with known virological outcome of pregnancy.

Forty-four percent of women underwent amniocentesis, and congenital CMV that's the endpoint, primary endpoint was achieved at amniocentesis in 18 fetuses and at birth in 27 newborns.

So overall transmission rate was 37 percent, 45 infected fetus/newborns out of 122, and the result is that transmission rate was 30 percent in the Cytotect arm and 44 percent in the placebo arm. So we had a crude reduction of 14 percent between the two arms. Now, the difference was not significant. Right now, the statisticians are busy in looking at

other variables. Of course, there are many in this study: the time of gestation at primary infection, number of treatments, and what I think will be the most interesting aspect to be analyzed is the actual time elapsed from the presumed onset of maternal infection and the first treatment, but we have to wait a little bit.

So if we I've got to be finished? Time is gone? Yeah?

MALE SPEAKER: Please finish.

(Laughter.)

DR. REVELLO: What?

(Laughter.)

MALE SPEAKER: Please finish.

DR. REVELLO: Oh, my goodness.

Well, now it's difficult because what I wanted to point out is that whenever we are looking at the immune response following primary CMV infection, I think that as far as antibody is concerned, and not just antibody, we have to focus our attention on two aspects. One is the early phase of antibody or immune or even cell-mediated immune response, and the other

one, as far as antibody is concerned, is the functionalities of these antibodies, and so far, we have been very happy in determining neutralizing antibody as a potential marker of protection, but, as correctly Deborah Spector pointed out, there are other aspects that in my opinion are worthwhile to be explored, and cell-to-cell spreading, for example, or CMV transfer from infected HUVEC to peripheral blood leukocytes and so on.

Just to briefly tell that the two most widely used anyway that's neutralization and avidity are assays that need to be standardized in order to give comparable results in particular when we are talking about vaccine efficacy evaluation.

And just briefly to tell you that, indeed, if you look at the antibody kinetics in transmitter and non-transmitter models, and if you focus on this very early time, that's something we are working on, you can spot some major differences in between the two groups.

I cannot thank goodness I have no time go into many details, but because this is something that we are really working on it.

And as far as cell-mediated immunity is concerned, let's just have a look at what we have found in transmitter versus non-transmitter models. And we have been able to spot only two parameters that behave differently in between these two groups, one is the proliferation, which is very much delayed in women who will eventually transmit the infection compared to women who will not, and the other significant parameter is the appearance of effector memory cells reexpressing the CD45RA, and again this is highly significant difference in between the two groups as far as these two parameters are concerned.

And this last slide shows you that even though there was no difference in between cytotoxicity activity between transmitter and non-transmitter models at least we have not been able to detect it still cytotoxicity activity was much higher in women clearing the virus earlier compared to women with late virus clearance, and new data just becoming available indicates, seem to indicate, that transmitter mothers have a clearance of the virus that takes much, much longer compared to women who do not transmit the virus.

So, in conclusion, what I can tell you is the initial viral load I didn't have time to talk about DNA, but it's a crucial parameter to be investigated, an early immune response seem to be important in congenital infection. We have major limitation in our studies that CMV is a retrospective diagnosis by definition and that unless there are studies going on, particular studies, there is inconsistent follow-up of these pregnant women. And then, of course, additional studies on innate immunity on the combined role of cell-mediated and humoral immunity, individual antibody specificity, and functional antibodies are very much needed.

Thank you, and I apologize for being late.

(Applause.)

DR. MOCARSKI: Stanley, you need no introduction, and will tell us about previous vaccine trials.

And thank you very much, Grazia.

DR. PLOTKIN: So, let's see, how do I get my slides?

DR. MOCARSKI: I'm sorry. That was my talk.

Okay.

DR. PLOTKIN: Okay, so CMV vaccine development has a long history, and I think we can derive some very important and interesting lessons from this past history.

Now, my first two slides summarize the candidate vaccines that have been developed. The live-attenuated Towne virus, which has had clinical testing and efficacy trial, the Towne-Toledo recombinants, which have had some clinical testing, but not efficacy yet. Recombinant gB subunit, which, as you know, has gone to efficacy trials. Viral vectors have also been tested. Canarypox in particular has had clinical testing. Other vectors, like MVA and non-replicating adenovirus have been proposed preclinically; I do not know of any clinical data.

Alphavirus replicons have had preclinical testing and clinical testing. Peptides, again, have been proposed, but I am not aware of any clinical test data. DNA vaccine has indeed gone to clinical tests and even efficacy data, as I will show you. Dense bodies have been proposed preclinically but not yet tested

clinically. And also other approaches are under investigation: virus-like particles, lymphocytic choriomeningitis virus, and replicating adenovirus vectors.

Now, way back in the 1970s, an attenuated virus, the Towne strain, was tested in seronegative volunteers, and this slide simply shows that both antibodies and cellular immune responses were induced by the attenuated virus.

I'm going to skip that.

And this slide summarizes some of the results of the subcutaneous inoculation of the Towne attenuated CMV. There was a local reaction at the site of injection in the second week after injection but no systemic reaction. There was no virus excretion in the throat or the urine, no evidence for latency in immunosuppressed renal transplant patients. There was CMV-specific CD4+ T cell proliferation in all vaccinees, CD8+ mediated CTL induced in most vaccinees but was relatively short lived.

Interestingly, a skin test, which is positive with CMV antigens, which is positive in naturally

seropositive individuals, converted to positivity after vaccination. However, in one trial, the vaccination of mothers who were exposed to toddlers excreting CMV did not prevent their acquisition of the virus.

Nevertheless, the vaccine was tested in renal transplant patients, and the important result there, shown here, is that in seronegative recipients before transplantation who received a kidney from a seropositive donor, although, as you can see from the left-hand column, the vaccinees compared to the placebo column, the middle column, there was not much difference in the infection rate. The severity of disease was much reduced in the vaccinees.

Indeed, if you look at the right-hand column, which is the seropositive recipients who received a donor kidney from a seropositive individual, the protection was about the same against the severity of disease.

And lastly, and also interestingly, there was a reduction in rejection of the kidney in the vaccinated group.

So these studies show that vaccination could

influence the pathogenesis of CMV infection.

Now, because the vaccine had not, in that study, prevented acquisition of the virus by mothers exposed to CMV, a group of recombinants, four recombinants, were made by MedImmune, and this combined the Towne virus with a Toledo low-passage virus. In each case, the ULb prime region of Toledo was placed in the recombinant, which, of course, means that the pentameric complex, in principle, should be produced. These recombinants, unfortunately, have been tested at this point only in seropositives but tests by Stuart Adler in seronegative individuals are just beginning, and those results, of course, will be of importance.

Now, the next efforts were with the gB glycoprotein. As you know, this is the chief inducer of antibodies that prevent entry into fibroblasts. It was originally developed by Chiron, now Novartis, together with MF59 oil-and-water adjuvant. It was literally tested in hundreds of vaccinees, it was well tolerated, and was immunogenic both in adults and in particular in toddlers in the three-dose regimen given at zero, one, and six months. Now, gB glycoprotein, as

a vaccine, is now being developed by Sanofi Pasteur and GlaxoSmithKline.

These are the results of the study conducted by Bob Pass and his associates on the efficacy of the Chiron, now Sanofi Pasteur, gB MF59 against CMV acquisition of infection in adolescent girls, 20 micrograms given three times, and this is the Kaplan-Meier curve showing that indeed there is a separation between the vaccinated group and the placebo group, and over 42 months there was a 50-percent prevention of acquisition. However, as you can see from the Kaplan-Meier curve, the protection was concentrated in the first 18 months.

Now, no correlate of protection has been established in this study. However, I think it's interesting to show these data, the neutralizing antibodies in the study, and you can see the peak after the third injection with the loss of high-titer antibody subsequently. So, in other words, the major efficacy was contemporaneous with the height of neutralizing antibodies.

In this study, the seropositive individuals

were also tested, and it's important to note that they did have boosts in neutralizing antibodies after receiving the gB. It's also important to note that CD4+ T cell responses were seen in the seronegative vaccinees.

Now, this same gB was tested by Paul Griffiths and associates in kidney and liver transplant patients, in other words, solid organ transplant recipients. What you see in this slide on the top is viremia, on the bottom, antiviral use, comparing placebo group to the vaccine group. And in the first left-hand you see the donor positive recipient negative group, in other words, the primary infection group, if you will, and you can see that there was really a striking difference in the viremia and in the use of antivirals, and this difference also was seen in what might be called the reinfection group donor-positive/recipient-positive group. So this study indeed showed that gB apparently can prevent the transfer, if you will, or the importance of the transfer from the donor organ to the recipient.

GlaxoSmithKline is developing its own gB.

This is given in 15 micrograms, also three doses, with the ASO3 adjuvant. Now, this adjuvant contains MPL and QS21, and the MPL, as you know, is a TLR4 agonist, so this is able to induce innate immune responses.

Now, what you see here, looking at the lower left-hand graph, is the neutralizing antibody response. You can see that significant levels of neutralizing antibody are produced, but, again, the antibodies fall. If you look at the upper right-hand, you can see that avidity, high avidity, does develop after the third inoculation of the gB vaccine. And I think, importantly, on the lower right-hand, you see the evolution of gB-specific memory B-cells. Now, considering that the incubation period of CMV infection is relatively long, an anamnestic response may be of importance. With this vaccine, also CD4+ T-cell responses were also elicited.

Now, vectors have been used to present CMV genes, and what this slide shows is the results of a study with a canarypox vector containing the gene for pp65, the major tegument protein, and after two doses, only two doses, the volunteers all developed strong CTL

responses. The seronegative volunteers are shown in the black triangles. So they all developed strong CTL, indicating again the importance of pp65 as a major stimulator of cellular immunity.

Vectors have also been used in prime/boost regimens: the canarypox followed by gB; the canarypox followed by Towne; DNA plasmids coding for gB, pp65, and IE1 followed by Towne; and in the rhesus, DNA followed by the MVA vaccinia.

Just one slide to show that, indeed, there is a difference in the that is, the prime does do something. In this study, the volunteers were primed either with the canarypox gB or canarypox rabies as a control, and if you look at the 180-day results, you see that priming with the canarypox gB followed by the Towne virus, in this case, did result in higher titers after the boost.

A replicon vaccine based on Venezuelan equine encephalitis, an alphavirus, has also been developed as a vaccine. This is, as you know, a self-replicating RNA, or replicons, and this was used by David Bernstein and his associates to present gB or a fusion protein of

pp65/IE1.

If you looked at this graph, I call your attention to the HD groups that is, the high-dose groups and you can see on the top the evolution of neutralizing antibody, and you see that indeed there was stimulation of antibody, particularly in the high-dose groups. On the bottom you see pp65, and again the high-dose groups did show some ELISPOTs related to pp65. The IE1 results were not quite as positive, so what one can say, though, is that at least the gB and the pp65 were immunogenic in this format, and this vaccine is the property of Novartis.

Now, Vical has been developing a DNA vaccine, and the tests have been conducted. This efficacy trial has been conducted in hematopoietic stem cell recipients who received 2.5 milligrams each with poloxamer in four doses after the transplant. And here you see the comparison given to me by Rick Kenney and his group. The comparison between the vaccinated group and the placebo group with regard to clinically relevant episodes of CMV viremia. The red is the control and the blue is the vaccinated group. And, in

fact, the prevalence of viremia was reduced from 62 percent to 37 percent.

Another graph from this study shows a combination of viremia and antiviral use, and again you see a difference between the vaccinated group and the placebo group, a reduction in antiviral use from 71 percent to 44 percent.

Lastly, I just want to mention the dense body approach by Bodo Plachter and his associates, which is the result of the fact that dense bodies are produced in cell culture, they're easily purified, and they contain both the envelope glycoproteins and the major constituents, such as the pp65 tegument protein, and that they can be genetically engineered to put in other proteins, like the IE1 protein, but this approach has not yet been tested clinically.

So I conclude, my first conclusion slide, that both antibodies and cellular immunity, if strong enough, can prevent CMV infection, but what this slide attempts to show is on the left-hand column is virus dose, so that, of course, the larger the dose, the less the protection is going to be. On the bottom you see

antibody, and antibody, I think the evidence is that it can control at least disease and also, in some cases, infection. And again on the right hand you see cellular immunity, and once again, if the cellular immunity is poor, severe disease may result, whereas if it's strong, one may obviate severe disease.

So what are the lessons learned from these CMV vaccine trials, in my opinion? Neutralizing responses to gB can be elicited by live virus, subunit glycoprotein, poxvirus, and alphavirus vectors. gB, if adjuvanted, is a protective antigen against CMV infection in seronegative women and solid organ transplant recipients. Live, attenuated virus also protected immunosuppressed solid organ transplant recipients against disease. CTL cell responses, T-cell responses, to pp65 can be elicited by live virus, poxvirus vector, alphavirus vector, and DNA plasmids. pp65 is a potent inducer of CD8+ and CD4+ T cell responses, and together with gB, reduce viremia and disease in seropositive stem cell recipients. Priming with DNA or vectors coding for CMV proteins followed by various boosts may improve response.

There are two, however, negatives: one is that duration of protection is yet uncertain; and, secondly, the importance of anti-epithelial cell antibodies induced by the pentameric complex is currently unknown.

But protection has been demonstrated clinically with known antigens. Clinical trials to show prevention of acquisition by women are clearly feasible. Logically, prevention of infection in women means no transmission to the fetus. Clinical trials in transplant recipients to show reduced disease are feasible. And many candidate vaccines are available.

I hope you will forgive me, ladies and gentlemen, if I conclude on a personal note by saying that when I started in the field of CMV vaccine many years ago, it was a wilderness. Now the wilderness is well populated and I am relatively confident that a licensed CMV vaccine is in the future.

Thank you.

(Applause.)

DR. MOCARSKI: Stanley, thank you very much for keeping to time.

And Mark Schleiss will actually now finish

the session with a discussion of animal models of CMV congenital disease.

DR. SCHLEISS: Well, thank you very much, Ed.

And I want to also thank Phil Krause for all of his work in organizing this workshop. It really was an extraordinary effort and much appreciated.

I've been charged with the task of talking about animal models of congenital CMV infection with an eye toward vaccines with a question of whether or not these can inform clinical trial objectives in humans.

When Ed was giving his presentation, I kept seeing on his slides "Correlates of protection MS," "Reduction in critical threshold of viral load MS," and I was worried that I was supposed to answer that, but then I realized that those weren't my initials, so I'm grateful for that.

(Laughter.)

DR. SCHLEISS: Because I don't have a lot of those answers, but I do want to try to give you some kind of perspective on what animal models might have taught us to date and how I think they might be improved in the future.

This is just a slide from a recent paper showing some of the phylogenetic relationships of human cytomegalovirus to other betaherpesviruses. And here is rhesus macaque CMV, a close relative, and I'll come back to the rhesus model later when we talk about potential future studies. Here are the muromegaloviruses, murine CMV and rat CMV, more closely related to human CMV than is the Cavia herpesvirus, or the guinea pig cytomegalovirus, which I'll also talk about, but this is just to remind the audience that cytomegaloviruses are extremely species specific by definition, and so it is very difficult to evaluate human vaccines in animal models. You can certainly quantify immune responses to human vaccine candidates, and a lot of work has been done to do that, but then to challenge with human CMV is very difficult.

And so I want to sort of reflect a little bit on this question of species specificity. How absolute is this? What are some of the insights that we might have learned some lessons from in various experimental models, and what are priorities for future research?

Some number of years ago Stanley's lab

actually demonstrated nonproductive infection of guinea pig cells with human cytomegalovirus, and here are the original EMs from that study showing binding, penetration, and then release of the virion in the cytoplasm of guinea pig cells. And, in fact, the species specificity issue has been explored in a number of cell culture studies. There are a number of papers, including this one from Dick Spaete, showing that chimpanzee fibroblasts are fully permissive for human CMV replication, another study showing porcine CMV replication in human fibroblasts.

And I think it's of interest to consider the work of Wolfram Brune in this context, who has shown that it's induction of apoptosis that really limits cytomegalovirus cross-species infection, and in this paper, when he blocked apoptosis, he was able to get, as you see in this slide, replication of rat cytomegalovirus in human cells. Wolfram has taken that work another step further and identified in a spontaneously arising mutant of MCMV that at least some of the genes that are important in this species restriction are encoded by the M112/M113 region. And

making a mutant in this region restored replication or allowed replication of murine cytomegalovirus in human cells.

And so I think this species specificity issue is something that could be looked at in greater detail to try to increase the relevance of these animal models.

Markus Wagner in Ulrich Koszinowski's lab some years ago used BAC technology to make a chimeric virus expressing the human cytomegalovirus UL97 gene in the context of the mouse CMV genome. Alistair McGregor, in our group in Minnesota, took this work and applied it to the guinea pig model and ended up with a result that actually was medically and biologically relevant, the idea of making a chimeric virus that's more human in nature. So in this experiment we've inserted the UL97 gene from human cytomegalovirus into the guinea pig CMV genome using BAC technology.

Guinea pig cytomegalovirus is intrinsically highly resistant to ganciclovir, but this mutation of conferred ganciclovir resistance excuse me, a susceptibility to the guinea pig virus, and that, in

turn, has allowed us to do some in vivo modeling of ganciclovir therapy in guinea pigs. And this is just the Western blot confirmation using a monoclonal antibody from Don Coen demonstrating that the recombinant virus did express human UL97.

And so I think humanizing CMV to express relevant vaccine targets is one area for future development. We've applied this to glycoprotein B and made a chimeric virus which unfortunately is insufficiently virulent to cause disease in animals, and so we're trying to refine that by looking at key domains of gB in recombinant cytomegaloviruses.

Another technique that makes an animal model more human, if you will, was described by Raj Khanna and colleagues in which they used human gB vaccines with a variety of adjuvants, immunized mice, and then challenged with the recombinant vaccinia virus encoding gB and assessed viral load, in this case, vaccinia viral load, and demonstrated that human gB vaccine did reduce viral load with this recombinant vaccinia challenge.

So arguably that's one step removed from the

biology of CMV, in particular, congenital CMV, but I think it's another interesting way to make these animal models more humanly relevant.

Animal models that have been used through the study of CMV pathogenesis, particularly congenital CMV, are summarized in this slide.

One interesting model is that of porcine CMV. Edington, at the Royal Veterinary College in London, in 1988 actually did an interesting experiment in which he infected, reinfected, sows that were already porcine CMV seropositive and demonstrated a reinfection and congenital transmission rate in those fetuses of about 33 percent, and, in fact, there is a disease phenotype in newborn pigs associated with porcine CMV, so that's a model that perhaps hasn't been developed well enough.

I'm not aware of much in the way of vaccine studies, if any, with rat CMV, but there are studies looking at murine, guinea pig, and rhesus macaque CMV, and I'll briefly review those in the next few minutes.

When looking at these animal models, I think these are some of the key questions. What patient population am I going to recapitulate in this vaccine

model? And we've already heard information today from Dr. Plotkin about the relative role of vaccines in immunocompromised or transplant populations versus vaccines for targeting prevention of congenital infection, and these different models may have different strengths for those various patient populations. Are the key immunologic targets conserved? This is a much easier issue with things like conserved envelope glycoproteins, which seem to be important targets of immunity for all of the animal cytomegaloviruses, a little less clear for cell-mediated immune targets, which might vary from one species to another. And then is humoral or cell-mediated immunity the effector of protection?

So to reflect a little bit on mouse cytomegalovirus vaccine studies, one early study looked at a formalin-inactivated vaccine which was found to protect against mortality but not infection in the lethal challenge model. There have been passive immunoglobulin studies. Again, these protected against lethal challenge but not infection, which I think is interesting to reflect on particularly in light of the

data that Maria Grazia shared with us a few minutes ago.

More recently, Bill Britt and Stipan Jonjic, Russell Bradford, and others have developed a very elegant model to look at neuropathology in neonatal mice infected with murine CMV and shown that neural pathology can be attenuated by polyclonal as well as gB-specific antibodies, and I think it's of interest to reflect on whether or not that model could be tweaked to look at vaccines prior to delivery of these mice with an eye toward passive antibody protecting the fetus or the newborn mice. And then to underscore the role of cell-mediated immunity, Matthias Reddehase showed some number of years ago that adoptive cellular immunotherapy was protective in an interstitial pneumonitis model.

Other studies in mouse CMV looked at live, attenuated vaccines, including a series of papers of temperature-sensitive mutants by Sweet and colleagues. More recently, the actual attenuated mutations in these TS mutants are beginning to be mapped and identified, and so I think it will be interesting now with more

modern molecular biology techniques to try to understand what the temperature-sensitive mutations were that conferred attenuation in these experiments.

And then an interesting paper from MacDonald and colleagues with a mouse CMV mutant called RV7. This particular mutant had a deletion in the M137/M141 region, 7.7 kb, and this was actually a quite effective vaccine. Protection seemed to be most importantly mediated by CD8+ cells because protection was retained in B-cell deficient mice that were vaccinated, but depletion of CD8+'s remove the protection.

In the discussion on this paper, the authors commented that the lack of establishment of latency was an attractive feature in this particular vaccine, and I'll come back to that point in a moment.

There have also been subunit vaccine studies with recombinant vaccinia viruses expressing gB, gH, and lethal challenge models from Rapp and Koszinowski's lab; Shanley and Wu, recombinant adenoviruses expressing MCMV gB and gH. And although these vaccines do provide some protection against lethal challenge, particularly in the Rapp papers, protection against

infection was non-sterilizing in nature, so you could get reductions in viral load, but not sterilizing immunity.

And then a series of papers from Debbie Spector and Chris Morello looking at a variety of DNA vaccines in mouse cytomegalovirus including a very striking result in which sterilizing immunity could be induced by prime/boost combinations of plasmid DNA and formalin-inactivated MCMV. And Chris Morello is currently looking at this also in the guinea pig model.

Well, I want to reflect on this quote from the transcript from the FDA VRBPAC hearings in 1999 when the Towne-Toledo chimera vaccines were originally being considered for a Phase I study in seropositives, and I think it's an interesting quote. If we had all the information that we had about T cell responses, B cell responses, memory, and knew about the virulence genes in these viruses, then we could construct a virus, a new virus, that would retain those antigens that we need and delete those virulence factors that we don't need, and this was really a very prescient, I think, reflection by this committee member in these

hearings, and Koszinowski and colleagues did exactly that. They used BAC technology to generate a number of optimized live, attenuated vaccine candidates, including one that deleted large blocks of immunomodulatory genes. This vaccine was highly attenuated but very protective as was a spread-deficient mutant with a mutation in M94.

More recently, work by Stipan Jonjic and colleagues has looked at, I think, a very novel approach to recombinant mouse CMV vaccine using MCMV engineered to express a high affinity ligand for NK-activating receptor NKG2D, and this ligand, RAE1 gamma, was cloned into the MCMV genome.Here you can see a figure summarizing this study. This is wild-type MCMV encoding gene products that are important NK cell inhibition. By cloning in extra copies of RAE1 gamma, NK cell activation could occur with increased viral clearance, a robust immune response, minimal viral replication in vivo, and protection of these mice against challenge with virulent salivary gland-adapted virus.

Now, the discussion in this paper reflected

on the fact that the establishment of latency was demonstrable, and that was a good thing, that there may, in fact, be a boosting that could occur if the vaccine virus was latent, a little bit of a different conclusion or reflection than the MacDonald paper, and I think that's an important question; if live, attenuated vaccine models move forward in animals, to really drill down on this issue of safety, the issue of whether or not establishment of latency is going to lead to long-term deleterious consequences because, of course, that's a huge issue from a human vaccine regulatory perspective.

So I think the mouse CMV model has, in vaccine studies, told us that humoral immunity induced by either passive or active immunization appears to attenuate disease but not prevent infection. In cell-mediated immunity, particularly CD8+ T cells may play a more important role in sterilizing immunity or more robust protection, and that BAC-engineered live, attenuated vaccines that overcome viral evasion of innate responses may be a very compelling strategy for further study.

Now, a number of heroic efforts in the '60s and '70s to try to get mouse cytomegalovirus to transfer to the fetus were all unsuccessful, and this lack of fetal infection is an important shortcoming of the mouse CMV model, the mouse placenta, a hemodichorial placenta, different in histology and function than the human placenta. This may be an issue that contributes to the lack of infection. But we really have a difficult time modeling congenital infection in the murine model.

And so here is where the guinea pig cytomegalovirus becomes very useful. Here is a number of pups with intrauterine growth retardation and mortality either in utero or early after birth due to overwhelming viral infection. The guinea pig placenta, similar in histology to the human placenta, and here is a control placenta and a CMV-infected placenta from a guinea pig showing a leukocytic infiltrate. And so this model has been used extensively for a vaccine study. Live, attenuated vaccines and envelope antigen vaccines in the early '80s showed some degree of efficacy. Immunoaffinity-purified native glycoprotein

vaccines were quite protective in this model, as was passive transfer of antibody, although I will note that in the Bratcher paper, although passive transfer of antibody was protective against disease, particularly mortality, it was not protective against infection, and that, I think, is interesting to put into context in light of the data that we just heard from Maria Grazia.

We have looked at subunit vaccines, in particular, a truncated secreted form of the guinea pig homologue of glycoprotein B in this model. Immunization, mating, third trimester challenge, and then looking at pup mortality, maternal viral load, and infection rates is the basic strategy.

We do see high ELISA and neutralizing antibody titers, but one thing that's been quite reproducible, even though we see dramatic impact on pup mortality in this model, the magnitude of viral load reduction is at best modest. We've looked at a variety of antigens, a variety of adjuvants, a variety of expression strategies, but by and large, we typically won't see more than about a one to one-and-a-half-fold reduction in the magnitude of maternal DNAemia. So,

again, we have a situation in which antibody, although protective against disease, has at best a modest influence on maternal viral load.

To try to look at and compare to live, attenuated vaccine strategies in more detail, we looked with Mike McVoy in this collaboration at a number of MHC class I homologues encoded in the guinea pig CMV genome, and this is just the Southern blot confirming the deletion of these three genes, these three class I genes. This deletion resulted in a virus that replicated efficiently in cell culture but was very highly attenuated in animals with essentially avirulent with minimal, if any, viral replication.

In spite of that, immunization of guinea pigs with this vaccine candidate induced high ELISA titers and neutralizing titers and conferred an additional log or two of reduction of DNAemia in dams compared to the adjuvanted glycoprotein approach. And so this is an area, I think, for further study in the animal model. It is inferred, although we don't have direct evidence yet, that these MHC class I homologues may play a role in NK cell evasion as well, again analogous with the

work from Jonjic and colleagues in the MCMV model.

So humoral immunity in the guinea pig model induced by passive or active immunization, again, attenuates disease, but it's not clear whether or not this can be a sterilizing immunity preventing infection. A marker of protection of the fetus is reduction in maternal viremia. So I think it is possible to define a critical viral load threshold below which these pups are at least protected against mortality. Sterilizing immunity to date has been difficult to achieve, and I think the potential for live, attenuated vaccines may be greater than for subunit vaccines in this model.

It's not clear if the benefits of maternal vaccination are in the maternal versus the placental versus the fetal compartment. We need more information on that. And I think this is the most important limitation to date in these studies, which is that these endpoints may not be highly relevant to CMV disease in infants. We challenge these animals with large amounts of salivary gland-adapted virus to a degree that can produce substantial pup and sometimes

maternal mortality, but the more subtle endpoints of neural development sequelae, sensorineural hearing loss, have not been well studied in a vaccine experiment in guinea pigs, and that's an area for future work. The role of mucosal immunity and inoculation remains incompletely defined, as do the cell-mediated immune targets.

I won't say much about rhesus CMV because Bill Britt reviewed what I think is very important information from Klaus Fruh and Lou Picker and others. I do want to reference some of the work of Peter Barry and colleagues in the rhesus CMV model. A major advance in this model has been the establishment of rhesus cytomegalovirus seronegative colonies in which to model these studies, a variety of DNA vaccine studies including prime/boost studies has shown variable effects on both systemic viral load as well as inflammation at the site of inoculation. In particular, in this paper by Abel in 2011, three out of six monkeys showed a 1-to-3 log reduction in magnitude of salivary shedding of rhesus CMV, and the interpretation in that paper was that that 50-percent

efficacy was very similar to the 50-percent efficacy that Bob Pass reported in the human clinical trial of gB. But, again, no sterilizing immunity in any of these vaccine studies to date.

One very provocative paper has looked at a really different approach to immunization, which is to make inactive mutated proteins based on the rhesus cytomegalovirus IL10 homologue. Immunization with these then induces antibodies that inactivate the activity of the wild-type IL10, and it is inferred then that by neutralizing IL10 encoded by the rhesus CMV, you might get better immune responses with primary infection. So I think that's a novel and interesting approach to vaccination.

The paper by Hansen has already been referenced, and I think this is tremendously important since rhesus cytomegalovirus is the closest relative to human CMV and since reinfection seems to be a very predominant feature in this model. I hope that in further discussions in this conference over the next 2 days we can come to some consensus on this issue that came up this morning in the panel discussion on what

can we do to improve on natural immunity? Is there a way to make a vaccine that's actually better than natural immunity?

And so this is my last slide. Animal models demonstrate some role for antibody in reduction of viral replication and viral load but a substantial role for attenuation and reduction of disease.

Live, attenuated vaccines are highly effective, and BAC engineering, a very powerful tool through deletion or modification of immune modulation genes.

I lied, this is my last slide. Can we humanize the virus, humanize the animal? We need more emphasis on long-term safety questions in animal models, particularly looking at this increasing body of knowledge about the long-term all cause mortality risk being CMV seropositive. I like this idea of vaccines that target not just viral gene products but viral immunomodulation proteins, increased attention to routes of challenge, innate responses, and more subtle and important and clinically relevant neurodevelopmental outcomes, and strategies in animal

models to deal with the issue of strain variation and reinfection.

Thank you.

(Applause.)

DR. MOCARSKI: So largely due to my own poor control of time, we really have run right up against the next session, and so I think I've gotten the

DR. KRAUSE: No, what I would say, let's have a panel discussion for 10 to 15 minutes.

DR. MOCARSKI: Okay.

DR. KRAUSE: We'll start the next session perhaps 10 minutes late

DR. MOCARSKI: Okay, so can I take it

DR. KRAUSE: 5 minutes from perhaps

DR. MOCARSKI:I misunderstood. Okay.

DR. KRAUSE: Right. Okay. All right.

(Laughter.)

DR. KRAUSE: I imagine you should make Mark sit down.

DR. MOCARSKI: Okay. So all the members who spoke, Mark, Bill.

FEMALE SPEAKER: I share the blame with you

for being late.

DR. MOCARSKI: So the panel is open for discussion and questions.Yes. And please say who you are.

DR. HARPAZ: Rafael Harpaz, CDC. So we haven't heard that much this morning regarding reactivation, and, in particular, whether exposure to CMV boosts immunity and could reduce the amount of reactivation. And let me just give context for the question. Consider a country like Brazil, with 96-percent seroprevalence, and the burden of infection there is largely due to some mix between reactivation and reinfection, and if you reduce the force of infection through vaccination, you're going to get rid of all that reinfection and as well as primary infection, but you might theoretically cause a boost in the reactivation and paradoxically lead to an increase in the burden of infections rather than a decrease. So I'm wondering if anyone could say whatever, anything, to kind of counter that possible scenario.

DR. BRITT: It's a possible scenario, but I don't know that you have, I have, or anyone in this

room has evidence for this reactivation that you're talking about.

DR. HARPAZ: I know, but it's

DR. BRITT: I mean, of course, the problem is the biology of CMV, and I think there are some people in the room who would agree with me, and probably others would argue with me, but, you know, it's a combination of a persistent it's a persistent infection at that, and we don't really know the contribution of reactivation from latency versus chronic low-level production in different compartments of the body. So the question is, if you had a vaccine that would eliminate reinfection, presumably a vaccine that would eliminate reinfection, potentially could eliminate the consequences of low-level reactivation, the consequences being that the virus would reactivate at some compartment and would have to move to another compartment to infect the fetus or the placenta. I mean, that's how I would possibly

DR. HARPAZ: I agree. Just I work on VZV and the impact of or sell a vaccine on shingles reactivation and so on and so forth, but I think that

your point is exactly right, that any vaccine trial needs to explicitly look at the impact on reactivation as well as on reinfection because otherwise you might end up with an effect like that.

DR. MOCARSKI: A side issue there is the detection of reactivation in healthy seropositives isn't a very easy process to address. Despite some very early literature suggesting CMV DNA was more or less readily detectible, that hasn't been the case in healthy seropositives. So it really does require very careful evaluation.

Debbie?

DR. SPECTOR: Actually, I want to take off on something that Stan pointed out, and that had to do with the difference between the MF59 gB and the GSK, where the length of the protection seemed to increase. And I want to bring up the point of that the adjuvant is going to be critical, and the key, as Mark showed, we get sterilizing immunity, the key to that is the adjuvant, and it's an MPL alum adjuvant, and the mechanism of this has actually been just written up in PNAS by Pippa Marrack and John Kappler, who showed that

what the combination is doing is allowing you both to get durable memory and they were doing CD8+ and CD4+ as well as converting it to a cytotoxic T cell. So it's just a point that sometimes looking at what you want to get in terms of durability, that going back and saying, well, these inactivated virus vaccines did not work, they didn't work, they were in PBS, we know that, we can do a comparison.

DR. MOCARSKI: Debbie, just to clarify, I think Sally will clarify the adjuvant is not an MPL alum.

DR. SPECTOR: It is a derivative of it.

DR. MOCARSKI: Let's let Sally clarify.

DR. MOSSMAN: That's right actually. I want to clarify on both fronts because Stanley described it as AS3, it's actually AS1 adjuvant, and the components in the adjuvant are MPL, yes, but also QS21, and there's no alum there, it's a liposomal formulation.

DR. SPECTOR: That's the MPL.

DR. BRITT: Just to add something to that, a long time ago, when QS21 was not part of GSK, we actually did a study with gB in QS21, and actually in

mice it induces CD8+, so chromium-release cyto -- (indiscernible).

DR. MOCARSKI: Ulrich, up in the back.

DR. KOSZINOWSKI: Ulrich Koszinowski, Munich.

DR. MOCARSKI: Please say your name and affiliation.

DR. KOSZINOWSKI: Is it working?

DR. MOCARSKI: You have to ...

DR. KOSZINOWSKI: Well, then I'll shout.

DR. MOCARSKI: Each one of the seats has a microphone, just push the button. Yeah. There you go.

DR. KOSZINOWSKI: Okay. I mean, I didn't want to close entirely the issue on

DR. MOCARSKI: Ulrich Koszinowski from

DR. KOSZINOWSKI: Ulrich Koszinowski, from Munich, Germany.

the issue of reactivation and superinfection. I mean, we have cloned many herpesviruses as BACs, and in all conditions, of course, there were always multiple strains, multiple strains, and we also had the case we published it recently where we, by error, we cloned a mutated version that we then later corrected

and went back to original sources, we found that under certain conditions even in vivo a mutated version, let's say, just a different version has a better chance to come up than under other conditions.

So if we see the situation in Brazil and having these multiple strains and finding in the pregnant women apparently different strains coming up, to me that would not entirely exclude it, that these persons had been infected by multiple strains in the first place. And in the second pregnancy, just another strain, for reasons we do not understand yet, makes a major impact, and we couldn't see it before.

DR. BRITT: I agree, but the question is to the immune system whether this is an exogenous new strain or an endogenous new strain may result in the same consequences.

DR. MOCARSKI: I tend to disagree, but I think it will come with whole genome sequencing clearly what's going on. I tend to think there are two categories here, one is strains which can be identified as strains that move around the population as well as strain diversity that gets generated in the infected

host, and I think the best example of that is when you compare populations of virus from different, very different, clinical settings, HIV versus congenitally transferred virus, you get the same distribution, they're just different in each individual largely. So there's a level, just as with other viruses that vary take flu or HIV there are different strains, and there is also strain variation, and they're distinct.

Yes, Stu.

DR. ADLER: Yeah, just a comment for clarification. Clearly, being seropositive is protective against reinfection, Stan first showed that, but the protection is not 100 percent, it's going to vary depending on the frequency of challenge, the root of challenge, and the mode of transmission, and maybe immunological factors. As I'm going to show you tomorrow, for our day care center moms, we had about 93 percent protection. If we go to a different population and a different study design, you'll find protection against reinfection, but that rate will vary from population to population and study group, but I don't think we want to lose sight of the fact that being

seropositive does protect against reinfection, it's the rate in various populations that's going to change.

DR. SCHLEISS: But isn't it true, Stuart, that the biggest burden of congenital CMV economically, at a societal level, remains in those women that are reinfected in pregnancy? So in the context of these discussions about vaccination, I think it's still critical. Your statement is true, but we still have this problem with

DR. ADLER: I think you're correct if you look at the numbers of congenital infections, but whether the disease burden matches the primary infection, I think that's an issue that's still on the table.

DR. BRITT: I think that is an issue on the table because I think there is so much referral bias that's been placed into the data. If you look at the data that Mike Cannon published in a review article, there were about 450 cases that I think were included in that review in Medical Virology, and in many of those and they tried to sort through the series that did not have referral bias, but even the series that

they did, there clearly is referral bias there. I mean, I hate to say that our field would undergo the same problems that the people that worked on HCV did in the early '90s.

DR. MOCARSKI: Just so that's properly attributed, that was Stuart Adler, from Virginia.

Yes, Laura.

DR. GIBSON: Laura Gibson, University of Massachusetts. Mark, if you said this and maybe I missed it, Mark in an animal model, is there a model of a vaccine given to a pregnant animal that provides protection that transfers into the fetus? Because, in theory, you know, could we make a vaccine given to pregnant seronegative women that actually induces protective responses in the fetus?

DR. SCHLEISS: Well, I assume you mean something other than immunoglobulin, which is

DR. GIBSON: Yes.

DR. SCHLEISS:I guess, vaccination but passive immunization. Yeah, I

DR. GIBSON: Cell-mediated immunity or antibody generated in the fetus.

DR. SCHLEISS: Yeah, I've never tried those experiments. I think there is such a bias against giving a vaccine to a pregnant woman in general, it might be difficult to move that forward in the clinic, but it's an interesting idea, active immunization in a woman who has an infected fetus or who's at high risk. I'm unaware of any information in animal models.

DR. MOCARSKI: Sally?

DR. MOSSMAN: I think one potential issue with that strategy would be the timing so that the time it takes to induce a high-avidity antibody response and you saw in the data from GSK that Stanley presented that it takes those three doses to induce that response, so I think timing may be an issue with that strategy.

DR. MOCARSKI: Thank you, Sally, from GSK.

Bob Pass.

DR. PASS: Bob Pass, Birmingham, Alabama. Just a comment about the disease burden. Both of the slides that showed similar disease burden for babies born to mothers with primary infection during pregnancy and babies born to mothers who were immune prior to

pregnancy showed a substantial increase in disease burden in those with primary infection when you look at significant hearing loss that is, hearing loss likely to produce disability there was a clear difference between the groups from both places.

And then one question I wanted to ask Professor Revello regarding the Cytotect study and I think you were so pressed for time, the slides went by so fast, I missed it. Did you give information on difference in virology between the treatment and placebo groups? Was there any difference in quantity of virus in blood or in peripheral secretions?

DR. REVELLO: Unfortunately, the only result singular that I had was relevant to the incidence of transmission in the two arms. I have no additional data at this very moment.

DR. PASS: Okay.

DR. MOCARSKI: I think we've just been given the signal to move to the next session, and so, Stanley, I think I'll turn it over to you.

DR. PLOTKIN: All right. Well, so we are now going to talk about regulatory considerations and

manufacturers' considerations, and I am going to ask at least four of the manufacturers to give us very brief statements about their concerns and what they would like to see from the regulatory point of view come out as a result of this meeting. So where are the would the manufacturers come forward?

DR. MOCARSKI: Stan, I think we're going to start with Phil before lunch.

DR. PLOTKIN: Oh, I'm sorry. You're right. I beg your pardon, Phil.

(Laughter.)

DR. KRAUSE: That's quite all right.

DR. PLOTKIN: You have the first word.

DR. KRAUSE: Peter and I will give regulatory policy.

DR. PLOTKIN: Okay. Sorry.

DR. KRAUSE: And we'll have time for questions after that, and then we'll have the manufacturers session.

DR. PLOTKIN: Okay.

DR. KRAUSE: Which we may lose 5 minutes depending on where we stand.

MALE SPEAKER: Switch on because they're not on.

DR. KRAUSE: Can you hear me now? Okay.

So I'm here to discuss U.S. regulatory perspectives that may be relevant to CMV vaccines. So the most important regulatory perspective that I can give you is that regulatory decision-making on regulatory decisions are made based on the regulations, the underlying science, and the data that is provided in support of the application. And really the underlying science is the most important pillar of that, and as our understanding of that underlying science evolves, then the way we may look at a regulatory decision may also change, but one of the things that is critical about this meeting is that we have a very large array of experts on cytomegalovirus here who can really review the underlying science for us, and so we're learning from this meeting as well and hope to be able to use the summary of where we stand to support future regulatory decision-making as well. So this is a very important meeting for us.

So how do we approve a vaccine? Well,

vaccines are approved based on various regulations and laws, but basically a manufacturer has to show that they're safe, which means relatively free from harmful effects when prudently administered, that they're pure, which means relative freedom from extraneous matter, and potent, which is the specific ability the product will effect a given result. And then the manufacturing facility, of course, has to meet standards designed to ensure continued safety, purity, and potency. But only those vaccines that are demonstrated then to be safe and effective and that can be manufactured in a consistent manner can be licensed by the FDA.

So let's drill down a little bit and think about vaccine efficacy. And there really are three major regulatory pathways that can be used to demonstrate vaccine efficacy, and those we refer to as traditional approval, accelerated approval, and the animal rule. Now, the animal rule isn't relevant to CMV vaccine evaluation for two reasons, the main one is it's only applicable if there is no way to study the vaccine in people, and, of course, there is. And, of course, in CMV, we have the double whammy that there is

no good animal model for human cytomegalovirus.

Now, of course, for each of these regulatory pathways, safety has to be demonstrated also, but the major difference between these pathways comes in how it is that efficacy is demonstrated, and so I just wanted to go into that in a little more detail.

In a traditional vaccine approval, the approval, as is the case with an accelerated approval, is based on randomized, well-controlled trials. The endpoints have to be clinically relevant. Importance of specificity of case definitions is emphasized, and endpoints are usually clinical efficacy or effectiveness endpoints, but it's important to note that a laboratory determination that is expected to predict clinical benefit may also be used in a traditional approval, but it has to be expected to predict clinical benefit.

In an accelerated approval, the product is eligible to provide meaningful therapeutic benefit over the existing treatments for serious or life-threatening disease, but efficacy is based on a surrogate endpoint that is reasonably likely to predict clinical benefit.

So the fundamental difference in how we might look at a surrogate endpoint or a correlate of protection between a traditional approval and an accelerated approval comes down to a determination of how likely it is that that surrogate marker predicts clinical benefit. It has to be expected to in the traditional approval, but only reasonably likely in the accelerated approval. And if a product is approved under the accelerated approval regulations, a confirmatory post-marketing study to verify clinical benefit is required, and in general, it's expected that that study is underway at the time of licensure.

So there are several examples, recent examples, of accelerated approvals, including new seasonal influenza vaccines that have been approved since 2005, which have more than doubled the number of licensed influenza vaccines, and increased capacity for pandemic preparedness, and, in fact, just earlier, or towards the end of last year or was it this year? just recently we licensed Prevnar 13 at the very end of last year for adults age 50 and up under the accelerated approval regulations.

So these examples, these recent examples, of licensure under the accelerated approval regulations have involved immunogenicity endpoints as the surrogate endpoints reasonably likely to predict clinical benefit, but there is no regulatory requirement that that endpoint be an immunogenicity endpoint, it could also be some other endpoint that's reasonably likely to predict clinical benefit, and that might be something worth thinking about as we consider some potential pathways for CMV vaccine licensure.

So obviously correlates of protection are very important because they can play an important role both in the traditional approval and the accelerated approval, and so we study correlates of protection because we have an interest in determining if a particular type and quantity of immune response is associated with protection from disease or infection caused by fully virulent pathogens.

Sometimes we identify that immune correlate of protection from a successful efficacy trial because you can look and see who was protected and who wasn't and figure out what immune measures distinguish those

who were protected and those who weren't, but correlates can also be suggested from other sources; for instance, post-infection immunity.

Immune correlates thus are useful for interpreting trials with immune response endpoints, and although an immune correlate isn't required for licensure, it certainly is very useful, as I have just shown.

Now, we can also use immune correlates as well as other laboratory studies to do clinical bridging, which is an important thing to consider in vaccine development. The clinical bridging study is one in which a parameter of interest for instance, a population, a subpopulation, manufacturing scale, a formulation, or dosing schedule is directly compared with a different version of that parameter, and the purpose then is to determine the effect of changes on the product's clinical performance. And clinical bridging studies are used for the same product, not to compare different products.

So an endpoint that is used for a clinical bridging study does not necessarily have to be a

correlate of protection, but it should be something that is reasonably believed to correlate with vaccine effect.

So for a vaccine like one against CMV, one might consider the need to demonstrate vaccine benefit in various subpopulations, and as we go through different subpopulations in whom a vaccine might be useful in sessions three and four of this meeting for congenital CMV, one might consider the potential that there could be different vaccine responses in different subgroups, and if that's the case, though, one would want to know that the vaccine is efficacious or that it will work in each of those subgroups, and immunogenicity measurements may be useful in bridging then between age groups or subpopulations.

And then, as well, just a side note, or not a side note, but also a critical point, is that for any vaccine that's licensed, the Pediatric Research Equity Act requires evaluation of new products in pediatric populations unless there's a basis for a waiver.

Okay, so we've gone over efficacy and laboratory tests that can be used to study efficacy, so

I'm just going to say a few words about vaccine safety databases at the time of licensure. So, as I said before, safety database sizes are independent of the mechanism that's used to show efficacy or effectiveness. Typically, efficacy studies, however, have driven pre-licensure vaccine safety database sizes, as long as there are sufficient subjects in a study to detect adverse events, at a rate of around 1 in 1,000. So that typically means that we would like to see at least around 3,000 people in a vaccine safety database at the time of licensure, and for many vaccines, it's in the three to five thousand person range.

What I've graphed here and I don't have the names of the vaccines on them, but it actually shows the safety databases at the time of licensure for a variety of different vaccines over the last 20 years, and I'm not sure I know how to use this laser pointer but for the peaks here, these are actually the two most there it is, very light green, the two most recent ones, these are rotavirus vaccines, RotaTeq and Rotarix here, and in those cases, in fact, safety

considerations, the need to look at intussusception rates was a driver for the study sizes, but for other ones where you see the numbers peaking up higher here for instance, Zostavax is here, this is Prevnar 7, and this one is Infanrix, and this Havrix these were all driven by the need to perform fairly sizeable studies to establish the efficacy of the vaccines.

So if we do our studies at the time of licensure and can identify adverse events at a rate of around 1 in 1,000, then, of course, we would like to further characterize adverse events and get a better picture of vaccine safety, but typically that's done in post-licensure studies, and that's a whole additional talk of exactly how those post-licensure studies are done, but there is a lot of very exciting information about how the databases which can be used to look at vaccine post-licensure safety are being expanded.

And, in fact, to give you an idea, the expansion under those databases and the ability to look at them in the context, for instance, of the H1N1 pandemic influenza actually involved looking at close to 100 million U.S. citizens. Of course, not all got

the vaccine, but data from those people were covered in those databases, and so there are really very exciting advances in being able to look at vaccine safety that have come up recently and will continue to evolve.

I wanted to say a few words about live virus vaccines because they have played an important role in our thinking about CMV and we have learned a lot from them, and one of the previous speakers mentioned that the live, attenuated CMV Toledo-Towne chimeric vaccines were discussed at a vaccines-related biological products advisory committee meeting in November 1999. Key discussion items there included the demonstration of attenuation including and certainly regarding how much attenuation would be needed, potential for shedding, and potential risks associated with transmission to individuals not participating in the study, potential lifelong effects from a vaccine that establishes latency and could reactivate, as well as uncertainty regarding clinical disease associated with CMV, and potential long-term sequelae of vaccination.

And so these were all issues that were discussed, but I don't think that these are

insurmountable issues in the context of live, attenuated CMV virus vaccine because, in fact, similar issues have been considered in the context of other recently licensed live, attenuated vaccines, including the three varicella-zoster virus-containing vaccines Varivax, ProQuad, and Zostavax and, of course, VZV does establish latency and can reactivate. And, of course, in all of these cases, one has to be concerned, or at least has to evaluate the potential for viral shedding. FluMist is a nasal vaccine, certainly viral shedding was something that was evaluated and considered. And RotaTeq and Rotarix, as oral vaccines, had the potential for viral shedding as well.

A couple words to be said about adjuvanted vaccines given the difficult of achieving good immune responses and the potential need for CMV to achieve better immune responses than one might for some other pathogens, and I think the difficulty in reaching a vaccine candidate that is clearly effective suggests that stronger immune responses may be needed than in earlier generations of vaccines. And so adjuvants may enable generation of immune responses that are

sufficient to control CMV infection.

There actually was a workshop in December 2008 sponsored by FDA and NIH on adjuvants and adjuvanted preventive and therapeutic vaccines, and scientific issues were discussed then, and the minutes of that meeting and summaries are available on the internet.

There should be a scientific rationale for including an adjuvant in a product, and the potential for adjuvants to cause potential safety concerns has certainly been widely discussed, although it's hard to know exactly what the reality there is, but issues for consideration in clinical trial design for novel adjuvanted vaccines could include longer follow-up than is typical for non-adjuvanted vaccines, although for a vaccine where you have to follow patients for a reasonable period of time in order to establish efficacy, you may have that follow-up anyway; examination for potential autoimmune-related adverse events; and the potential for other inflammatory mediator-related events.

But Cervarix, of course, was licensed in

2009, contains a novel adjuvant, ASO4, which is a combination of alum and monophosphoryl lipid A, and other novel adjuvanted vaccines are developed in the U.S. also, so that need to include an adjuvant in a CMV vaccine certainly is not an obstacle to development.

I wanted to just briefly mention a few special regulatory options that other members of the organizing committee wanted me to mention.

The Orphan Drug Act with orphan drug designation, it allows for some exclusivity for a drug that's approved unless a competitor is shown to be better than it, and also provides for some grants to aid in development, and, in fact, there are a couple of herpesvirus vaccines that are currently designated under the Orphan Drug Act, including some Vical DNA vaccines as well as an EBV gp350 vaccine.

Fast track and priority review are both used in cases where there is an unmet medical need for a serious disease, and these are somewhat subjective terms, but under fast track, there is additional communication with the FDA as well as the potential for moving towards approval on the basis of a surrogate

marker earlier than what otherwise might, and under priority review, the regulatory timelines once the license has been submitted are shortened.

So just to summarize, as I see, key regulatory challenges for CMV vaccines, well, some of them we'll discuss at this meeting and we'll rely on what we hear the experts here say, identifying appropriate endpoints for Phase III studies, and, of course, that will be discussed in sessions four and five. Assuming efficacy can be shown in one population, what data could support bridging to additional populations? Development of surrogate markers of protection, potentially useful for assessing duration of effect, the need for revaccination, bridging between vaccine formulations, and bridging across age groups, as well as surrogate markers being useful in early stage evaluation of vaccine candidates by manufacturers.

And then, of course, there are some issues associated with immunizing pregnant women either as a target population or inadvertently, and Dr. Roberts, from FDA, will give a talk on that in session three.

So thank you very much. And I'm happy to take a few questions, assuming I'm not over time yet.

(Applause.)

DR. PLOTKIN: Thank you, Phil. Shall we leave the discussion until after lunch since we're having a roundtable?

DR. KRAUSE: So Pieter and I can sit in on the roundtable, or we can separate the manufacturers out. We can do that either way.

DR. PLOTKIN: Yeah, I think you should sit in.

DR. KRAUSE: Okay. All right. Sounds good.

DR. PLOTKIN: So Pieter Neels will speak for the EMA.

DR. NEELS: Okay. Good morning, everybody. I thank the organizers to have invited me and to give the European perspective on the regulatory affairs in CMV vaccines. I'm sorry to be the last person between you and your lunch, but I'll try to do it as fast as possible.

I'm here with a mandate from the CHMP and the EMA, but although I have this mandate, I'm not sure,

due to the fact that we are lacking guidelines, official adopted guidelines, on CMV, that everybody will agree on what I say, and certainly later on in the discussion I could give sometimes my personal view.

Having said this, listening to what Phil has told us, I realized that I forgot to mention a few slides, so I will start with two issues that he elaborated. The first one is on adjuvants. Indeed, we have in the EU licensed a few more vaccines with adjuvants, and maybe we have a little bit hangover on one of them. It has been licensed during the pandemic, it was Pandemrix, which is a GSK pandemic flu, which contains ASO3, and it has been extensively used.

And we realized, due to the pharmacovigilence in the pandemic period that we've seen a relationship, maybe it's purely epidemic relationship, but there is narcolepsy in 100 children that has been vaccinated with Pandemrix. Whether this has to do with ASO3, whether this has to do with the fact that these children were vaccinated very close relation to the spread of the wild virus we don't know, but this is an issue that is living in the EU. And, thus, if you will

come with a new adjuvanted vaccine, your database will be looked at very carefully.

Another topic that I forgot to mention is conditional and accelerated approval. Yes, of course we have guidelines, procedures for this, but we are not very fond of it, and I wish you good luck if you want to go for an accelerated approval, and if you want to go for a conditional one, it's the same issue.

So if you want to find some guidelines on the vaccine registration, it is on this website, and you can find this guideline, which gives you a rough idea on what you need to submit on vaccines.

This is another simplification, provided that your quality is okay, there is benefit balance of a new vaccine that is based on four pillars. This is simplification because any quality issue is, of course, related to a nonclinical issue to clinical issue and to the post-marketing as well.

So in pre-registration we have studies in the animal model. We would like to see the pharmacology and approve of concept and toxicology, and, of course, reprotox if you claim to have women of childbearing

age, and I said before inadvertently, we would like to see what is preclinical risk.

Then we have clinical data from clinical trials, comparative trials versus placebo, or active controlled trials, but real placebo controlled trials is rather difficult, as you know. It is ethically not easy to defend in vaccinology and most often another existing well-known vaccine is used as a comparator. In the post-registration, we need to have data on your risk management plan. We need -- this plan has to be approved at the time of registration, and it is based on two pillars: which are the risks and how you would like to avoid these risks or minimize the risks. And then the last pillar is the pharmaco- or the vaccino-vigilance, the organization of the reporting of spontaneous adverse events with analysis and interpretation and implementation of corrective actions.

This is the theoretical part. So vaccines, it is prevention of disease, so in a best case scenario, we would like to see clinical data randomized, double-blind, placebo-controlled supporting

the applicant's claim, prevention of clinical disease of at least clinical significant reduction of disease burden.

Unfortunately, we are not living in an ideal world, and due to a low incidence of disease, no clinical outcome data are not always feasible. Ethical aspects on the use of placebo is also coming up in the EU more than in the U.S., I suppose, and so placebo-controlled trials are difficult to accept.

Do we have surrogate markers for protection? And mostly, they are not available in early development of a vaccine.

What do you have to do if you can't do this? So I would say come and visit the regulatory authorities at an early stage of your development, the earlier the better, and no ostrich policy. And in this sense, we don't have an I&D process in the EU, but you are invited to come for scientific advice, but not forget, another slide I forgot, the Paediatric Investigational Plan. The Paediatric Investigational Plan has to be submitted at the EMA after your Phase I, and this will include your full development plan, in

adults, in adolescents, and kids and infants and prematures. And you will have to be very detailed in that one. So maybe within a few years you don't need scientific advice, you just need an approval of your Paediatric Investigational Plan.

What is the magnitude of the database? As said by Phil, we need to have at least 3,000, but it will depend on what indication you are seeking, and it might be that we will be able to accept a formal smaller database if you asked an orphan indication.

But don't forget this evaluation exercise is a balancing exercise on the benefit versus the risk, and the risks known and unknown. Severity of the disease, life-threatening or not, unmet medical needs, incidences and prevalence of the disease, and this versus a severe or life-threatening adverse event, concerns from animal data, but not concerns in humans, or occurrence of one or two very extreme rare events like Kawasaki syndrome or a narcolepsy case in your active group. How are we going to deal with this in the risk/benefit?

This slide I can skip because I learned much

more about it this morning.

We are dealing with two, I think, major indications. We have the congenital CMV and we have the immunocompromised like the transplant patients, and in the transplant patients we have roughly two groups, the HCT, the hematopoietic cell transplant, versus the solid organ transplant.

How are we going to prevent CMV infection in utero? It has been discussed this morning vaccination of the pregnant women first trimester but probably very difficult strategy because you need two or three injections. How to perform clinical trials in pregnant women? It might be possible to do that with inactivated proteins or polysaccharides. We have data for tetanus and pertussis, but how to do it with a live, attenuated vaccine?

To date, live, attenuated vaccines MMR as a relevant example are still contraindicated, not recommended, although thousands of pregnant women have been vaccinated with rubella vaccine, most of them inadvertently, and the data on outcomes have been published, and still more than 300 kids have born out

of seronegative, rubella-negative, women, and we still have recommendations and contraindications for these vaccines, which is for me, as an EU regulator, quite difficult because in some countries in the EU, if you have a contraindication, then pregnant women should get an abortion, which is not the recommendation.

How long is the follow-up needed? If a neonate has been born after a vaccination, is it one year? is it two years? or do we need five years? What psychomotor testing do we need to see whether the infant is normal? And are these tests validated?

Another element could be preconception consultation vaccination, but how feasible is it in the major parts of the world? How are you going to reach this target group? Because many women desiring a child don't seek advice before getting pregnant. And how to define the period between vaccination and conception?

What endpoints can be used? This has been already discussed in detail this morning.I don't think I can go into detail on that one.The same is true for the transplant patients. I think this is a very heterogeneous group. We all agree that HCT is not

the same as SOT. The level of immuno-depression is clearly not the same, so we will not be able to extrapolate from the one group to the other and vice versa. But what for the SOT, a solid organ? Is extrapolation from heart patients possible to kidney and liver or pancreas or lung? I'm not so sure. And donor versus recipient. Donor vaccination is an altruistic vaccination, and what is the benefit/risk balance for a seronegative graft to be vaccinated? What endpoints can be used in transplant patients? Again, we have to deal with very different situations: donor positive and recipient negative, and vice versa; or both negative; or both positive. Primary infection? And what about reinfection? Immunogenicity? Functional antibodies? Do we have sufficient standardization and validation to be convincing to the regulators?

So in conclusion, today we have no regulatory guidance written in stone for cytomegalovirus. Many questions are still open and need to be discussed. Which populations? Which populations we would start with? Discussions between stakeholders should be

encouraged, regulatory industry, and academia. More discussion would probably lead to more clear advises. And sorry that I can't give you more responses. We do not have them yet on the regulatory side.

Thank you for your attention.

(Applause.)

DR. PLOTKIN: Thank you. We'll have the discussion after lunch. And Phil has told me that if there is a crowd downstairs in this cafeteria, you may wish to go to the Natcher Building, which is the big white building out in the front entrance. It's a short walk. So you would have your choice of two places for lunch. What time should we come back?

DR. KRAUSE: In an hour, I think.

DR. PLOTKIN: So?

DR. KRAUSE: 1:45. Stanley, do you know if this room is secure? Can we leave our material in here, or do we have to take everything with us?

DR. PLOTKIN: The question is security. I suspect it's reasonably secure. I can ask at the front desk, but I don't know that there will be somebody standing guard.

(Lunch break.)

DR. PLOTKIN: Okay. Ladies and gentlemen, we're now going to have a foot race between the manufacturers. Each will have four minutes to tell us their concerns. So we'll start with Mark Feinberg from Merck.

DR. FEINBERG: Thanks very much, Stan. I want to thank Phil Krause and the meeting organizers for bringing all of us together today. I think it's going to be critically important if we're going to find a productive path forward to a CMV vaccine. And I also want to thank them for inviting manufacturers to share our perspectives with you.

You know, we feel that we are in this together, that success will only come from ways -- that we can find ways of working together effectively to address the current gaps in -- that are before us in developing a safe and effective cytomegalovirus vaccine. I'm going to share the perspectives from Merck but I wouldn't be too surprised if they're similar for the other vaccine developers as well.

Our desire is to meaningfully contribute to

the control of CMV disease. And we think the best way for us to do that is to develop a vaccine that would reduce the incidence of congenital CMV infection. We have explored a range of approaches, ranging from whole virus approaches to adjuvated subunit approaches. And we believe that there are biological promise for a number of opportunities in this area.

But moving forward, we would like clarity around a number of the issues that I'm going to be addressing today, in particular, for reasons of complexity and specificity, which you've heard a lot of information about in the earlier presentations today. Demonstration of prevention of congenital CMV disease is going to be very difficult in the context of a clinical trial setting and as such, acceptance of a congenital infection prevention endpoint, we believe, would enable vaccine development.

We also look forward to hearing the discussion about potential alternative endpoints that might be considered acceptable for regulatory approval, such as the prevention of acquired infection endpoint in women, which is the one targeted by Pass and

colleagues and their recent encouraging CMV vaccine studies.

When one is thinking about vaccine development, obviously you have to think about the population you're targeting. And one unique aspect -- well, not a unique aspect but a special aspect that we need to think about here is we're talking about administering a vaccine to one individual so that a second individual could be protected.

And while we all believe in herd immunity and we can cite the example of prevention of rubella infection according to the current approaches to vaccination, in CMV vaccine development in 2012, that may represent some unique challenges for us and we need to consider those.

You know, clearly, we also need to think about the population for vaccine development to consider what would be the optimal population to have the greatest impact on congenital infection and disease, and from a programmatic perspective, what would be the best approach for an immunization program policy to guide most effective public health outcomes.

You know, it clearly has been alluded to but I just want to reinforce again the need for clear and specific case definitions we believe to be of fundamental importance. And ideally, these definitions would serve across the field and at different stages of this scientific characterization, from epidemiologic and natural history studies to studies of clinical efficacy trials and other outcome studies.

For successful vaccine development for and commercialization of a cytomegalovirus vaccine, you know, we believe that clinical trial endpoints are of fundamental importance. And these endpoints really need to serve a number of purposes.

You know, first they need to serve is the basis of licensure but they need to be done in such a way that -- defined in such a way that pivotal clinical trials and confirmatory observational studies are both technically and operationally feasible. And we know that this will be discussed in Section 4 later. My colleague, Dr. Paula Annunziato will share our perspectives on this.

We think that, you know, the -- addressing

these is going to be complicated. So it may well be that the establishment of creative public/private partnerships will be necessary to answer some of these key development questions, such as a predictor of congenital disease.

You know, clearly, the clinical trial endpoints you pick are going to be necessary to also convince regulatory and advisory organizations to recommend broad implementation in the target population and also be able to provide sufficient ground foundation for education of health care professionals and customers on the benefits of immunization in reducing the burden of congenital CMV.

With respect to specific questions we'd like to put before you, we would really like to know, will prevention of congenital infection be sufficient to support licensure with a congenital disease prevention indication? Secondly, will a safe and efficacious vaccine that demonstrates prevention of congenital infection garner a broad and strong ACIP recommendation for girls and women?

We also want to know what the drivers of

value are for the ACIP in terms of health, economic analysis and budge impact. You know, what are the policy recommendations, expectations for cost effectiveness and disease burden? What are the expectations and how do they vary according to population for vaccine implementation?

What sources of public financing might be available for adults who might be indicated to receive the vaccine but that are outside the scope of the Vaccines for Children Program? And lastly, how would the vaccine be handled in the National Vaccine Injury Compensation Program if the vaccine is indicated for women of childbearing age, but it really benefits the unvaccinated child who is not covered in the context of that program?

So desirable outcomes -- quickly to close -- would be a pathway for developing well-defined case definitions, such as congenital infection and congenital disease, and tools to allow their consistent use across a range of studies that I've referred to previously. Ideally, coming out of this meeting as well would be assignments of responsibilities and

development of partnership to address these key gaps, particularly the link between congenital infection and congenital disease, and concurrence that prevention of congenital infection would be sufficient for a licensure and favorable ACIP recommendation. Thank you very much.

DR. PLOTKIN: Thank you very, Mark. Sally Mossman from GlaxoSmithKline.

DR. MOSSMAN: I'd also like to thank the organizers for giving us this opportunity. I think this is really something that we've all been looking forward to for a couple of years since we first discussed this with Stan. And I -- and I hope that we can really leverage the discussion that we have here today and facilitate CMV vaccine development moving forwards.

So the first slide, I'm just going to give you a brief overview of the GSK congenital CMV vaccine candidate. It's a recombinant gB antigen adjuvanted with AS01E adjuvant, which as we discussed this morning is MPL and QS-21 immunomodulators in a liposomal formulation. It's expressed in Chinese hamster ovary

cells. It's a truncated gB molecule from AD169.

And we recently published -- or at least discussed publicly at a conference a Phase I study in healthy mal adults, where we showed that the vaccine candidate was highly immunogenic with good persistence of the response, both antibodies as well as CD4 T-cells at 18 months post-third dose. And we continue to follow those subjects and we'll have four- and five-year follow-up data on the same individuals. GSK is currently modifying the gB construct before we proceed further with clinical development.

So then in the next two slides I'm going to go what we perceive are really the critical gaps and the things that give us pause for thought in terms of CMV vaccine development. I think the first one is how to identify the population segment that will most benefit from a CV -- CMV vaccine, while at the same time achieving adequate coverage from a public health perspective.

One potential could be winning -- women planning pregnancy but we know that less than 20 percent of those -- of women actually consult a

physician prior to pregnancy. So those people are really very difficult to reach.Adolescent girls is another proposal and that may be a way to improve the coverage and improve the potential to reduce disease burden. But in that population the benefit of vaccination will only be realized later in life, if and when those women actually become pregnant.

In addition there's -- obviously immunizing that population, you would have to show very long-term protection or boostability of the response. And I think a key question that we would like to see addressed is which data package then would regulators need to see to support licensure of an indication in adolescent girls?

We think there's clearly a medical need, and this has been discussed quite a bit also this morning, to protect against congenital CMV in both seronegative and seropositive women. How do we demonstrate the medical benefit in seropositive women above that afforded by natural infection? So can we consider, for example, having different clinical endpoints in the seronegative women compared to the seropositive women

and achieve an indication in women regardless of sero status?

I think the low public awareness of congenital CMV is also an issue that we all need to deal with and I think that will be discussed later in the meeting in terms of how we might be able to overcome that.

The next question here is really very much a scientific one. What is the profile of a protective immune response and the related question then, what should be vaccine composition? We've talked about neutralizing antibodies and the profile of fibroblast versus epithelial and endothelial neutralizing antibodies.

What's the role of T-cells in protection against congenital CMV transmission and would there be a requirement to test a congenital CMV vaccine in immunocompromised populations? And would we expect the same vaccine, in fact, to be effective in both populations?

Then the next point, how can -- how best can manufacturers really enhance the probability of success

with CMV vaccine development by demonstrating some form of clinical proof-of-concept prior to conducting large Phase III clinical studies? And I think it would also be useful to have some discussion at this forum about what the design and context of such Phase II studies could be.

Which Phase III endpoints have the right balance between clinical relevance and feasibility to demonstrate efficacy? Obviously, this is a key question that you will hear from, I'm sure, all of the manufacturers in this session and will also be the discussion of Phase -- Session 4 tomorrow. I think, like Mark presented, we're also interested to hear, what is the view in terms of protection against congenital CMV infection as an endpoint?

And then my final point here is we would like to also discuss at this meeting, what will be the mechanism for surveillance of post-marketing effectiveness studies and do we foresee a role for public health authorities in the -- in facilitating such studies? Thank you.

DR. PLOTKIN: Thank you, Sally. Next, we'll

hear from Phil Dormitzer from Novartis.

DR. DORMITZER: So first I'd like to thank the organizers. The meeting so far has been interesting. It's been informative and we're hopefully it will be also very useful going forward. The Novartis vaccine -- CMV vaccine candidate is from a collaboration with AlphaVax. I think probably most in the audience are aware of the paper from David Bernstein with Alphavirus replicon that expressed gB in this pp65-IE1 fusion.

Alphavirus replicon, for those who are not familiar, it's not a virus. It's -- lacks structural proteins but it looks like one in the little cartoon. And to the immune system, it enters and can undergo a single round of infection without producing infectious progeny. And as these -- I won't go over the data in any detail because they were shown earlier but you get both neutralizing antibody responses and T-cell responses.

And one hopes that this will combine some of the advantages of different modalities, subunits, nucleic acid vaccines, and possibly (indiscernible)

without some of the risks. One of the critical gaps that we see -- the first -- this is very similar to what's been presented before in fact.

The first is for the congenital indication, which I think, in our hearts is what we're most interested in. That's the need for a prolonged duration of immunity. And, you know, one can even say, not only do you need prolonged duration for your efficacy, do you even need it for safety? If you have a vaccine that just delays primary infection for 18 months and you give it to an adolescent girl at age 16 and now she gets infected at age 18 or age 20 for the first time, she's more likely to be pregnant at that time. Have you helped or hurt?

And similarly, so one possibility is establish duration of immunity in transplant patients but that's a pretty funny population and can you extrapolate that -- well, when -- from when you start your trials in your -- in the adolescent target population?

The lack of sufficient animal models has been mentioned and that has some very practical

implications. For example, you know, CMV, it's almost like a bacterium. It's got all of these antigens. So our typical bacterial vaccines are cocktails of antigens but you have to justify every one. Well, you're not going to be able to do that for CMV until in retrospect.

So we certainly don't want to go one antigen at a time, fail repeatedly, and then get the right combination. You want to go in with a combination that's going to work. But then you don't know why it worked because you have a bunch of antigens in there. And so that becomes a regulatory question that grows out of the lack of a good animal model.

Similarly, you know, in -- yeah, as those slides I showed before, you have your antibody results. You've got your set of T-cell results. There are bewildering number of so many immunity results. Which are the ones that are really important and which are really going to correlate? Without a good animal model, we simply don't know.

Similar problems for assessing transmission across the placenta. There's certainly a need for

agreed clinical endpoints. I think that -- it sounds like most people think that if the mother doesn't get infected, the fetus is not going to get infected. That seems imminently sensible. You go much beyond that though and you start looking at virological and other endpoints and what is enough of a surrogate for a clinical benefit to be useful?

And finally, in the transplantation indication, which may be the gateway to the congenital indication, because you get the human experience before you go into that population where you need such a duration of immunity, it's incredibly fragmented. You've got not only different types of solid organ transplants, plus stem cell transplants, you have different age groups, but you also have different regimens of immunosuppression of antiviral therapy.

And how many bridging trials does one have to actually do to go from one way of doing kidney transplants to the plethora of other transplant types and methods that are out there? That's it. Thank you.

DR. PLOTKIN: Thank you very much, Phil. And now we'll hear from Rafaela Dumas from Sanofi Pasteur.

DR. DUMAS: Thank you. First of all, I want to thank the organizer for organizing meeting for this opportunity you offered to the scientific community and also all the people who search for CMV vaccine. Now, I mean also the parents and future parents that are looking for CMV vaccine to (indiscernible) share views during this two-day meeting.

The Sanofi Pasteur Company is committed in developing -- sorry, I -- in developing a CMV vaccine for more than one decade. And this vaccine is based on the purified adjuvanted recombinant gB protein. That -- this protein is a major component of the viral envelope and is -- had been showed to be protective in (indiscernible) studies.

So we know that this protein can trigger cell entry neutralizing antibodies, both in fibroblast and epithelial cells and that gB now has been -- has to need -- need an adjuvant. And as we have seen this morning, we need to choose a proper (indiscernible) adjuvant that's a response to the needs that we have for this protein.

So in the -- my presentation, I will

highlight four main gaps that we consider as having an interest today. We have already given lots of them but I will go through. The first one is the definition of the endpoint efficacy -- the efficacy endpoint in the setting of congenital infection. The ultimate goal for our CMV vaccine is to prevent against disease and sequelae in newborns or in young children.

But is it an achievable goal without a standardization of the disease? We have seen that the disease can have various types of symptoms. The diagnostic can be delayed and there are long-term sequelae. So this endpoint can be discussed. And another one, that is the congenital infection may be achievable endpoint in pre-licensure.

At the time we write the -- our slide, we were thinking about the role of a -- the hyperimmunoglobilin treatment in the prevention because if it become a standard of care, obviously, it could interfere with any assessment of the vaccine in this -- in this endpoint.

And another endpoint is the prevention of infection in women of childbearing age or in maternal

infection, I mean, for pregnancy. That was the endpoint of the proof-of-concept of Bob Pass. And is it sufficient to demonstrate a benefit of the vaccine in newborns if we stop the infection at the level of the mother in the -- and consider it's the benefit for the vaccine? This is also a matter of discussion.

The second gap is also dealing with the adolescent target population. The -- in this population, is a database based on safety and immunogenicity bridge enough or not to give an indication in this population? That has to be discussed too.

So recently the focus was made on many cases of congenital infection in babies from woman who were seropositive the conception. And this set new expectation on the vaccine, of course. And some clarification are needed before looking to this population; how to demonstrate the benefit in those population, which set of data are expected pre-licensure, can we demonstrate the effectiveness based on the post-licensure study? That was mentioned by Pieter Neels this morning.

So the burden -- but does this burden also need to be clarified and the benefit in this population? A better understanding of the mechanism of facts -- of reactivation and reinfection would help also to design the study.

The fourth point it's the need for standardized relevant lab read-outs, particularly to support the robustness of surrogate markers and establish a correlate, and also to study the immune -- the protective persistence and the need for boosters and to allow comparison across different vaccines if necessary.

The last point, it's the lack of standardized efficacy in animal models, which limits the surrogate protection definition. Before any clinical trials, we need to better understand the mechanism of infection of the fetal transmission in these models. And this will allow the antigen justification, as said by my -- the previous speaker, and to contribute to moving forward to Phase III.

DR. PLOTKIN: Thank you.

DR. DUMAS: So thank you very much.

DR. PLOTKIN: Thank you. Our last speaker is Rick Kenney from Vical.

UNIDENTIFIED MALE: Hold on. I've got to get the slides up, Stan.

DR. KENNEY: Okay. I'd like to thank Dr. Plotkin and the organizers of this meeting. I know that the -- there's been a lot of effort over the last many months to make this a successful platform and we're excited to be here. Rather than going through the gaps in the development, which the other speakers have very elegantly described, we thought that we would give an introduction to our prophylactic vaccine because this really hasn't been published. And you may have some questions.

At Vical we focus on the development of DNA vaccines and now propose a vaccine that combines a plasmid that encodes the gB surface glycoprotein B with another plasmid that also encodes the pp65 to add a cellular component to the vaccine. Both of these are formulated in an adjuvant that we call Vaxfectin. Neutralizing antibodies to gB are, of course, critical for the prevention of CMV infection and transplacental

transmission and are likely to be a correlate of protection.

Bob Pass showed that recombinant gB adjuvanted with MF59 can protect postpartum CMV-seronegative women, reducing CMV infection by about 50 percent. The DNA vaccine would be expected to stimulate antibodies as well as antigen-specific T-cells to gB.

In addition, the importance of pp65, we think, can't be understated. Sylwester showed that this tegument protein is the most prominent T-cell antigen, stimulating both CD4 and CD8 positive responses in a large majority of infected people. Mark Schleiss went on to show that an alphavirus expressing this protein as a guinea pig homologue can elicit both CD4 and CD8-positive T-cells.

The vaccine protected the guinea pig dams from infant mortality and also reduced maternal blood viral load. The Vaxfectin adjuvant itself is a cationic lipid base formulation that's composed of GAP-DMORIE, which is a cationic amphiphile and DPyPE, a neutral phospholipid in a 1:1 molar ratio.

This adjuvant can be used in both DNA and protein-based vaccines and has been studied in lots of different animal models of influenza, CMV, TB, HIV, rabies, malaria, the list goes on. This was recently reviewed by Sean Sullivan and the CMV results were presented last summer in San Diego.

Finally, we have now done three Phase I trials with the Vaxfection adjuvant in influenza vaccines, found that the vaccine was well tolerated and induced neutralizing antibodies and interferon gamma-producing T-cells in humans after only two doses. The CMV vaccine is ready to go and into the clinic and we're currently looking for a development partner.

Now, the clinical strategy, I think, is fairly simple to -- or at least relatively straightforward for most of these types of products. We think that the optimal product configuration should be established in Phase I. And it's probably easiest to use a three-dose series that's compatible with the schedule for HPV.

Once the best doses of antigen and adjuvant are selected, we move into a proof-of-concept study.

After lots of discussion with Dr. Adler and others, we think that the daycare setting might be the most convenient, using CMV-seronegative mothers. There's nearly a constant exposure to CMV from the concentration of infected young children in the daycare setting, which helps to increase the power of the design.

Once vaccinated with the active product or the placebo, the mothers would be followed for CMV infection for 18-24 months, using a serological or viremia endpoint.

Of course, other Phase II studies would be needed to establish safety and immunogenicity in adolescents as well as CMV-seropositive subjects. And the seroepidemiology would need to be established to define the geographical locations that you'd want to go for Phase III.

Finally, the pivotal trials depend highly on the intended target population. We think that the first indication should be for young women who could either be seronegative or seropositive. Depending on the outcome of this conference, we propose to focus

either on maternal endpoints or congenital infection. The indication could then be expanded to a universal vaccine by studying discordant couples and their protection from infection. Thank you.

DR. PLOTKIN: Thank you. Thank you very much. So we're now going to have some discussion. And -- but the -- but first I -- where's Phil? Yes, please come up.

DR. KRAUSE: Okay.

DR. PLOTKIN: And Pieter? I -- there's one chair here --

UNIDENTIFIED MALE: And one on the end.

DR. PLOTKIN: -- one on the end.

UNIDENTIFIED MALE: Can it fit in there?

DR. PLOTKIN: No, that's okay. So Phil and Pieter, do you have any comments first before we ask some specific questions on what you've heard from the manufacturers?

DR. KRAUSE: Obviously I think it's very exciting to have this high level of interest in CMV vaccines from all the manufacturers. And there's obviously a lot of similarity between some of the

comments and some of the gaps as they perceive them and as well as, you know, with the agenda of the meeting, I think that some of the questions that are listed as questions for regulators really are scientific questions and are questions -- because as regulators, what we're going to do is we're going to look at, what does the science support?

And so obviously, we're happy to attempt to answer those questions. But in some cases, that will need to be with reference to the data and to what it is that the epidemiological studies and the basic science studies show.

DR. PLOTKIN: Pieter, do you have any comment?

DR. NEELS: Indeed I'm also quite excited to see that we have four -- five projects that will come to us in the near future. And I really want to invite you to come also the European Union for your questions -- for your open questions where you really need to make decisions in an early phase.

I really want you to invite - to come and discuss that with the regulators because many of the

questions you have are open and should be answered before you start your clinical trials. Otherwise, you will get criticism afterwards.

DR. PLOTKIN: Okay. I --

UNIDENTIFIED MALE: Fair warning.

DR. PLOTKIN: I would like to make a point myself. And -- well, first of all, we're not discussing endpoints here, although, obviously that's a key question but it's going to be considered in a subsequent session. Similarly, target groups also will be specifically discussed.

But the point I would like to make is the utility and importance of Phase II trials in defining the correlate of protection, which, in fact, is the key to move forward in CMV since we don't have an animal model. I would also again draw the analogy to HIV, where the recent trial in Thailand has uncovered what is at least a putative correlate of protection, an antibody function which was not known before the Phase II trial.

Similarly, in a Phase II trial, whether it's in a daycare setting or other settings, such as Bob

Pass's trial, they can -- if properly constructed, can define a correlate, admittedly not necessarily with the power you would like, but the confirmation of that then occurs subsequently in Phase III trials.

So the definition of a correlate is far from hopeless. In fact we now know that there is some efficacy. And the question now is can we correlate that efficacy with a particular immune function? So that's a point I wanted to make.

So we have -- we heard from the manufacturers a range of different vaccines, although unfortunately, from my point of view, I didn't hear anything about a live vaccine, despite the points that were made earlier concerning the very interesting data from animal CMVs, how you could tailor a live vaccine to be both safe and effective.

Also I did not hear -- and I would like some comment about -- we've heard gB, we've heard pp65. What about the pentameric proteins? Anybody want to comment on that or is that too upstream?

DR. DORMITZER: Well, it's impossible not to be interested in them. I mean -- I mean, that's --

that's about it.

DR. PEREIRA: Stanley, I'd like to comment. Lenore Pereira. In my lab we work with the human placenta and we have been doing studies that enable us to understand virus transmission during first trimester and the role of hyperimmune globulin in allowing the placenta to develop after treatment.

And we have also established models of the human placenta as explants, in which we have been studying antibodies, hyperimmune globulin, so Cytotac, Cytogam, and also now, human monoclonal antibodies to the different proteins. And so we can actually see the levels of protection.

And I can say that the antibodies to each of the different glycoproteins are more effective even than hyperimmune globulins, the preparations that are currently on the market. And that ranges anywhere from 100 to 3000-fold more effective in protecting the placenta, a single antibody.

And we've also looked at trophoblast progenitor cells that are the stem cells of the human placenta. And these stem cells allow development of

the placenta from mid-gestation on. The first half are fetal stem cells that allow the development. And we can also see protection of individual antibodies. And in this case we have seen a fabulous gB-specific monoclonal antibody as the most protective of all.

So I just wanted to give you this information to tell you that there is a lot of support for antibody protection of the human placenta. And I would propose that immune sera that are elicited in response to the different vaccines can also be tested in the explants -- placenta explant model.

And I can also say that we have also developed a SCID/hu placenta, a xenograft model, and the paper now is ready for submission, in which we can show pathogenesis, differences between the AD169 strain, which is the attenuated lab strain, and the virulent strain, VR1814, and how those viruses affect the development of the placenta over a three-week period in vivo. So --

DR. PLOTKIN: So --

DR. PEREIRA: -- there's a lot to learn.

DR. PLOTKIN: So Lenore is suggesting that --

I think that antibody is the effector mechanism. We've heard from Rick and Phil that there can -- that they are including pp65, at least in the -- in the vaccines. So do you want to make any argument for pp65 in the vaccine, how it -- how do you -- what's your rationale so to speak?

DR. DORMITZER: It's a great question and it depends on which immunologist you want to ask. You can say, "Look, as was stated, this is the most prominent T-cell antigen but all these people are infected. They didn't control their infections." So does that mean it's the best antigen or the worst antigen? I mean, you make a lot of -- you make a lot of -- a lot of T-cells against it and you still are infected and you still have a good chance of transmitting to the fetus.

So I don't know. When I sort of surveyed experts in the field, they all say, "Oh, you've got to have a T-cell component and, yeah, it's got to be pp65." Where's the proof?

DR. PLOTKIN: Well, I think that argument is probably fairly convincing in the transplant situation. But --

DR. DORMITZER: Yeah.

DR. PLOTKIN: -- what's your -- what's your take?

DR. KENNEY: I think the answer's going to be empirical. I think Bob Pass did a great job with getting the 50 percent protection with the gB protein alone but that's not considered adequate. And so if you want to expand on that, you may need to add the cellular arm of the -- of the response. And Mark showed that the pp65 is adequate on its own to protect guinea pig model.

DR. PLOTKIN: Okay. I would also like to ask about duration. Now, I -- the point has been made by several speaks and I think it's absolutely the case that one is going to need a vaccine that gives reasonably long duration. It may not have to be for the lifetime but at least over some period of time.

We saw one slide -- I showed one slide of B cell -- induction of B cell memory. Personally, I would like to see more such studies because we need to know whether we have effector memory, which would give us an animistic response, and indeed, whether we can

produce long-term effector memory. So are the manufacturers considering following up on those data?

DR. MOSSMAN: And maybe I can comment on that. So as I mentioned during my four-minute talk, we have generated some quite nice data showing that after 18 months post-third dose, we do still see quite a good persistence of a neutralizing response above the level seen in natural infection.

And as I mentioned also, we will continue to follow those subjects. And it's our expectation that there will be a plateau of the response at a steady-state level, which, you know, I think, which will be quite telling in terms of what we can expect from perhaps a formulation, including a more potent adjuvant that gives you a higher threshold response to begin with and then a higher steady-state level of antibodies.

But I think your point about B cell memory is crucial as well because I think that tells us a lot about boostability.

DR. PLOTKIN: Just parenthetically most of our vaccines require boosters. So it is not impossible

that one would vaccinate at a relatively young age and boost later in life. That is a very common phenomenon. Yes, Debbie?

DR. SPECTOR: I think this is actually directed to both Phil and to Stan, and that is your comment about immunizing -- and again, it's get to the durability of immunizing adolescent girls and simply postponing the time at which they get the primary infection. And I -- and I know I was very struck also by the original gB study, that the protection was in the first six months.

Did you have, Stan, when rubella -- when you were developing the rubella vaccine, were there similar issues that were brought up on this or was rubella such a durable vaccine that you could boost every five years and you're fine?

DR. PLOTKIN: Well, of course similar questions arose. The live vaccine, in fact, does give very good persistent antibody, and there are many studies that show that, and even more persistent immune memory. But that, of course, is a live virus. But the point I would stress again is that with rubella we had

a correlate of protection, neutralizing antibody.

And that was demonstrated with gamma globulin. It was demonstrated in other ways. So as long as we had antibody, we could predict protection. Yes, Florian?

DR. SCHODEL: Yeah, both (indiscernible) reasons because the public health impact will make it necessary to immunize before pregnancy, obviously, and maybe much before pregnancy. And because we've been very poor at delivering vaccines to a pre-pregnant population for other vaccines, such as for example, Gardasil and Cervarix, I think it'll need to be studied whether the vaccine works and where most of the transmission happens in toddlers.

And that may actually also be -- may also be easier -- and I'm grateful that one of the colleagues said that -- it may also be easier to establish a correlative protection there because the attack rates are much higher. And then obviously you can follow such a population over the long run.

And so I'm wondering whether a package in which protection of toddlers from infection, which have

a very high level of infection, together with prevention of infection of children born to mothers who develop CMV during pregnancy, would be a reasonable package for potential licensure based on the current available data, plus, duration, of course. I mean, that's the other important piece.

Because the other thing that's sort of unspoken in the room or only barely mentioned is that it's very hard to mention any of the disease outcomes in newborns. So if that were the package, I think nobody would want to develop a vaccine anymore.

DR. PLOTKIN: Well, that's the endpoint discussion, which we will hear shortly. But as far as pediatric studies -- there may be some comments on this -- I think that every vaccine we've heard that there were pediatric requirements in any case. And so it certainly would make sense to study the vaccine in toddlers for prevention of transmission. But any comments on that from the manufacturers?

DR. DUMAS: I can comment on a point of view because the congenital infection is a public health issue. And when you are developing your vaccine, even

if we will -- we will target also the infant -- the -- also regulatory requirement, looking close to our endpoint is the -- I think the faster way to know if the vaccine is efficacious. And then you can also delay the vaccination and look at the duration.

But first, knowing if this vaccine is efficacious in the target population who will be pregnant, I think it's a priority. And then a comment on the -- your point, Stanley, on the duration, it -- I think it's more a matter of adjuvant and any other antigen that you will -- had -- I'm not sure if -- we don't know but I'm sure they will give a benefit in terms of duration.

DR. PLOTKIN: Okay. Well, we did hear from the regulators -- I've -- I was quite pleased actually -- a definite statement about the size of the safety population. And that was -- you -- 100 people heard you -- a size of about 3000 would qualify. Now, I'm sure that the manufacturers are going to do more than 3000. But --

DR. GRUBER: Can I make a comment here? It's up here, Stanley. Marion Gruber, the Office of

Vaccines. We've heard statements about, you know, safety, sizes and databases (indiscernible) database as part of the presentation this morning. But I would not really take home the message that 3000-5000 subjects is enough for every vaccine antigen, every subject population.

So you really cannot make an across-the-board judgment. It really depends. So it could be that especially for some of the (indiscernible) adjuvants that the size of the safety database that is required to demonstrate the safety in the pre-licensure arena is going to be higher.

DR. PLOTKIN: Yeah.

DR. GRUBER: I just --

DR. PLOTKIN: Well, I didn't doubt that but the -- never -- nevertheless, it was nice to hear a ballpark figure, which I -- which personally I think is quite reasonable that an event of less than 1 in 1000 is something that you're going to have to discover after licensure rather than before licensure.

So we talked about pediatric -- orphan vaccines. Now, I'm a little confused about that. We

have -- let's see -- five companies here. Does that qualify as an orphan vaccine?

DR. KRAUSE: Well, you know, an orphan vaccine in the US is defined by the statue, the Orphan Drug Act of, I think, 1983 that specifies basically that it should be for a market of 200,000 people or less. But, of course, this is an act that was originally designed really more for drugs than for vaccines but that's -- still has been the basic idea that has been used for vaccines.

So obviously a vaccine for congenital CMV or a vaccine that is contemplated for universal immunization wouldn't qualify. On the other hand, for transplant populations, there are limited populations in the market -- may not be large enough that a company could reasonably capture all of its development cost to the marketing. Those are the situations where the Orphan Drug Act ends up applying.

DR. PLOTKIN: Uh-huh. Okay.

DR. KRAUSE: I think Pieter has a comment. Pieter?

DR. PLOTKIN: Yes.

DR. NEELS: Yeah. In the EU the orphan definition is 5 in 10,000 so -- in a population in prevalence. If we agree, it will depend on your definition. And if you go for kidney transplant, I'm pretty sure you will get that in the definition. But, of course, then you have to come for heart transplant and for pancreas transplant and then you will have to do a clinic trial in all those.

So it -- it's bouncing on a cord -- balancing on a cord, I think, in how to define your way forward. If you go for an orphan, you have to be the first one. Yeah. And then it is for a very small population. And then you will need -- you can't extrapolate your data to another orphan indication.

DR. PLOTKIN: Yes?

DR. KENNEY: Phil mentioned that our transplant vaccine has orphan designation and I think it's very appropriate in that setting. There's -- the ability to actually recruit 10,000 people is nil in that type of a study. But we have purposefully changed the formulation to make it more appropriate for a prophylactic setting. And that's why we don't think

that the prophylactic vaccine would go for orphan.

DR. PLOTKIN: Okay. So -- well, actually one question I think a couple of manufacturers raised was ACIP recommendations. Now, I certainly cannot speak for the ACIP but I -- but I think from observing the ACIP, what it's going to come down to is a cost benefit analysis. The IOM has already done this once but it will be done again and again for a CMV vaccine.

From what data are out there at the present time, there's no question that a CMV vaccine would be cost effective and, therefore, I think it's likely that ACIP would endorse it. I don't know if anyone from the CDC wants to comment or if the manufacturers would like to -- yes, Mark?

DR. PICKERING: Yeah, Stan, I can comment on that during the next discussion -- if you all get off the stage, we can have it right away -- when I talk about ACIP.

DR. PLOTKIN: Okay. We'll let -- we'll let you --

DR. FEINBERG: There is -- there -- Stan, there is one integrated --

DR. PLOTKIN: I'm sorry?

DR. FEINBERG: -- aspect of that. As you know, what the ACIP does is largely guided by what the FDA does. And it really gets to the point about what is considered an acceptable endpoint for licensure and how compelling that is for policymakers to take that and figure out how to decide to implement it or not.

DR. PLOTKIN: Yeah, okay. We're -- the time is moving on. I do want to make one point, which I believe was raised by somebody, and that concerns the compensation system, in other words, would there be compensation for a significant reaction?

Two points I would make and others may wish to comment. One is in relation to what Pieter said. I don't think any manufacturer is going to recommend this vaccine for pregnancy. It will be a pre-pregnant vaccine, whether it's one month pre-pregnant or five years pre-pregnant, but it will not be during pregnancy.

There are 500,000 American lawyers who will make sure that that does not occur. But my understanding -- and someone may wish to correct me if

I'm wrong -- my understanding is that just as with HPV vaccine, if it's recommended by the ACIP and the -- and there's an event that occurs, it -- there will be a compensation program for the vaccine.

Now, of course, one will have to show that the reaction was related to the vaccine. But from what I understand, I do not think that will be an inhibitory problem for this vaccine that will be designed, at least in many cases, for adults.

DR. FEINBERG: Yeah, the unique aspect of it though is that the Vaccine Injury Compensation Program is designed to compensation the actual recipient of the vaccine.

DR. PLOTKIN: That's true, yes.

DR. FEINBERG: It is not -- it does not actually speak to the issue about a potential secondary individual fetus or newborn who might be harmed.

DR. PLOTKIN: So -- which again speaks to the point that the vaccine would never be recommended for pregnancy. It would be a contraindication.

DR. FEINBERG: No, that's true. But as, you know, both our colleagues at GSK and we know from our,

you know, HPV vaccine studies in the course of our clinical trials, although women were counseled not to become pregnant, many of them did. So we both had an ample safety database for the vaccine in pregnancy. So in actual practice, that is surely going to happen, particularly when you're targeting women of --

DR. PLOTKIN: Yeah.

DR. FEINBERG: -- reproductive age.

DR. PLOTKIN: Okay. Stuart, did --

DR. ADLER:Just a quick comment. A number of manufacturers mentioned public awareness. Public awareness is an issue and that's correct, at least in the United States. There's not much public awareness. However, if you mentioned CMV to any woman who was either pregnant, planning a pregnancy or knows somebody who is and has internet access, within 10 minutes they know everything that we know about CMV, I can assure you.

And it happens very quickly. And if it -- if it got into the newspapers that there was a CMV vaccine even on the way, you would have an educated population very quickly because of internet access.

DR. PLOTKIN: Michael?

DR. KATZ: Yeah, I can add to that because Sally Mossman listed it on her slide.It takes very little time of concerted effort to transmit this message. There are patient organizations. There are foundations such as ours and so on. So I would say six months, the whole country would know.

DR. PLOTKIN: That's Michael Katz from the March of Dimes. Well, any final statements from anyone on the panel? If not, then my conclusion is that there are no real obstacles to moving forward and we have five companies that are moving forward. So thank you very much.

DR. SEWARD: I'm Jane Seward from the CDC. While Larry is pulling up his slides, this is Session 2 -- 3, target populations for a CMV vaccine for non-transplant indications. And our first speaker is Larry Pickering from CDC, who's going to talk to us about considerations and parameters of interest for ACIP recommendation of immunization of various populations.

DR. PICKERING: Okay. Thank you, Jane. There are four objectives that I have for this

discussion. One is to discuss the responsibilities and a little bit about the structure and function of the ACIP. Secondly is to review the process of immunization policy development in the ACIP, and then to highlight the key issues facing CMV vaccine recommendations as I go through these various areas, and also to summarize implementation issues facing CMV vaccines other than the ones that we've already heard about.

This is the first slide that shows that in 1986 there were eight vaccines on the immunization schedules. Now, there are 17. And this is something to think about because any new vaccine has to be integrated into an already complicated child and adolescent schedule and, thankfully, becoming a more complicated adult immunization schedule as more vaccines are added in to prevent disease in adults.

Now, a little bit about the background. In 1964 the ACIP was established. The role of the ACIP is to provide advice and guidance to the director of the CDC and the Office of the Secretary of HHS on the most effective means to prevent vaccine-preventable diseases

in the civilian population in the United States.

So ACIP recommendations are not official until they are accepted by the director of the CDC. Now, we deal almost always with vaccines but the charter of the ACIP states that also recommendations can be made for antisera, immune globulins and antiviral agents. And, of course, antiviral agents were voted upon for influenza but most of what we deal with is vaccines.

The job of the ACIP, as somebody just alluded to, is a little bit easier because most of the times the ACIP will only deal with vaccines that are licensed by the FDA. The FDA licenses vaccines. It -- they don't make recommendations. They license it. The ACIP makes the recommendations.

There's one other recommending body in the United States and that's the Committee on Infectious Diseases, sometimes called the Red Book Committee, of the American Academy of Pediatrics. They also make recommendations for the AAP in infants, children and adolescents in the United States.

ACIP was designated as a FACA committee, the

Federal Advisory Committee Act. Therefore, there are various stringent rules and regulations that all FACA Committees, including the ACIP must follow.

Now, the structure of the ACIP group, I call it, has four main structures. One is the ACIP committee, which is the only voting group in the room during the ACIP meetings. There are 15 members. They serve four-year terms. The four-year terms is important because, for instance, CMV may be considered and in the middle of a CMV discussion, may go on for a year, a year and a half, there may be some members that leave ACIP. So it's a continuing educational process for all old and new members.

There's very strict screening of conflicts of interest of all ACIP members. The second group are the eight ex officio members. They represent government organizations that deal with vaccines, the FDA, NIH, CMS. They -- members and representatives are all at the -- each ACIP meeting so that if there are any questions that arise, they can be immediately answered.

There are 30 liaison organizations. These are representatives of the professional society and

organizations responsible for vaccine development and immunization programs. And these are the organizations where they really implement vaccine usage in the United States.

And these organizations have the following roles in the ACIP process, and they're very significant roles. The members serve on various work groups. Members attend and participate in every ACIP meeting. There are five organizations that assist with the harmonized childhood schedule and adult immunization schedule. And the organizations support the ACIP recommendations. So when the CMV vaccine gets to this stage, there'll be a lot of work with various organizations as well as with ACIP and ACIP members.

Now, the work groups -- a work group -- a CMV work group will be formed at a certain stage when we know that this vaccine or a vaccine will be filed with the FDA. And the time before which it's filed -- the BLA is filed is variable for the various vaccines. The work groups are really the engine.

They gather and analyze and prepare information for the ACIP to consider. They develop

draft policies or options for review by the full ACIP. They do a lot of work by teleconference. Right before a meeting work groups are meeting by teleconference probably at least every week. A work group is chaired by an ACIP member. It has to have another ACIP member. It is run by a CDC staff person.

And then there are a lot of people, experts throughout the country, who serve on ACIP work groups. And they average anywhere from about 20 to 40 people on an ACIP work group. They're task-oriented work groups generally and it -- they're disbanded. So if a CMV vaccine comes before the ACIP, terms of reference will be formed and they will be completed, and the work group may be disbanded until another vaccine comes from another manufacturer. So sometimes the work groups go on for long periods of time.

The work groups then -- the bottom are the task force work groups and the top are the permanent. The permanent put out publications every year for three of them and every three years for the General Recommendations. The bottom, the task force -- you can see there's some of them been -- that have been around

for a long time and that's because different immunization recommendations were made.

For instance, CMV, there may be -- the first recommendation may be for pregnant women, the second for various childhood groups or adolescents or whatever. So they -- the -- that group -- or the work group of CMV may, once it's constituted, be around for awhile.

The General Recommendations is published every three to four years. And that's where all the information that's pertinent to all vaccines are gathered, immunizations of people with primary and secondary immune deficiencies, storage, vaccine handling, and so on, are all put in the General Recommendations.

Now, one of the things that we've done is try to standardize processes that the ACIP uses that makes it a lot easier for people to understand the process. Because clarity, consistency and transparency are critical for this committee. A couple of these, guidance for pregnant and breastfeeding women. This is not a guidance on how to do studies. It's a guidance

on how studies will be written into the documents so there's some consistency from one pregnancy recommendation to another for various vaccines.

Economic analysis guidance is a very critical part, as Dr. Plotkin mentioned. Their standardization on how economic analyses are presented to the ACIP and then the evidence-based recommendations down at the bottom were just enacted. Evidence-based recommendations were approved for usage by the ACIP in October of 2010. The system to be used and that will be used is the GRADE system, grading of recommendations, assessment and development and evaluation.

This was implemented for new recommendations at our last meeting in October of 2011. HPV vaccine for males underwent the GRADE evaluation, as did Hepatitis B vaccine in people with diabetes mellitus. Both of these recommendations were published on December 23. The tables were not published in the MMWR but they will be on the website and the links will be very obvious to find them.

Now, what evidence does ACIP use when it

considers? What will be necessary for a CMV vaccine to be recommended? And we've heard a lot of that already today. First of all, the FDA licenses the vaccine and ages at which it should be given. So that makes it a little bit easier for ACIP to construct the recommendations around this licensure.

Disease burden overall and in high-risk groups, vaccine efficacy and effectiveness, data on safety in general and in specific groups, feasibility in the context of existing recommendations and equity in access to the vaccine and good use of public funds -- and that's where we're getting to these economic analysis issues -- and then recommendations of other groups.

Now, the ACIP-recommended categories will be A and B. Category A is recommendations are made for all persons in an age- or risk-factor-based group. And B, recommendations are made for individual clinical decision making, clinical decisions between physicians and their patients. The evidence tables are used to summarize benefits and harms and strengths and limitations of the body of evidence. And they will all

be posted for each of the recommendations on the ACIP website.

The body of evidence is categorized into four types with the strongest, randomized controlled trials as a -- as a one, so on down to the various evidence types. Two things to remember about this. Number one is that the committee decided not to use grades or numbers but they will put the types of studies that were done.

And the second thing is, SAGE, which is a Strategic Advisory Group of Experts for World Health Organization, will have an article on vaccines in a couple months about their process. SAGE and ACIP sort of followed this process of developing GRADE together. Their process is a little different because they use Number 4 as the strongest ranking. So that could be a little bit confusing. But as long as we know that there are differences, that may help avoid some of the confusion.

Oh, one of the things about GRADE is it -- for people who haven't done it, it's very complex. So we put a lot of things on our website. The GRADE work

group website has a video or there are two lectures. One is an overview of the GRADE approach and the process and the second is assessment of the quality of evidence. This was given to people at CDC by Holger Schunemann and Faruque Ahmed.

So they are up on the -- on the website. We don't expect this to win any awards but it may be nominated. It's really very good and very clear. Slide presentations, the New Framework for Development of Evidence-Based Recommendations, also has been posted. And then Faruque's article, which is in Vaccine -- it came out -- is available on the ACIP website. And the SAGE article also will be published very soon -- and now, going through clearances, the technical document for this process that ACIP and CDC will use.

Now, the thing -- two of the last slides I want to show are the immunization policy product. There are two immunization schedules that everyone in the room is familiar with. The first is a harmonized schedule. It's not only an ACIP schedule; it's harmonized between ACIP, American Academy of Pediatrics

and the American Academy of Family Physicians. This was first harmonized in 1994.

Before then, as some of us remember, there were differences in recommendations between the American Academy and the CDC. And that led to a lot of confusion. IN 2007, the format of the childhood and adolescent schedule was changed to have two or three different tables.

The second is the ACIP, the American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, and American College of Physicians, which publishes in Annals for the last three years, produce the harmonized adult immunization schedule.

Both schedules are updated annually and beginning last year and again this year and in the future, they'll be published in February rather than January. It was too hard to get all of the recommendations that were made in October into the next year's schedule if it was published in January because we have to work with all the other professional organizations. So they will come out in February from

now on.

They display the complete schedule with this -- each vaccine. Now, this shows a schedule. And again, with a CMV vaccine, as was mentioned earlier, if we've got three or four or five doses of a vaccine -- not that that's going to happen -- they have to -- going to have to fit into it. So the more simple the CMV vaccine schedule, the easier it will be to fit in either to the childhood schedule or into the adult immunization schedule.

And the adult immunization schedule I really like. I like the childhood too -- one too but the adult is interesting because it gives the age ranges, as shown on the top, but it then also gives the various conditions that people might have. And pregnancy, of course, is the first one. And it gives the immunization schedule and what is recommended and not recommended for pregnant women on out through various other primary and secondary immune deficiencies.

This is an article that was in Annals. It sort of explains the whole ACIP process. It's on the ACIP website if anyone is interested in reading it.

It's a real page turner so be ready for a half-hour's worth of reading. The ACIP website is kept up to date. We're very lucky to have a good web manager. And you can see here the next ACIP meeting is February 22 and 23 at the usual place, at the Global Communications Center in Atlanta.

This is a picture I took last night when the plane landed. It was that bad that -- so that's my comments. And I think, Jane, we're going to have a couple talks. Do you want me to just go ahead and introduce Gail or --

DR. SEWARD: Well, are there any clarifying questions -- questions for Larry? He finished a minute ahead of time so we'll give him the option of -- if there are any clarifying questions, we'll take them. Otherwise, we'll go on to ask Gail Demmler to present. Mark?

DR. FEINBERG: Thank you for your helpful summary, Larry. I guess, you know, one question in the -- I know you can't speak for the ACIP but in thinking about how the ACIP would consider a FDA license for an infection indication versus a disease indication, you

know, those could have important implications for how the ACIP thinks about the weight of evidence as well as how they would approach cost effectiveness calculations.

And I'm wondering what your thoughts are about what differences might exist in those kind of deliberations and discussions at the ACIP level.

DR. PICKERING: Yeah, that's a tough one to answer. But I do know that basically all pediatricians on the committee have seen children with -- have seen infants with CMV. And many of the people who don't care for children but who care for adults, have seen transplantations with CMV. So I think this is an area to answer your question generally, that is a very important one, and clinically these conditions need to be prevented.

So I think that just to say as a general comment, a CMV vaccine would be of interest to anybody who is actively seeing patients and many of the people on the committee are. As far as specifics go, I -- you know I can't answer that one. I wish I had a crystal ball. Then I could but I can't do that.

DR. SEWARD: Okay. Thanks, Larry. Without further ado, we'll introduce Gail Demmler, who's going to -- from Baylor College of Medicine in Houston. And Gail's going to be talking to us about adolescent females and adult women as potential target groups.

DR. DEMMLER: All right.

DR. SEWARD: And I've got the timer on.

DR. DEMMLER: Oh, okay. I'd better -- I have no relevant disclosures. I'd like to first start with a -- these words, target groups for vaccination would be girls and women before the age of childbearing and certain groups of seronegative prospective transplant recipients. Now, these words are the last sentence in Dr. Stanley Plotkin's chapter, CMV Vaccines, in his book CMV -- in his book, Vaccines.

This was in the first edition of his book. And with each subsequent edition, even though the pages got longer in the chapter, these words always ended his chapter, which leads me to believe that our illustrious and wise Dr. Plotkin has not changed his mind and that these are indeed the target populations. So we could just stop here and take a break or with Dr. Plotkin's

indulgence and permission, those of us that move at more mortal and modest rate -- would you allow me to go through the nine points that the committee has charged me with? I'll take that as a, "Yes."

So the first question that they posed to me was, "What is the CMV seroprevalence among adolescents and women of childbearing age and what impact might vaccination of women of childbearing age have on primary infection, reinfection and reactivation?" We've heard this morning already about CMV seroprevalence. It certainly varies between 10, 20, 30 percent to 70, 80, 90, up to 100 percent. It varies with demographics, geography, age, lifestyle.

But what I would like to focus is -- try and drill down just a bit is the prevalence in adolescents. And so I've chosen a few studies over the years, not all that are available, but a few to help give us some sort of glimmer into the adolescent world of CMV.

Dr. Mary Kumar published a study in 1984 on pregnant adolescents. It was a prospective study of 3253 adolescents. Their mean age was 17 years. One thousand four hundred and four or 44 percent were CMV

seronegative. So her CMV seroprevalence rate of her population was 56 percent. Fourteen out of those 1400 or 1 percent acquired CMV during their pregnancy.

And she was able to identify the trimesters of where those primary infections occurred. Seven of the fourteen adolescents delivered newborns with congenital CMV infection. And this is for you, Lenore. Nine out of the fourteen, there were placentas available. What she did with them was just grind them up and culture them. And two out of those nine that she found were CMV-culture positive.

Some other studies that were done, primarily in Texas -- when I was a fellow and a young faculty member with Dr. Martha Yow, she was very interested in teenagers and teenage pregnancy and the role of CMV. And so we did a CMV seroprevalence study in Texas of children and adolescents and young adults between the ages of 6 and 22 and we had three groups. Group one was 511 children, ages 6 to 22, from pediatricians offices. And that CMV seroprevalence rate was 34 percent.

Group two was 920 A&M Aggie students, ages 8

to 21 [sic]. And this is probably the only Aggie-specific CMV seroprevalence study available. And it shows that their prevalence is 24 percent. And group three is 113 young adults at the University of Houston at Baylor College of Medicine. Once again, their CMV seroprevalence rate was relatively low at 28 percent.

So I sought a more diverse group of teenagers, those that perhaps got out of the study carrels a little bit, and partnered with somebody -- another individual, Rick Lampe. And we looked at other teenagers and -- whose mean age was 16.8 years over several areas of Texas. And we found that overall 41 percent of teenagers were CMV seropositive.

In that lower income -- and pregnant girls were more likely to be CMV seropositive, significantly so. And then finally, more contemporary data, I think, just confirms what we've been -- what we've known actually since the '60s through the '80s and now in the new millennium about CMV seroprevalence. In this study, once again, this confirms that the CMV seroprevalence of teenagers is probably around 42 percent for most of them.

So let's look sort of a different way at CMV seroprevalence and maternal age and trying to get at the question of who should receive the CMV vaccine. And I think we can get some information from the congenital CMV disease registry. Many of you in this room were there at the CDC decades ago when we met similar to this to discuss the problem of congenital CMV.

And at the end of that the one that we did was start a CMV disease registry. And, yes, it's still alive. It's on life support but I still keep it moving along. We actually now have almost 900 cases. But this analysis of -- is of 786 cases. And this is a physician-based voluntary, one-page reporting form.

And it was -- it was established to look at the characteristics of congenital CMV, to try and define trends over time, to -- also to have a CMV surveillance system in place because at that time, as you may recall, we were very hopeful that there would be a CMV vaccine in the very new future.

And what we found from this -- from -- at least from the data submitted to the CMV registry is

that maternal age is very young in these severely symptomatic babies. And when you compare the statistics to the CMV -- CD -- to the CDC 2004 national statistics, these babies reported to the CMV registry are more likely to be preterm, low birth weight and relevant to this discussion, to have mothers who are less than 18 years of age.

Another sort of Texas study is our Houston congenital CMV longitudinal study. This study was started 30 years by Dr. Yow and I've continued it. And we now have a long-term follow-up of over 200 children who were born with congenital CMV. Many of them now are in their late twenties. But relative to this discussion is maternal age of these -- of these -- of the mothers of these children.

Of the 77 symptomatic children, the mean age in our cohort of the mothers was 23.78. Of those that were born with asymptomatic CMV, identified through a newborn screening program conducted over 10 years, is 25, and of uninfected controls from the same population was 28. And there was a significant difference between the mothers who gave birth to the children with

symptomatic CMV compared to those with asymptomatic CMV and compared to those who were uninfected controls, once again, I think telling us that young age is very important.

And then just to look at it one more way sort of with histograms, the controls of those that did not give birth to babies that had congenital CMV, the mean age of mothers was around, you know, 28 to 30. Of those who gave birth to a child with asymptomatic CMV was not significantly different even though there is a little wider spread. But when you look at the maternal age of the mothers who gave birth to the babies who had symptomatic CMV, they were significantly younger. The youngest was 13 and the oldest was 43.

And so I think a CMV vaccine must be administered to young adolescents before the age of 13 to have the greatest impact on congenital CMV disease and that their age risk probably continues to 43.

So the next question, if the target population is women, would a CMV vaccine be administered to both CMV seronegative and seropositive women, i.e., routine immunization, or just to CMV

seronegative women; that is sort of a selective immunization strategy? No, I would favor routine immunization. I don't think it's harmful.

I don't know of any evidence that the CMV vaccine administered to CMV seropositive females would be harmful. We could think about possible scenarios but I don't know of any evidence. Is there evidence for benefit perhaps for CMV seropositive females? Do we have any data to that effect? It is cost effect. That's been published in at least one cost analysis in 1990 but we do need more contemporary analyses.

And there's precedent. Successful vaccine delivery strategies for other vaccines do not require serotesting and do not administer only to CMV -- to only seronegatives. Now, a selective immunization strategy is also cost effective but it will miss many high-risk pregnancies and it's a big barrier, I think, to vaccine delivery.

To serotest first and only vaccinate the seronegatives requires an extra step for non-pregnant females. Females wanting to get pregnant will then have to practice family planning, consult their

obstetrician three to six months prior to planned conception, then receive the CMV vaccine. And is that really realistic, especially when you look at the demographics of the mothers giving birth to the more severely affected children? Most 14 and 15 year olds don't plan their pregnancies.

And then health care plans will probably need to cover the costs of this additional CMV serotesting in addition to the CMV vaccine. But there's more. There's a -- sort of a third way maybe to look at it and that's sort of to adopt the rubella model. Say we choose to vaccinate one year olds with the CMV vaccine and that little girl at one years of age receives her CMV vaccine, and she grows up to be an adolescent or an adult female at her future prenatal visit.

If she might be -- if she's CMV seronegative, then we could either provide her information on behavioral and hygienic precautions during pregnancy and then administer a CMV vaccine postpartum or if she's seronegative, administer a vaccine at the beginning of pregnancy. That would be a little more controversial but that's one of the issues that I was

asked to bring up. So there's other models that we could maybe look at.

Next question, what duration of protection would be required from a vaccine for adolescents of women in order to achieve a reduction in congenital CMV? And if pre-pregnant women are vaccinated, will protection during one pregnancy suffice or would boosters be needed?

Well, based on the age range for congenital CMV disease, the most severe, 13 to 43, I'd say we need 30 years' duration of protection to cover that. So that should be easy, right? There's really no vaccine precedent for that. And it's ideal but honestly, it's not realistic.

How about 10 years' duration of protection? Perhaps more realistic and with some precedent. We could perhaps do an initial vaccination at age 12 to 13. That would be the routine, along with other adolescent vaccines, which are now coming into play. And then subsequent vaccinations at ten-year intervals might be optional.

I firmly believe all pregnancies should be

protected. Not one pregnancy is any more prime than others. And the need for boosters would actually depend on the woman's family planning so that if she finished her childbearing years at 22, she wouldn't need a booster. But perhaps if she wanted to have children through her thirties or forties, then perhaps she would.

Now, if a CMV vaccine is targeted for women of childbearing age, is it going to be necessary to have demonstrated safety in pregnant women? And is there a role for vaccination during pregnancy or would pregnancy be a contraindication? I say, no, it's not necessary if pregnancy is a contraindication for the CMV vaccine, for you to really look at CMV vaccine safety in pregnant women.

I think it's probably to wise to contraindicate a CMV vaccine if it's a live vaccine and probably wise also if it's a non-live or a subunit vaccine. And then I think a CMV reporting system should be established so that -- it's inevitable that CMV vaccines will be administered inadvertently to pregnant women. And I would also urge you to carefully

establish what you would want to do at each scenario so valuable information might be learned from these inadvertent immunizations.

But what about yes? Only, I think, if a CMV vaccine is to be administered during pregnancy should we spend a lot of time determining the safety in pregnancy. Is there really any reason to believe a CMV vaccine would benefit a woman and her fetus if it's administered during pregnancy? Do these data even exist? And if they do or if we're contemplating it at all, it should be a killed or a non-live CMV vaccine.

So CMV vaccine during pregnancy, I think that role -- that primary strategy is limited. There's a lot of logistical plans. What is the earliest a CMV vaccine can be administered during pregnancy? The first prenatal visit is usually six to eight weeks gestation.

A CMV vaccine, what does efficacy kick in, two weeks, eight weeks, twelve weeks? Your first trimester and part of your second trimester is already not protected. And then there's further delays if you adopt a CMV serostatus strategy. Then of course

there's the obvious safety issues.

My next charge is to discuss the advantages and disadvantages of various strategies for delivering a CMV vaccine to women in terms of program implementation in these various groups. So I sort of simplistic table to summarize very simplistically but I think it gets the main points.

What if we immunize all females of childbearing age? The advantages would be universal, simplistic and cost effective. The disadvantages would be that some won't be -- some will be vaccinated unnecessarily. How about adolescent females? It's a high-risk age that would be protected. So that's an advantage. It's cost effective. But the disadvantage is access and the need for a booster. It's hard to get adolescents into the doctor.

Pre-pregnancy, the advantage is full protection during the pregnancy. The disadvantage would be access. And you really would need some careful pregnancy planning. During pregnancy, access actually is an advantage because most people do seek health care when they're pregnant. But major

disadvantages of lag time and safety risks.

And then postpartum, what are the advantages? Access, once again. You usually have a -- or at the doctors postpartum and it might be a useful way if you supplement it with other strategies. However, vulnerable pregnancies won't be protected.

Another question, what are the gaps are there in our understanding of the epidemiology of CMV that affect our ability to predict the potential impact of a CMV vaccine in adolescent females or adult women? In my opinion, there's no gap significant enough to delay moving forward with a CMV vaccine. Current data likely underestimate the potential benefit of a vaccine.

Here's a few ides to consider though. CMV mononucleosis, it's probably 5 percent of primary CMV infections. Will CMV vaccine reduce this burden and would an EBV-CMV combined mono vaccine be feasible and more palatable to adolescents and their parents? What is the role of the male sexual partner? What do we know about fetal loss?

Cost effectiveness, we definitely need a comprehensive, contemporary analysis. And we need a

congenital CMV surveillance reporting system, I think, in place before -- or at the time a CMV vaccine is licensed. And final -- the final question, what do we wish we knew from previous trials? Long-term immunity? Will it reduce the risk of CMV mono?

Will it reduce the risk of other diseases that aren't even under discussion right now like atherosclerosis? And what about the geriatric age? And does the mode of CMV acquisition of the size of the inoculum affect CMV vaccine efficacy? And we also need more toddler vaccine trials.

So in closing, I'd like to leave you with another quote. "In the long room, the prevention of congenital CMV disease requires a vaccine program. Accomplishment of this goal will require participation of the NIH, private research organizations, the CDC, the pharmaceutical industry, physicians and parent groups. This effort must be a shared responsibility and we should not wait another 20 years."

And this was written by Dr. Yow and myself in 1992 in an editorial in response to a paper written by the Aldema (ph) Group on the role -- the protective

role of maternal antibody. We are now here almost to the day 20 years later. But the good news is that all of the vital components are here. And so failure's not an option and we should succeed.

But if we stumble, it won't be because we lack for technology or vision or motivation. This room is dripping with all of this. But it will be because we cannot set a direction and we cannot march collectively into the future. We should be not only wise but we should also be decisive. Now, Rafiki is not quite as wise as Dr. Plotkin but he is also very decisive.

And I'd like to leave you with a quote from Rafiki from The Lion King, "It is time." It is time for a CMV vaccine. And I also say that a vaccine administered to adolescents is not only reasonable but probably desirable. Thank you.

DR. PICKERING: Gail, thank you very much. Don't run because I -- we're going to have a few minutes for questions. But I remember in the early '70s when I went to Houston and met Dr. Demmler and Dr. Yow and remember the rubella clinics. Dr. Yow had

rubella clinics where two or three days a week all you would see were children with small heads, hearing aids and cataracts. It was awful.

We don't see those anymore. Hopefully in the future we won't see CMV anymore. So great talk. Thank you.

DR. DEMMLER: Thank you.

DR. PICKERING: Dr. Plotkin?

DR. PLOTKIN: Well, Gail, I agree with everything you said, of course. But --

DR. DEMMLER: All right.

DR. PLOTKIN: -- I just wanted to point out somewhat along the lines of what you're saying, as far as the issue of vaccinating adolescents and then possibly boosting later, we are using the HPV vaccine, where we don't yet know what the duration of protection will be. That doesn't bother us because we know that at the -- at the peak of sexual activity, there is protection.

And indeed, we have a correlate of protection in that -- in that -- for that particular vaccine. So I just wanted to point that analogy. We are using a

vaccine in adolescence where we don't really know how long it's going to protect. But if the data show, let's say, after 10 years that it's not longer protecting, then -- and women are still sexually active, then boosting those would be --

DR. DEMMLER: Then we just boost them. It's not the end of the world. Yes.

DR. PLOTKIN: Yeah.

DR. DEMMLER: Yeah, exactly.

DR. PLOTKIN: Uh-huh.

DR. PICKERING: Okay. Yes?

DR. NEELS: May I give a critical voice? You said up to -- that these vaccines will be cost effective. Based on a clinical trial published 22 years ago, I doubt that you can put that up not knowing the price of those new vaccines. Don't forget that the colleagues of the pharmaceutical industry are very inventive in putting a very high price.

I will give you only one example. The rotavirus vaccines are not recommended in the EU, only in three or four countries, due to the very wrong price setting. They are asking 150 euro per child to be

vaccinated. And in Finland, where they could get the price to 50 euro, it is cost effective. So --

DR. DEMMLER: Well, I agree with you. We don't have contemporary good data on current practices. The -- I put on my slide the only really well-designed full study that I could find by Porath and it was -- you're right -- decades ago. I did put on one of my slides what are the gaps. And we do need a well-done or maybe several contemporaneous studies looking at the impact of a -- of a CMV vaccine.

Children with congenital CMV disease now live longer. They have more doctor appointments. They have more therapy. They have more surgical procedures. They have more medical interventions, nutritional interventions, mobility devices. Am I right, mothers of CMV children who are here? Hear, hear. So I do submit that I think the vaccine will be cost effective if it's -- if we do a contemporary analysis.

DR. SEWARD: Let's -- I mean, I think the roundtable is the time for broader discuss because after the break, we've got our presentations covering children, modeling and other things that are going for.

So we'll take a break now for 20 minutes. And if we're back here at 25 to 4:00, then we're only five minutes off target. So exactly we'll start at 25 to 4:00.

DR. PICKERING: If everyone can sit down? You can go ahead and round them up out here.

DR. SEWARD: Could everybody take their seats so we can get the session started so we can finish on time tonight? Thank you.

DR. KRAUSE: Just as a clarification -- although, it is not just a question of finishing on time -- we will be asked to leave the room at 5:30.

DR. SEWARD: Right.

DR. KRAUSE: And if the discussions are not finished, we won't have the discussions. So it's absolutely --

DR. SEWARD: Right.

DR. KRAUSE: -- critical that the meeting keep as close to time as possible.

UNIDENTIFIED MALE: Be out of the building by 5:30?

DR. KRAUSE: Well, out of this room. The building maybe by 6:00 or something. So maybe you just

put the -- put the next speaker up and get going?

DR. SEWARD: Okay. So our next speaker this afternoon is Paul Griffiths. Is Paul here? Could everybody take their seats, please? I don't think Paul's back. Well, if Paul's not here, we'll bypass Paul or go onto the next speaker. Just kidding.

UNIDENTIFIED MALE: You can leave him off. That'll shorten things.

DR. SEWARD: Yep.

UNIDENTIFIED FEMALE: I think he's right out here.

DR. SEWARD: Okay. Maybe we can pull up his presentation.

UNIDENTIFIED MALE: Yeah.

DR. SEWARD: Okay. Here we go.

UNIDENTIFIED MALE: Paul?

DR. GRIFFITHS: Okay.

DR. SEWARD: Okay. So Paul is going to -- is from the University College London. And he's going to be addressing children as a potential target group population for CMV vaccine.

DR. GRIFFITHS: Thank you very much. The

organizing committee gave me the task of asking, "When we immunize children, should it be given just to females or to boys as well?" And I supposed the standard assumption would be that a girl should bear the risks associated with any CMV vaccine because she may be a mother in the future so the vaccine is not indicated for boys.

And having written that down quite boldly, I wonder if there are people in the audience who wouldn't quite agree with that and would think that it perhaps doesn't represent authentically how those burdens should be shared because can't we argue that a boy should bear the risks because he may a father in the future and fathers should share these responsibilities, shouldn't they?

We also need to think of family dynamics. Families are clearly affected by the medical, social and financial effects of having a child who needs extra help. Everyone in the family has an interest in reducing this risk, mother, father, daughter and son, half of whom are male and half of whom are female. If everyone benefits, shouldn't they all share the burden?

So let's look at that standard assumption; it's in the interests of both boys and girls to reduce their chance of having a future baby damaged by CMV? A CMV vaccine should therefore be offered to both boys and girls. We have a precedent for this in the case of rubella. Rubella is clinically mild unless a pregnant woman contracts infection, which usually comes from a child, as it does from CMV, and rubella vaccine is already given to both boys and girls.

And there are two approaches that have been used in the literature to control congenital rubella, the first, in the United States, where the population targeted was toddlers, and the second, in the UK, where vaccination was given to seronegative women.

It's probably easier to say -- make this next sentence than it is for other speakers because it's quite clear that the policy pursued in the United States was superior to that pursued in the United Kingdom.

The evidence for this comes from congenital rubella in the United States, where starting in 1969, down in the 19 -- middle of the 1980s, congenital

rubella had been brought down to a very low level, whereas, in the UK, the incidence of congenital rubella was staying at about the same level and was being controlled really by these quite large numbers of selective terminations of pregnancy in women who'd been proven to have rubella infection.

So in 1988 the rules changed in the UK to immunize children as part of MMR vaccine. And as expected, congenital rubella came down to a very low level and subsequently disappeared. So the rubella example gives us experience of vaccine effectiveness. So that's how it actually works in the community rather than in clinical trials. And it clearly shows that vaccination of toddlers, both boys and girls, is superior to vaccination of seronegative women.

So how should we use that information? Shall we now repeat the experiment of CMV or shall we learn from the rubella experience and simply apply it to the case of CMV? Let's consider whether vaccination of toddlers would help to control CMV. To do this, I've done a BOTE analysis. I'm not sure if that translates across the Atlantic either but BOTE is, "back of the

envelope."

This is real-world modeling of what might happen of the following circumstances. And we need to look at the incidence of congenital CMV for the United States population. This is using the data from the CDC. And this paper by Wang estimated the proportion of a primary and non-primary. So non-primary includes reinfections and reactivations.

And taking the paper from Brazil, Yamamoto estimating that perhaps 40 percent of them are reinfections. We can debate that figure if anyone's interested. Using Sheila Dollard's data from the CDC of how many go symptomatic, how many develop sequelae and how many of the asymptomatics got disease. Again from the CDC, the report that sex is much less important than children as a source of CMV.

And how would you use the vaccine? Well, taking the Institute of Medicine report, the recommendation, it should be given to boys and girls, age 12 years, and adding in, give it also simultaneously to toddlers. So it will hit the community in two different age groups to try to bring

the infection under control.

And to begin with, let's have an unrealistic target but 100 percent efficacy at 100 percent uptake of the vaccine. So given all of those criteria, if you work through the numbers, there are about 38,000 cases of congenital CMV in the USA each year. And using those figures, about half of them, 19,000, are babies who are born to women who reactivated their own virus. So this is endogenous reactivation of CMV.

Introduce -- the youngest age is 16 for pregnancy in the -- in this example. Introduce a vaccine at age 12. You have a lag period of four years then, before girls start to enter the pregnancy population, having been immunized at age 12. And so the proportion of women who contain -- who have latent CMV that can reactivate goes down and down with time.

And this process speeds up when the children who were immunized as toddlers now join the childbearing years. But even so, it's still taking a quarter of a century to actually start to bring this virus under control. So doing a reality check on that (indiscernible) does that seem right? It certainly

does but it's going to take several generations to get this chronic, persistent virus out of our antenatal population.

In contrast, if you look now at women who at risk of getting primary CMV infection, typically these are -- these are women, let's say, age 20 years of age, so who, therefore, have avoided this virus for a fifth of a century now. Their family members are often seronegative. Their partners are often seronegative.

What's changing in their life is that they're coming in contact with a child who's excreting CMV, either their own child -- their first child, who's now socializing with other kids or they're involved in childcare contact themselves, and so acquiring virus from those cases.

If we could immunize the toddlers at that time and render them less infectious to their mother, you'd expect a dramatic reduction in congenital CMV because these women don't have other sources of CMV infections. It's quite reasonable to expect them to come to down at a dramatic rate. They won't come right down to zero because the partner is still a risk for

them.

But with time, those partners, once they start to have benefitted from vaccine themselves as adolescents, will bring this down to an undetectable level. And eventually, you'll come to a zero risk of congenital CMV in this particular group from primary CMV infection. And this model looks -- it is about the right time, just as these children are coming through, having been immunized as toddlers to enter the childbearing years.

This subset of the community, who, of course, only represent a minority of the total cases, can actually be -- you can be anticipating good control of congenital CMV infection. So whereas, the discussions we've had today have focused a lot on immunizing toddlers and asking how long their immunity is going to last, of course, that's very important, but for this group of women at risk of primary CMV infection, it could possibly all be over by the time those kids make their way through into the childbearing years.

So let's just pause and have a reality check on that. Does that seem realistic? It seems overly

optimistic. But consider what you're trying to do at this particular point here. Here is a woman who's seronegative who's going to collect her child from the daycare center, for example, giving the child a big kiss, acquiring CMV from the child's saliva and so, because she's pregnant, risking damage to her current pregnancy, her current fetus.

What we're hoping to do is give a vaccine to her toddler so that the child is still going to daycare center but hasn't picked up CMV and so is non-infectious to his mother. We don't need that child to be rendered to have sterilizing immunity so the child has no virus at all. We just want to be able to reduce the risk that that child transmit virus to its future sibling by crossing the mother's placenta.

We don't know all the factors that control that transmission from mother to child but we do know that two-thirds of women who have primary infection during pregnancy at the moment do not transmit in utero. It's not difficult to imagine that the one-third who are lucky -- who are unlucky are the ones who have a high viral load.

If that is true, then simply by giving a vaccine to toddlers, such that it reduces the quantity of virus that they challenge their mothers with, may nevertheless give a substantial benefit to their future sibling by not infecting it in utero. I know that's a bit of handwaving but I think it is a realistic approach and says that one of the attractions of these models is not necessarily to believe the numbers but actually to generate some questions that can be asked in future studies.

And someone on the panel asked for collaborations between the public/private sector. Here's one perhaps that when people are doing their immunization studies of toddlers, we should be looking not just at them as cases of infection -- are they protected -- but do they -- not to transmit virus to their mothers and also if those mothers are pregnant, does it reduce their risk of transmitting virus in utero?

Okay. So those are the ones for primary infection. And the ones in the middle have an intermediate category, the ones who are being

reinfected. So these women have become seropositive. They have acquired CMV somewhere along in their life. They probably have another child infected with CMV. They may have a partner who's CMV seropositive They carry on for a while but by reducing the infectiousness of their children and the other children they meet, you'd expect them to come down at a reasonable rate. Their partners still are seropositive. But even so, on this analysis, they're still coming down almost to negative by the time that the toddlers are making their way through in the community.

So for CMV and rubella, the major risk to a -- to a fetus comes from its older sibling, who's bringing virus home to infect their mother. Older siblings can be boys or girls so CMV vaccine should be given to all. We also need to consider the question, is CMV mild in males as it is in rubella?

Well, there are solid organ transplants. There are bone marrow transplants in the community, if we assume that those are 50/50 male or female -- we also have AIDS patients who are clearly overwhelmingly

male overall.

We also need to consider -- the sentence is often stated that CMV is only important in the immunocompromised. And here I've taken a couple of quotes from the bible of virology, Fields Virology. "As a rule, acquired CMV infection in the normal host is clinically silent." That is a true statement of fact.

Another one, "The importance of CMV as a pathogen has risen with organ allografting and AIDS," another true statement. Unfortunately, many people in the literature may take a shortcut. They say that CMV's only important if the immune system is damaged or immature. Where's the evidence for that?

In order to come to that conclusion, you would have to follow up individuals who are seropositive but who are not immunocompromised and seeing whether or not there's any adverse outcome for them. You don't have to look very far. I just looked back in last month's Journal of Virology and could find one very easily.

"CMV, while normally benign, is a significant

pathogen in immunocompromised individuals," a written statement in a peer review paper. How can they say that it's normally benign? We don't know it's normally benign, do we? We haven't done the study. The study has now been done -- it was done last year -- what happens to the seropositives in the general population.

Simanek and colleagues used the NHANES data looking for CMV, age-stratified population that you're familiar with. Fifteen thousand were tested for CMV IgG antibodies that had also been tested for C-reactive protein. They had a mean of 13.7 years of follow-up and had to be at least 25 years of age in this study. Death was found in 19 percent of them overall and cardiovascular disease in 8 percent. And they used Cox proportional hazards models to tease out the relationships between CMV and overall mortality.

All cause mortality is significant and quite strongly associated with CMV serostatus. These are the seronegatives and these are the seropositive. I suspect most people in the audience would rather be seronegative than be seropositive over here. CMV had lots of bivariate significant associations with other

confounders, including obesity, smoking, poor -- low educational standard, et cetera. But when all of those were controlled for, this effect of CMV still remains significant, albeit attenuated.

So I have a proposition for you to consider. CMV is an important pathogen for females and for males. It is true that overt disease is restricted to two particular groups but they have an excess of males. Subclinical infection is associated with excess mortality, as I've just shown you. While this association has not been proven to be causal, a reasonable presumption is that the benefits of vaccination will not be limited to females.

So the recommendations are that the model proposed by the Institute of Medicine, whereby children of both sexes are offered vaccines, should be accepted, that the evidence is so strong that the onus is now passed onto those who disagree with this to provide evidence against vaccination of boys as well as girls or to put that graphically, when you look at the evidence from the literature -- I've shown you some examples from families, from the rubella model, from

transplant and AIDS patients, where there's an excess of males, and also now from the NHANES data set.

Those suggest we should be considering protecting boys as well as girls. And I can't think of anything to put on this other side of the scale. Perhaps I've been unfair and now is your opportunity to tell me if I've been wrong. Thank you.

DR. SEWARD: Thanks, Paul. And any clarifying questions?

DR. SPECTOR: Paul, I want to say that I really want to commend you for bringing that up in terms of the other things that cytomegalovirus may be associated with that we're ignoring here because it may not happen until you're 50 or 60 years old. And the study you brought up is not the only one and that is if you go into the literature now and you don't just look at seropositivity, but you look at levels of antibody, there's a very strong correlation with atherosclerosis.

And there are other things we could talk about but I really want to commend you for bringing up, that just because you're old doesn't mean that you won't be harmed by this virus.

DR. GRIFFITHS: Thanks, Debbie. I think you and I perhaps may be gaining a conflict of interest in speaking up on behalf of the older half of the population perhaps.

DR. SPECTOR: We might.

DR. GRIFFITHS: But you're right. I didn't mention the other things. There is substantial evidence that those in the top quartile of the CMV IgG antibody level have more evidence of atherosclerosis than other inflammatory conditions. The trouble is we don't know that that is causal.

And also they are selected populations, whereas the NHANES data set has a real advantage in that it is age stratified and properly structured for the whole of the United States. And it's a substantial size of 15,000. I think we need to take that information seriously.

DR. PICKERING: Okay. We will have a question-and-answer period in a moment with all of the speakers. So I think we'll move on. And Dr. Lanzieri is going to talk about modeling of CMV transmission in disease. And while she's finding her slides, Stuart

Adler has a piece of information about a website that can help us with cost effectiveness. Stuart, did you want to --

DR. ADLER:I don't have a website but I have other information. No, I don't have the information but I do have the program. The Institute of Medicine 1990 report on vaccines for the 21st Century has online an Excel spreadsheet that allows you to do your own cost benefit analysis for a CMV vaccine using a whole variety of assumptions, including obviously the cost of the vaccine, cost of care, durability of immunity, et cetera.

So for anyone who's interested in the cost benefit question, that Excel spreadsheet's available online.

DR. LANZIERI: Good afternoon. Today I'll be presenting some preliminary findings from the work we have been doing on modeling the impact of vaccination on the epidemiology of CMV infection and congenital CMV in the United States. I have no conflicts and no disclosures to make.

And the rationale for using modeling to

assess the impact of CMV vaccination was that modeling can help us to better understand the disease dynamics and knowledge gaps in the epidemiology and natural history of disease. It can also help us explore the potential impact of different vaccinations scenarios on the CMV seroprevalence and congenital CMV infection. As well, it can help us support the design and implementation of Phase III vaccine trials and in the future inform and guide vaccine public health policy.

Well, previous models have been done. And the work by Azevedo using data from Brazil suggested that the optimal age for vaccination would be two to six months for a vaccine with lifelong protection. However, if immunity wanes before 20 years, an increase in congenital CMV infection might occur.

Then, the best strategy would be universal vaccination at the -- at age one year, plus, a second dose at 12 -- at 10 to 11 years. Earlier Griffiths -- it's not the BOTE analysis but the analysis he published in 2001 -- he showed that a vaccine with 60 percent efficacy given to children less than one year could potentially eradicate infection.

And the potential benefits of CMV vaccination of children one to -- less than one year would start at the first year of vaccination program due to reduced number of infectious children less than one year or toddlers transmitting CMV infection to their mothers.

So the objectives of this modeling is -- are trying to respond the following questions. One, what's the potential impact or routine CMV vaccination and congenital CMV infection in the United States and how does it vary by age group vaccinated, by vaccine efficacy and by duration of protection?

Second, how long it would take to achieve such impact on congenital CMV infection, and third, what are the key uncertainties that affect our understanding of the potential impacts of routine vaccination on congenital CMV infection? And we've been all day long discussing these uncertainties.

Well, the model -- this slide shows the model structure. And I'm not going to go through any Greek letters. And the susceptible individuals acquire infection and remain infectious for six months and develop latency and then may experience a reactivation

in 20 years.

Vaccinated individuals would then become -- sorry, vaccinated individuals would be protected from primary infection. So this model is only assuming protection from primary infection and later, reactivation. Although, we will -- we will incorporate reinfection in the future. We were just time constrained in preparation for this CMV workshop.

And although I don't show the age structure here in this scheme (ph), it was incorporated into the model. It's just that it would be very overwhelming to show that to you. And the impact on congenital CMV would occur as a result of prevention of primary infection in individuals 10 to 39 year olds and later reactivation.

And the reduction was estimated by comparing the number of individuals in this age group in the infected compartment that I've shown -- I've shown before post-vaccination to the number pre-vaccination. How we fitted this model? We used U.S. data on CMV seroprevalence derived from NHANES III. And we estimated data for the age group zero to five so we

still lack this kind of data.

We fitted the seroprevalence to a constant force of infection and also to different transmission matrices that were adapted from the work of Azevedo. And to do all this calculations, we used Berkeley-Madonna software.

The results I'm going to show on the impact of routine vaccination on CMV seroprevalence and congenital CMV infection will have the following assumptions: 70 percent vaccine efficacy, 90 percent vaccine coverage, 5 years of duration of protection and 20 years for reactivation of latent CMV infection. Can I get some water before?

This slide shows the effect of age at vaccination on CMV seroprevalence. And the black dots represent NHANES data and, therefore, no vaccination. Not much change would be expected with vaccination of teenagers shown in the blue and the orange lines that overlap close to the dots.

And vaccination at 12-18 months, shown in the green line would potentially eliminate infection. However, is that feasible? Let's bring it to

discussion later. And vaccination at 12-18 -- sorry, did I say, "12-18?" I -- the green line indicates vaccination of 0-12 months and that is the one who -- that would eradicate infection.

Then, I'm going to show the red and blue lines that show vaccination of 12-18 months and in the red line. And in the blue line you have vaccination of 12-18 months, plus, a booster for 10-11 years. So this would have the highest impact in CMV seroprevalence.

In the next slides I'm going to show the impact on congenital CMV infection. I will now show the effect of vaccine efficacy and coverage on congenital CMV infection. With routine vaccination at 12-18 months, assuming duration of protection of 5 years, 70 percent efficacy and 90 percent coverage, thus, about 63 percent protected. The reduction in congenital CMV infection would be about 30 percent.

Considering the same graph and the same line, I'm going to walk you through how the results would vary in vaccine efficacy. And now, assuming a lower vaccine efficacy, let's say, 45 percent times 90 percent coverage, about 40 percent protected. Then the

reduction would be about 20 percent of congenital CMV infections.

Now, I will show the effect of age at vaccination on congenital CMV infections. You're already seen the impact of vaccination 12-18 months, shown in the red lower line -- or the lower red line. And the upper red line shows the reduction in congenital CMV infections by vaccinating at 10-11 years. Given the same assumptions, a 10 percent reduction would be expected by vaccination 10-11 years -- the 11 year olds.

Now, I will show the effect of duration of protection considering vaccination of 12-18 month olds. You already know the red line, right? Right? So the reduction in congenital CMV infections would range from 25 percent with 2 years for protection and 45 percent with 20 years of protection. The longer the duration of protection, the highest the impact. So you see also the highest -- the higher the coverage or the higher the efficacy, the higher the impact.

Next, all these results I've been showing to you are predicted reductions for the steady state. So

it means that it would occur several years or several decades after a vaccination program started. So in the next slides I'm going to present how long it would take to reach this steady state and then achieve these reductions.

So considering we start vaccinating in 2020, and again, vaccinating at 12-18 month olds, the -- it would take at least 100 years to reach that level of 30 percent reduction with a vaccine that is 70 percent efficacious, 90 -- with 90 percent coverage and assuming 5-year protection. Although, much of the gains would be achieved much sooner, perhaps in about 30 years when the -- when 20 percent of reduction is achieved.

What would happen -- could we achieve these reductions earlier? So if we start a vaccination program that considers vaccinating 12-18 month olds, plus, a booster dose a 10-11 years, then these reductions would probably be achieved sooner. And 20 -- the red line you already know and then the blue line indicates the vaccination at a young age, plus, the booster dose at 10-11 years. And then this reduction

of 20 percent that I've been talking about would be achieved probably 10 years earlier.

Another important aspect to consider is whether vaccination would increase susceptibility to primary infection in women of reproductive age, thus, increasing the risk of congenital CMV infection due to primary infection, which is associated with higher risk of sequelae.

And if immunity wanes before 20 years, as shown by Azevedo, vaccination of infants could increase congenital CMV infections. Using data from the U.S., we do not observe this perverse -- adverse event of the vaccination program. And the graph shows the reduction in congenital CMV infections due to primary maternal infection post-vaccination, depending on the duration of vaccine protection.

However, we also fitted the model to Brazil seroprevalence data. And although we could observe a decrease if the vaccine protection lasts forever, a vaccine with a shorter protection, about five years, would potentially increase the number of congenital infections due to primary maternal infection.

And in this slide I'm going to show how the potential increase in primary infections relate to the burden of disease. Given that we don't know much, it's all -- I'm always considering various assumptions. So in the United States, we believe 25 percent of CMV infections are due to primary infection during pregnancy. And this is translating to 7000 cases of the 28,000 newborns with congenital infections.

In the U.S., vaccination of 12-18 month olds would reduce congenital CMV infection by 20 percent due to primary infection, preventing 1400 cases of congenital CMV infection due to primary infection, as -- and as I presented previously, a 30 percent reduction in overall number of cases, which means less 8000 cases annually.

In Brazil, an estimated 1 percent -- and there is a question mark there -- should be actually -- 1 percent of congenital CMV infections would be due to primary infection of the mother, since Karen Fowler this morning showed this is a very high seroprevalent population.

And this would represent actually about 35 --

sorry, 350 cases of congenital CMV infection due to primary infection in -- during pregnancy. And then that relative increase that I have shown in the previous slide for vaccine that gives protection for five years would translate an increase of 20 percent of cases or an additional 70 cases annually.

However, the reduction in overall congenital CMV due to the impact of vaccination would be 10 percent of overall cases, which would represent 3500 cases of congenital CMV infection of the total newborns that are born annually with congenital CMV in Brazil.

We used modeling to explore the influence of different age at vaccination, vaccine efficacy and coverage, as well as duration of protection on the epidemiology of CMV and congenital CMV infection in the U.S. And I'll be talking about our first insights in future work.

So the highest impact would be achieved by vaccinating young children. And route vaccination of 0-12 month olds could potentially eliminate CMV after several decades of vaccination. However, what would be the feasibility of developing a vaccine to be given at

such young age?

Additional questions to be addressed also relates to, what is the role of passively transferred maternal antibodies in protection against perinatal or postnatal CMV infection and would could be the impact of this on vaccine effectiveness? Also we need seroprevalence data for the age group 0-5 years to better understand the age for vaccination of young children that would have the biggest impact in reducing congenital CMV infection?

And CDC is collecting samples of children at this age group that will be tested for CMV. That's done through the NHANES V. And additional questions would be what are the rates of CMV infection in the perinatal period and in young children? How long do young children shed virus and how much do young children transmit infection?

I think this is my last slide. And so our second insight and -- but really belonging to the first insight because it's all preliminary -- the baseline seroprevalence is an important determinant on -- in the impact of vaccination on congenital CMV infection. And

modeling suggests potential for a relative increase in congenital CMV due to primary infection in high seroprevalence populations, despite the overall reduction of disease.

And in populations with high CMV seroprevalence, congenital CMV infection currently mostly occurs as a result of non-primary maternal infection. And then we need better understanding of the role of reinfection on severity of disease to understand if there are any scenarios in which a relative increase in congenital CMV infections due to primary maternal infection could result in an increase in burden of disease. Thank you for your attention.

DR. PICKERING: Thank you. That was very excellent and very clear. Are there any pressing questions that someone will want to ask before our question-and-answer session with all the speakers? Yes?

DR. FEINBERG: So a very pragmatic question related to actually designing clinical trials. This is modeling what happens out 30-100 years, when there's 90 percent coverage. Your first clinical trial, there's 0

percent coverage in the population. And the biggest fear is when you first go into an adolescent population and there's zero population cover, that in that trial you increase congenital infection rates.

Have you done any modeling to address that concern, which is certainly the most pragmatic one that's holding up even getting into an adolescent population for an early-stage trial?

DR. LANZIERI: So the question was if we give vaccine to adolescent population?

DR. FEINBERG: Just in that initial clinical trial, could you actually find that -- when you're in your efficacy trial, when there's no coverage of the population overall, just your trial, could you actually increase congenital infection rate in your subjects' infants?

DR. LANZIERI: Oh, I understood you're trying to think -- if the vaccine trial could actually do harm to the population?

DR. FEINBERG: Exactly.

DR. LANZIERI: That's an interesting point I would have to think about. Yeah.

DR. FEINBERG: Okay.

DR. SEWARD: Thanks, Tatiana. So let's -- our next speaker is Jeffrey Roberts from FDA, who's going to give perspectives on maternal immunization strategies.

DR. ROBERTS: All right. So as Dr. Demmler pointed out, Dr. Plotkin has spoken fairly unequivocally about the prospects for pregnancy-specific indication for a CMV vaccine. So I kind of felt like maybe we should take a break during this period. But I think it's worth forging head, if for nothing else, to kind of provide some perspective from a regulatory standpoint and some clarification.

So I'll start with some ethical and regulatory considerations. It wasn't that long ago that FDA recommended that pregnant women -- not only pregnant women but all women of childbearing potential be excluded completely from clinical trials in the -- in the wake of the Thalidomide tragedy.

And we've reversed that policy in 1993. And in fact, now we have regulations that define the conditions under which studies in pregnant women may be

conducted. And I think we've also seen that among external stakeholders, there's increasing support for studies in pregnancy generally.

And I'll point to this particular WHO collaboration that establishes ethical guidelines for biomedical research. And one of those guidelines specifically was that pregnant women should be presumed eligible for participation in biomedical research. So I think -- I think it's clear that there's no regulatory or ethically prohibition on studies in pregnancy.

And I would suggest that the barriers, to the extent that there are barriers, they're perhaps more of a medicolegal nature. And I reference this commentary from Glezen in which he talks about the Vaccine Injury Compensation Program and how it doesn't -- hasn't been interpreted to apply to pregnant women and fetuses.

So specifically about a maternal immunization strategy to prevent congenital CMV, I think we're all familiar now with the epidemiology, including that among these long-term causes of disability, congenital CMV is more common than many of the better-recognized

one, such as fetal alcohol syndrome and Down Syndrome and neural tube defects.

We also have several clinical trials that have produced some promising results. So I think that at this point, the benefit-risk assessment justifies clinical development of a maternal immunization approach.

So far I've used this term, maternal immunization, because it's commonly used in the -- in the medical community. And I just pulled this quote from this commentary from Drs. Gall and Poland in Vaccine last year, in which they define maternal immunization as all women contemplating pregnancy, pregnant women and postpartum women.

But from a regulatory perspective, the term, maternal immunization, has little meaning. So from our perspective, the important distinction is between females of reproductive potential and pregnant women. And in terms of the regulatory path, I'll kind of talk about both of these separately.

And so for perspective with regard to females of reproductive potential, I think the HPV vaccines are

a -- are an excellent place to go in terms of a template. And so I'll just review a little bit about what happened in those development programs. So pre-clinical reproductive toxicity studies were conducted for both Gardasil and Cervarix.

Both of those studies were published in literature and the details are available. I've referenced them. And then just to pick out Cervarix and look at the clinical development, in the pre-licensure trials, there are approximately 24,000 women or females, 9-26 years of age. Each of these subjects was instructed to avoid pregnancy and they were screened with a pregnancy test prior to each vaccination.

And in spite of these measures, 761 of these women became pregnant with the last menstrual period within 45 days of vaccination. So that's a relatively small number compared to the 7000 pregnancies in that trial -- in those trials. These were the ones that occurred only proximately to vaccination. So it speaks to some -- the inadvertent exposure we can expect, particularly after licensure.

But those data represent important safety data and they are in the label, both for Gardasil and for Cervarix. And then pregnancy registries were established for both to collect data on pregnancy and newborn health status outcomes for both the HPV vaccines. And thus far, those data have been -- have been reassuring. So that's really it in terms of females of reproductive potential.

The more difficult issue obviously is pregnancy. So first of all, this is kind of the current status of at least U.S.-licensed vaccines from the -- from 20,000 P (ph). So we have regulations that require that each product be classified according to these pregnancy categories, A, B, C, D, and X. And for the most part, the vast majority of vaccines have a pregnancy category of B or C, and this includes all the inactivated, the subunit, the polysaccharide conjugate vaccines.

And then most live attenuated vaccines are contraindicated in pregnancy. And as I mentioned, whatever human safety data there is is generally limited to the data that was collected after

inadvertent exposure. For the most part, this is only in the labels of Gardasil and Cervarix.

And so the bottom line is that no U.S.-licensed vaccine label contains any clinical efficacy data in -- specifically in pregnancy, and obviously, no vaccine has an approved indication for use in pregnancy so with -- so little kind of precedent with regard to this. I went back to, you know, some basic regulatory definitions.

And Dr. Krause has already covered this but I think it's interesting to look at how we define particularly safety and that we mention indirect -- persons that would be indirectly affected and in the fact that we talk about safety in relation to the condition of the recipient at the time. So it gives you a sense of why it's so important to characterize safety so fully, given that generally vaccines have been indicated for healthy people.

And so briefly some observations from a regulatory perspective in the different phases of development. To start off with, reproductive toxicity says generally recommended if the intended use will

include either pregnant women or females or reproductive potential. And there's some difference with regard to the timing -- the expectation of the timing of these studies.

And this is a quote from our Guidance for Industry about developmental toxicity studies. And it basically says, "The expectation is that these will be done prior to initiating studies of the intended use is in pregnancy." And then in Phase I, in Phase II, obviously depending on the -- whether or not the product and the adjuvant are novel, in any sense, the safety and immunogenicity generally would be expected to be characterized, at least very early in clinical development in healthy non-pregnant subjects.

But then also, obviously, if the intended use is in the pregnancy, you would be expected to begin to define safety and immunogenicity in pregnant individuals and infants early in development. And at this point, you start to characterize infant growth and development and start to characterize efficacy endpoints.

And then in Phase III, in general most

probably the expectation is that you will conduct a pivotal efficacy trial in the target population, in other words, in pregnant women, with a clinical endpoint, and also better define the human immunogenicity and characterize the human safety, both in mothers and infants.

So I feel like I ought to issue the same disclaimer that Dr. Neels did earlier. You know, which -- without having -- us having a guidance on CMV and with having so little precedent for developing vaccines specifically for use in pregnancy, it really just -- all I can do is point to the questions and considerations less than give you answers, and certain with regard to this first bullet point, the overall size of the safety database. I think we'll leave it to Dr. Gruber and Dr. Plotkin to discuss this further in the roundtable.

And in terms of maternal and fetal safety monitoring, what will be necessary beyond what's routinely provided in prenatal care? This will be particularly important if trials are conducted in developing countries. And then some other

considerations are establishing appropriate sequential monitoring and/or halting rules.

There will be statistical challenges in analyzing data in pairs or perhaps more, both from the safety and an efficacy perspective. And then probably the most important thing that we've been talking about a lot is establishing the appropriate efficacy endpoint for the pivotal trial. In the case of the CMV vaccine, it's in the spectrum from maternal infection to neonatal to infant disease with the sequelae. Where will that endpoint be? And then -- and then there's always the quite controversial issue of, what will be the appropriate length of follow-up for infant developmental outcomes?

So finally, I'd like to kind of step away from the -- from the regulatory and talk a little bit about scientific considerations, particularly with regard to safety in pregnancy. I think for vaccine trials in pregnancy, it may be useful to think about dividing safety outcomes broadly into these two categories, which are fetal development and then maternal immune tolerance versus rejection, and the

importance to inflammatory mediators play in that pathway.

I think it's clear that most of the efforts to define safety in pregnancy with -- in terms of drugs have been focused on fetal development and congenital anomalies, and rightly so. I mean, these are receptor-mediated teratogenicity that arises from these drugs that cross the placenta for the most part.

But what I would suggest is that the -- another important kind of group of outcomes is along this spectrum of this delicate balance between maternal immune tolerance. And I've listed some of these outcomes here and we can perhaps discuss this more in the roundtable.

So in summary, from our perspective congenital CMV is a medical need relating to pregnancy that has the potential to be addressed through maternal immunization. We encourage sponsors to pursue the most promising strategies through adequate and well-controlled studies. And, you know, echoing on some of the things that Dr. Krause and Dr. Neels have said, we really encourage engaging early in the development

program to establish the appropriate parameters, both for pre-clinical testing and clinical trial design. Thanks.

DR. PICKERING: Good, are there any pressing questions? Yes?

DR. NEELS: Jeff, you said that no vaccines are licensed in the U.S. for pregnancy. And if I'm well informed, ACIP has given out the recommendation to vaccinate pregnant women against pertussis. How are they going to do that?

DR. ROBERTS: Yeah, this is perhaps a question for Dr. Pickering more than I.

DR. SEWARD: Well, I mean, ACIP does make off-label recommendations. And so there's recommendations for vaccination of pregnant women -- I'll be going through some of this in my talk -- for influenza vaccine, TIV and for pertussis. And that's on the basis there are some data available on benefit to the mother and the infant for both of those diseases. But there's not a license to indication.

DR. PICKERING: Yes?

UNIDENTIFIED MALE: There was a recent

convening by the Gates Foundation on maternal immunization. And I understood from speakers from the FDA who attended that meeting that there are considerations within the agency of moving away from this category, A, B, C, to another approach. Can you update us what the thought is on that?

DR. ROBERTS: Yes. I think Dr. Gruber would be the best person to update you on that. It's -- yes. We've been moving in that direction and we're going to get rid of those categories at some point but how close we are is a -- that's a good question.

DR. GRUBER: Right. That is true. I mean, we're still pursuing this. I mean, the goal is really to replace these categories with, you know, more information regarding data available from immunization of pregnant women. And that data will be included in labeling, you know, provided -- well, the FDA will have to do a review to see if the data from, you know, that are derived from studies in pregnant women are adequate to be included in the label.

But what I wanted to actually clarify is -- and to put this a little bit in context, we seldom have

well and adequate-controlled studies -- pre-licensure studies of vaccines in pregnant women, which is the reason why we don't have a specific label or a specific indication for use of the currently licensed vaccine in pregnant women.

But the pregnancy categories as they currently exist, specifically B and C and most of our products are labeled, "B," and, "C," do not represent a contraindication for use of this vaccine in pregnant women. So that is, you know, these vaccines can be used to immunize pregnant women if clearly needed. And as such, there is really not a -- you know, there is not a conflict between the ACIP recommendations and the FDA label, if you want.

And the reason why we want to move away from the pregnancy categories is because they're not very informative. And under the new labeling regulations, once approved, you know, it will be allowed -- permitted to also include data from studies that are not necessarily derived from pre-licensure studies.

So this could be, you know, studies published in the literature, provided again that the FDA has made

the determination that they can be included in labeling. But the rule is moving to be finalized. You know, guidance is being developed but I cannot give you a date in terms of when this rule is going to go into effect.

DR. PICKERING: Good, thank you. Yeah, I think anything that would help clarify that, to make immunization of pregnant women appropriate immunization easier would be -- would be very helpful. So thank you for doing that. Okay. We'll have a question-and-answer session if Jane leaves us any time following her talk. And the title of her talk is Lessons Learned from Other Vaccines.

DR. SEWARD: Thank you to the organizers for inviting me. And I've changed the title of the presentation just slightly, as you can see there. And I'll be going through lessons and covering these target groups that we've all been talking about in this session and some of the issues that I'll be commenting on are listed there on the right.

So let's start with infants. I don't think all infants sit quietly like this and receive a shot in

the arm but this infant did. In the United States -- and I'll be mainly commenting on experience of vaccine programs in the United States -- we've had focus on achieving high coverage and monitoring coverage among preschool children since the mid-1990s.

And you'll see why in a couple of slides but this was really because of the measles resurgence in the late 1980s that highlighted our appallingly low vaccine coverage in the preschool age group. Most infant vaccines are inactivated, either whole virus or toxoid, recombinant subunit or conjugated polysaccharide vaccines. And we have an increasingly complex schedule.

And you've seen this schedule already but just to highlight that, for infants, they get 10 vaccines routinely recommended that deliver -- protect them from 14 different vaccine-preventable diseases. And that's not even counting polio as a combination vaccine that it is. And so it's a complex schedule and it's not simple to add another vaccine.

We always worry, as more vaccines are added -- it's great. We want to protect but other vaccines

may suffer in terms of coverage. And so there's a very integrated program that needs to be monitored. The vaccines, as you saw, are commonly three to a series in infants up to four and six months.

The age at administration is a balance between providing protection as early as possible, the immune response by age and effective maternal antibodies. Most infant vaccines provide protection from severe disease outcomes during infance [sic] for the vaccine recipient. There are -- there's one major exception to that, which is rubella, but I'll address that later.

Combination vaccines are clearly an advantage because they decrease the number of shots that infants will have to get to get those 10 vaccines in or the 14 antigens. But there are challenges to manufacturing combination vaccines as well. And complex trials are needed for co-administration when any infant vaccine is added to the schedule. Companies have to do co-administration trials with all those other vaccines.

Cost barriers are minimal for vaccination of infants in the United States with our Vaccine for

Children's program, which covers about 45-50 percent of the birth cohort for vaccines, the government-funded program. But new, more expensive, vaccine series have provided a few challenges and rotavirus is one of those.

And so this shows vaccine coverage on preschool children in the 1970s and '80s, which really was in the range of 60-70 percent, which is why we had this measles resurgence. And then you can see from the 1990s on, with a big focus on improving vaccine coverage and monitoring it, which wasn't being done very well before that -- you see we achieve very high coverage for all our infant vaccines.

And I don't think this is working very well but you can see over here in the right, rotavirus going up very strongly there in the black line. Vaccination of children -- so by definition children start at 12 months of age. You know, a child is considered a child at 12 months and below 12 months, we have infants.

And so live viral vaccines are typically administered to children above that age. There are exceptions, of course, oral polio virus vaccine and

rotavirus vaccines. But there are advantages in terms of the number of doses. And Stan brought up some of the advantages this morning in terms of much smaller number of doses and much more durable immunity because live viruses replicate and provide a much better immune memory.

They're given at a time where maternal antibody has declined and that's why we give them at 12 months or older. Influenza vaccine is given annually now and booster shots are given to children. And childcare and school entry requirements in the U.S. are an effective strategy for achieving high coverage for many of our vaccines. And so this is just the vaccine schedule for children showing the viral vaccines coming in -- the live viral vaccines, MMR, varicella, at 12-15 months, and then booster doses for other things.

So on to adolescents. Vaccination at 11-12 years was promoted by ACIP, AAP and AAFP since 1996 for catch-up vaccinations. So if children didn't get the vaccines you saw on the previous schedule, they needed to get them when they were adolescents. But adolescents were recommended for routine vaccines at

11-12 years after licensure of meningococcal conjugate vaccine in 2005.

And so current recommendations are to give routinely four vaccines at this age, MCV4, Tdap, influenza and HPV, and then catch-up for other vaccines. And you've seen this schedule as well. So the yellow bars -- yellow is routine and green is catch-up.

Here we see coverage for our adolescent vaccines for children -- teens 13-15 years between 2006-10. And you can see that the uptake of Tdap and MCV have been roughly parallel and also second-dose varicella. But concerningly, HPV is quite different. And we've had -- we're increasingly concerned about the slope of uptake of MCV -- of HPV, both for one dose and for the series, which is much lower.

If we look at this uptake against the infant vaccines though, in fact, all the adolescent vaccines are having great uptake, with the exception of HPV. And so I'll talk about that next. In considering vaccinating adolescents, we have to think of opportunities for visits. And this was a study

published a few years ago, looking at adolescent visits in females and males.

And the dark blue bars is visits to pediatricians' offices.The hatch bar at the bottom is family practitioners. The light green -- light blue is obstetricians. And so you see for females that adolescents do continue to go to the doctor but increasingly, as they stop going to the pediatrician, they start going to the obstetrician.

And so if we're going to vaccinate in older adolescents and young adulthood, then OBs need to play a very important role in vaccinating. For boy teens, really when they stop going to the pediatrician, they stop going to the doctor. And so you have a pretty dramatic drop-off. And so I think we might have some challenges with HPV vaccination of boys.

Some of the challenges identified at adolescent vaccination at the family/adolescent level -- and you can just look at these. I'm not going to read them through. At the provider level, you know, just less years of experience with vaccinating this age group. But I think the slope of uptake for the -- for

Tdap, mening [sic] and two-dose varicella are optimistic that the providers will get there and the families will get there with getting these vaccines. But single vaccines may be much easier than a series of three.

At the systems level, there's some, you know, perhaps less programmatic infrastructure, concern about insurance lapsing at 18, when children age out of the Vaccine for Children's program -- although, we hope this will all be covered under health reform in the future -- vaccination of adults and then monitoring vaccines when some of the vaccines are given outside the medical home.

Specific challenges for HPV -- and I think this may, you know, CMV may have a lot of -- there may be a lot of similarities if we're thinking about a three-dose series for adolescents at an early stage perhaps. The benefit of vaccine -- the outcome prevented isn't apparent for years or decades later. It's a sexually-transmitted disease.

Vaccine recommendation and acceptance is lower at 11-12 years than in older adolescents,

possibly because of the fact that it's a sexually-transmitted disease, we think. Research has shown that. It's a three-dose series, more challenging. Factors affecting series initiation versus completion may differ and so solutions for dealing with starting the series and completing it differ. And initially, for HPV vaccine there was vaccination for girls and women only.

And so data to inform some solutions to this -- this is a survey of physicians about their attitudes about recommending HPV to their female patients in different age groups among both pediatricians and family physicians. And you can see there's quite dramatically lower proportion in the range of 50 percent only who are recommending at the recommended age group of 11-12 and far fewer below that. And at the older age groups, you know, less of those kids come in, especially the boys, as we get to vaccinate boys.

Missed opportunities is a very big factor. And if every opportunity that a physician -- that an adolescent was in the office was taken to vaccinate, we would immediately achieve these coverage levels for the

three vaccines but we're only talking about HPV-1 here and not the series.

Just before I go onto immunization in pregnancy, I'd say that, you know, at CDC we're focusing with partners very heavily on the problem with HPV vaccination. And we're not accepting this low coverage. We're doing a lot of work with AAP, with AAFP, with ACOG, to try to improve the coverage.

Looking at alternate venues, we know Australia, we know UK has been dramatically successful in achieving more than 90 percent coverage for their series with vaccinating in schools. So it clearly can be done. We're just not managing to do it here yet.

So immunization in pregnancy -- vaccines recommended before, during or after pregnancy, I'll cover that and I'll focus on experience with influenza vaccine because it's by far the most experience in studies done with that.

This table is on the CDC website. And before pregnancy is sort of women of childbearing age. I mean, it's catch-up vaccination for those age groups. I think this is a very difficult group to reach. I

think women of childbearing age in general are a very difficult group to reach unless you get them during pregnancy or immediately after pregnancy. And I'll talk about that in a minute. But if you can get them, it's a good thing to do.

There is a lot of experience with a captive population of, you know, testing during pregnancy for two live viral vaccines, that both can cause both defects like CMV, if they infect during pregnancy, both rubella and, more recently, varicella vaccine. So both of these cause infection of the fetus if the mother is infected during the first or slightly longer than that stage of pregnancy, rubella up to 85 percent infection -- risk of congenital rubella syndrome -- not just infection but syndrome described in the literature.

Varicella is much lower risk of 1-2 percent for infection in the first 20 weeks or so. And so for many, many -- for years and decades pregnant women have been tested routinely during pregnancy and that's now a recommendation for varicella as well. You test during pregnancy.

That allows you to manage -- to have

awareness to avoid or manage exposures during pregnancy for a seronegative woman, and then to guide post-vaccination before discharge. You can have standing orders in the hospital, which really increase adherence and compliance. And this is really for rubella and I think it will become standard of care for varicella, longstanding experience in acceptance of this -- And it's a very captive population -- to protect the subsequent pregnancy.

So a few words about effects of medications and vaccines during pregnancy. Jeff just covered some of this so I won't go into it in detail. Pregnant women are traditionally excluded from pre-marketing clinical trials. And so there's little information available at the time a vaccine is licensed. And almost all information on vaccine use in human pregnancy with some exceptions, such as Cervarix, comes from observations of exposures post-licensure.

And so the big question and the difficult question is do benefits exceed the potential risks of teratogenicity? You know this already. I think it's just been said so I won't go into that -- and the

vaccine FDA use in pregnancy ratings. A correction here, I correct myself, having heard Jeff just now, that FDA pregnancy categories recommending vaccines are either B or C.

Some of the challenges with administering vaccines during pregnancy, safety evaluations -- you know, there can be lots of coincidental events. And so are things coincident versus causal if you get something -- an adverse event reported after vaccination in either the mother or the baby? And in the mother, these things are short and long-term -- in the baby these long -- how long is long? As we heard today, maybe five years.

There's traditionally been very low acceptance of vaccines during pregnancy. Seasonal influenza has been recommended for decades -- strongly recommended since 2004 with coverages of 15 percent until 2009. And Tdap was just recommended this year. So during pregnancy, we do in the United States have two vaccines that are recommended specifically during pregnancy, influenza, specifically trivalent inactivated, and pertussis vaccine.

There are changing attitudes to vaccination during pregnancy. During the 2001 H1N1 pandemic, there was heightened awareness of the increased risk of severe illness among pregnant women because it was studied and well described. And so ACOG and CDC worked to put messages out about this and to increase awareness. And the result was dramatically increased coverage among pregnant women to 50 percent -- from 15 to 50.

And that also carried over to seasonal flu vaccine and it has carried into the last season as well. So last season's flu vaccine with an internet survey was 49 percent. Just two more slides showing the very, very, very strong influence that a provider recommendation has, not only for pregnant women, but for children, for adolescents. It's the most important thing that affects vaccine uptake, is the provider recommendation.

And you see here that if a provider recommends and offers vaccine to her -- to the pregnant patient, 71 percent of them got vaccinated, compared to 8.5 percent of those whose provider didn't offer or

recommend the vaccine. So very, very dramatic difference. The main reason for not getting influenza vaccine among unvaccinated pregnant women was concern for the safety for the baby.

So in summary -- just one slide -- vaccines are usually targeted at age and risk groups most severely affected by the disease. Rubella vaccine is an exception but that was implemented 50 years ago in response to a highly visible global pandemic with severe disease burden. And I'm not sure if we were implementing rubella now without a big pandemic that we'd have the same -- that we'd get the same policy as we have.

Risk-based vaccine recommendations are usually poorly implemented. Vaccine cost-benefit is important to consider, including the need for booster doses. With infant and childhood vaccines we have achieved very high coverage, sustained high coverage in the U.S. Adolescent vaccines, we're getting there. We have some new challenges, especially with HPV.

Pregnancy, there's high acceptance of catch-up vaccines before and especially after pregnancy. And

there's changing attitudes to use of vaccines with several now recommended routinely during pregnancy but whether that momentum and coverage will be sustained over time, only time will tell.

I'd like to acknowledge some staff at CDC who helped with some of these slides. Thank you. So let's have the rest of the panel.

DR. PICKERING: Yeah. And I might ask, is Anna Jacobs here?

MS. JACOBS: I'm right here.

DR. PICKERING: Oh, good. We had some questions this morning -- this is a special treat. We had some questions this morning about the Vaccine Injury Compensation Program and VCF, when infants are covered and children are covered and adults covered and if a woman is pregnant, is her infant covered? Maybe you can clarify all that for us.

MS. JACOBS: Okay.

DR. PICKERING: Okay, good.

MS. JACOBS: Okay. So basically in order for an injury to be compensable in the program, first, the vaccine has to be covered on the table. There's a

vaccine injury table. And so in order for a vaccine to make its way onto the table, there needs to be a recommendation by the CDC for routine use of that vaccine in children.

There can be other recommendations but there at least has to be a recommendation for routine use in children. And then an excise tax needs to be imposed. And when that all happens, the secretary can add the vaccine to the table. So if the vaccine is on the table and someone files a claim, then they need to basically be able to show that the injured person received the vaccine.

And then they also need to demonstrate either that the vaccine caused the injury or that there was a particular injury that's listed on the table within the time frame on the table. But when it comes to maternal immunization, I just want to point out that the requirement in the statute that the injured person must have received the vaccine can get a little tricky when we're talking about immunizations to pregnant women, particularly if they're alleging that it was -- that the fetus was injured because there's a question, well,

did the fetus receive the vaccine?

And there's an open question -- I believe it was referenced earlier but there's an open question as to whether injuries to children that are sustained in utero are compensable injuries in the program because of that language. The court that adjudicates the program that sets a binding precedent has not even had the occasion to address that question.

A case - raising that question has never even come before that court. So absent a decision from that court on that issue or some type of statutory amendment that just flat out clarifies whether in utero injuries are covered and compensable, it's an open question. So hopefully that should answer --

DR. PICKERING: Yeah, so the VFC program, again, only covers people from 18 years of age and younger. So let's take the varicella zoster vaccine. It is recommended for children. The varicella vaccine is recommended for children but the same vaccine or a variant of it, zoster, is given to adults. So adults would be covered for the --

MS. JACOBS: Absolutely.

DR. PICKERING: Because that vaccine itself is recommended for children?

MS. JACOBS: Exactly.

DR. PICKERING: So if you have a CMV vaccine that were recommended -- was recommended for an infant but it would also be given to an older woman, pregnant woman, that person would also be covered because it was recommended under VFC for children?

MS. JACOBS: Exactly.

DR. PICKERING: That's very good. Thank you.

MS. JACOBS: Uh-huh.

DR. PICKERING: Any questions?

DR. KRAUSE: Although, as I understood it -- this is Phil -- the question -- it wasn't clear that if the fetus was injured, that that fetus would be covered; is that right?

MS. JACOBS: Correct. Yeah. So even if the vaccine were on the table, there's an open question as to whether in-utero injuries are compensable injuries.

DR. KRAUSE: Okay. So what that suggests then is if concern over coverage of fetal injuries is important to the manufacturers, it sounds like the key

way to address that would be, I guess, either by the court hearing a case or by legislation --

MS. JACOBS: Yes.

DR. KRAUSE: -- that clarified the issue.

MS. JACOBS: Yes.

DR. PICKERING: Thank you very much.

MS. JACOBS: Sure.

DR. PICKERING: You were very helpful.

DR. MOCARSKI: Can I just add one thing to that because it's a curiosity that I've tried to follow? CMV is associated as well with in utero death, spontaneous abortion. And that has not come up for discussion, is not factored in, and as far as I can tell, is not valued in medical terms, that is to say, in value for benefit. So that feeds into the issue of compensation for damaged fetus.

There is actually for -- obviously for the well-known pathogens that only cause fetal demise. They don't get much airplay but CMV has a play over there as well. It's not discussed because it doesn't have a -- there's no way to deal with the impact.

DR. SEWARD: So Stan?

DR. PLOTKIN: Two points or questions, one to the modelers, Paul and Dr. Lanzieri. There's no reason we have to exclusively vaccinate one age group. In other words, we don't have to contrast necessarily infant vaccination with adult vaccination. Even in the case of rubella, as was said, vaccine is offered not only to infants, but also to women.

And I don't see any reason why one couldn't combine an adolescent program, for example, with an infant vaccination program, which would immediately get you a result in public health terms. And indeed, that's the way in Latin America they have been able to eliminate measles and rubella rapidly, by vaccinating multiple age groups. So I'd like to hear some comment on that.

And secondly, as far as vaccination in pregnancy is concerned, now, we all know that there are multiple vaccines one would want to give in pregnancy. And if we ever have a group B strep vaccine or an RSV vaccine, they would be given during pregnancy but they would be given late in pregnancy. Here, we're talking about a vaccine, which logically would be given early

in pregnancy, at a time when spontaneous abortion has a very high rate. And to ask manufacturers to take that risk without legal protection is, I think, speaking for them, is a non-starter.

DR. GRIFFITHS: Okay. Well, I'll have a go at Stanley's first question. I agree with you, just to clarify, but the modeling that I tried to do was simultaneously starting a vaccine program that gives it to adolescents and also to toddlers. And I agree; you get much more rapid, more effective control. In fact, I would also add back in the possibility of giving it postpartum in the way that Bob Pass did in his study.

But I think probably we could think of that as a booster approach. If that first community-level immunization for everybody didn't work, that would be a readily, easily thing to introduce. And it would be directly comparable to rubella of course that's given postpartum.

DR. ADLER: Yeah, I guess two comments to follow up on Stan's. I can't -- I can imagine a scenario where you might want to give a vaccine to a seropositive pregnant woman to boost antibody titers

and protect against a reinfection, let's say.

But I can't imagine a scenario -- though it's possible -- where you'd want to give a vaccine to a seronegative woman -- and I think Gail mentioned this in her talk -- because they come in at 6-12 weeks. You've got a window for immunity so probably not going to be a viable option.

The other comment was apropos of Dr. Griffith's talk. He probably doesn't know this, maybe because I didn't publish it. I can't remember. But if one has an infected child in the family, CMV transmission to the father and the mother occur with equal rates. So one can make a very strong argument for immunizing both parents in that situation, as well as perhaps other children in the family.

DR. GRIFFITHS: That's great. I think you should write that up, Stuart. That would be very nice to quote.

DR. SEWARD: Bob?

DR. PASS: Yes. I wanted to ask Drs. Griffith and Lanzieri about force of infection and constant force of infection. When you say, "Constant

force of infection," I assume you mean that the population incidence of infection is the same age by age or year after year or which? Because certainly by age, there is tremendous difference in force of infection.

DR. LANZIERI: That's a good question and thanks -- because then I can clarify. A constant force of infection would be just like assuming a very simple model and then just a starting process.And then everybody would have the same chance of acquiring infection in the population.

But then we'd know that the force of infection varies with age. And that's why you incorporated the age structure in the modeling. So we -- from different models and also from the work we've been doing, we observed that the higher force -- the highest force of infection occurs among children.

And also to account for the uncertainties that we have -- because the only data we use in this model is the data derived from NHANES, the seroprevalence data. And everything else is estimated or could be a little bit different.

But in summary, I tried to -- I used three different matrices to vary the contact rates among the population of -- in different age groups so that then we could evaluate the results as a sensitivity analysis, whether the impact of vaccination would be different with this different contacts that lead to transmission in the population.

DR. PASS: Okay. So one thing that made me a little bit concerned about that -- and this is a real difference between CMV and rubella is that if at the time you initiate a program from rubella, there happened to be some kids who have rubella, basically within a couple of weeks, it doesn't matter. They're no longer shedding virus. Their risk of spreading to someone else is minimal.

There -- Approximately 10 percent of infants will acquire CMV perinatally in the U.S. And they'll shed virus for years. So you don't take them out of the picture when you immunize toddlers or children less than one year of age. They'll continue to shed CMV, which could have an impact on force of infection for that age group, you know --

DR. LANZIERI: Yeah.

DR. PASS: -- for a few years.

DR. LANZIERI: Oh, that's a good point. I would have to think about how I deal with that in the equations. But we don't really have all the data for duration of the infectious period and also how seroprevalence goes up in such young age. And then, once we have more data, we will be able to improve the model. Yeah, thank you.

DR. SEWARD: Paul's going to comment.

DR. GRIFFITHS: Just to say that I think the models shouldn't be taken as gospel, that they give you an example of what might happen. And what would be really helpful is if people in -- people talked about collaboration from the last panel.

If the people conducting the vaccine studies would consider collecting the data and sending it, for example, to the CDC group, who are going to do -- be doing more and more sophisticated modeling, things like the seroprevalence at different ages would be useful, the number of children within a family, whether or not that indicates that the women are at high risk of

transmission.

Because you can think of the children as going and doing outreach and bringing more people into your family group, as it were, and so sharing more and more viruses. And those mixing proportions are quite important to put into a matrix as well. So as they say, it's parameterizing the analyses. It needs real-world data.

And people like Stuart -- Stuart just told us he's got actually quite an informative study sitting there that hasn't been written up. Actually it could be really useful to have that data and to use real-world values to go into these models.

UNIDENTIFIED MALE: Yeah, go ahead.

DR. SPECTOR: This is a question more for who makes the decision, and that is, we're seeing now that vaccines are being given in different arenas. I mean, you talked about going into the schools but just walking through your airport, you can get your flu vaccine. And certainly in your Ralphs or Vons you can get a number of immunizations.

They're not available for children yet.

They're -- at least my understanding -- and they're not all adult -- it wasn't discussed. Where's that decision made in terms of when can the pharmacist in your CVS give the immunizations, let's say, to this adolescent group, which is so hard to reach or going -- at what level do those decisions get made?

DR. PICKERING: Yeah, that's a very good question. At the last ACIP meeting, there was a little misinformation given about one of the states and their vaccines outside what we call the normal areas. At the next ACIP meeting, we're going to have a presentation about just this issue, about -- because there are lot of questions that arise.

When you get your immunization at a pharmacy or Kroger's [sic] or somewhere else, do they notify the immunization programs that monitor? Do they notify your physician -- the registries? Do they notify your physician? Do they have all the equipment there in case that somebody has a cardiac arrest or something?

So all of the things that the health care professionals have to ensure when we give immunizations, we're not sure about that. So at the

next ACIP meeting, we're giving you some clarification about where those decisions are made, who makes the decision. I think probably it's the organization makes a decision whether or not they immunize children. Most of them do not immunize children.

So stay tuned. You can -- you can watch the ACIP on the webcast next month and get the answers to those questions because there's a whole myriad of them that we want to -- we want to have addressed.

DR. SEWARD: I mean, AAP and AAFP have a fairly strong stance in this as well, you know, as the medical homes. And, you know, as a country, we sort of went with private providers providing the medical home. And most of our public-funded vaccine is delivered that way, as you all know. At the last COID meeting, there was some discussion about HPV and the series.

And, you know, it's tough for the parents to get back. It's tough for the children -- adolescents to get back. And, you know, some of the discussions included, "Well, should we give the first dose in the pediatrician's office and say it's okay to go to the pharmacy for two and three? And then how we will know

they get them? Do we want to give up and promote vaccination outside the medical home?" Pros and cons.

So I think there is a lot of -- I mean, those things -- the same for flu. I mean, with what's happening for flu in adults -- as you say, everywhere you go, you can get flu vaccine now. It's been just a sea change since the pandemic and availability of enough vaccine. It's going to start happening. It'll be taken away from pediatricians perhaps for flu vaccine unless they get on board and start to work with some of these other groups who can deliver.

DR. PICKERING: Yeah, and as the AAP and others will say, there's a whole lot of preventive services that a child should receive during a routine visit, not just immunizations. Although, they are, of course, very important. Yeah?

DR. MALDONADO: I was just going to add that at the last meeting at the COID, we think -- I think the issue of flu was a lot simpler because it's a single dose. It's almost -- you know, you have to do it every year. The issue of HPV and potentially CMV, I think they fall into that same gray area because you're

going to be talking about a variety of populations, some of which the AAP won't deal with.

For instance, pregnant -- older women, we'll probably not recommend all the way and if we do, it'll be ACOG that actually makes the primary recommendation. So a lot of these issues will still need to evolve for CMV, I think. And the medical home for adolescents is really important for pediatricians in particular.

DR. PICKERING: Yes, sir?

DR. SCHODEL: Florian Schodel, Philadelphia. I just wanted to really congratulate everybody in having this discussion about how the vaccine might be used now. I think that's a very important discussion to be had. And I'm particularly heartened by what Paul and Tatiana said about the modeling with all its imperfections.

You see, I mean, in order for the public usage -- if it turns out that the modeling is right and if it turns out that the biggest impact of such a vaccine would actually be had by starting to immunize maybe in parallel children and adolescents, then, you know, the FDA can't license the vaccine if the data

aren't there. Then the manufacturers would have to clearly get the message that such a vaccine would have a high likelihood of fast, universal recommendation because that's the only way you can get it used.

And then the appropriate clinical studies in peds have to be done rather than concentrate entirely on adolescent immunization and transmission. I think that's a really, really important discussion, together with the appropriate endpoints because it changes the direction that the manufacturers take for developing them.

You can't recommend a vaccine that doesn't have the license in this age group. And we've been there before with ACIP recommendations, where we've discussed in a frustrating way vaccines that we would like to use for certain populations but can't use because they're licensed in them.

So I would just recommend if we -- if we think strongly -- and I certainly do -- about a rubella-like strategy, with all its differences, to really continue that discussion and have a good discussion with the manufacturers to develop the

appropriate data and with the FDA, obviously, to get the vaccine licensed that way.

DR. SEWARD: I'd like to comment on that because I didn't have time in my talk. I would have liked to have had more time. You know, the lessons from -- I think things have changed over the years since rubella vaccine was licensed. And HPV may be a good example. I mean, it was not licensed for boys initially. And when it -- even when it was licensed for boys, the ACIP didn't recommend it until they were very clear that it was going to benefit boys individually.

It was not going to be recommended by ACIP on the basis of decreased transmission to females. That -- you know, I mean, it was clear that wasn't going to happen. And so I think it's not quite -- you know, vaccines are more expensive now to develop. They are much less cost effective. And it's not as much a slam dunk to get an ACIP recommendation on the basis of what a model shows, you know, unless it's extremely cost effective.

So I think there are a lot of things to

consider and HPV is one --

DR. SCHODEL: And I understood but exactly, that's why the discussion needs to happen because otherwise, you simply won't have the data. They won't be licensed that way. And it was -- with HPV it wasn't -- it wasn't just the male discussion. It was also the age discussion. And we continue -- we've had numerous discussions over the year about -- over the years about these things.

The data are not being generated if there is no reasonable discussion in the public space as to how these things will be used.

DR. PICKERING: Yes.

DR. SCHLEISS: So in light of your last point, Jane, I think it's troubling to sort of think about boys and how it's going to be justified to give to boys. These things about immunosenescence and atherosclerosis, although provocative, are, I think, too uncertain.

So I'm quite intrigued by your slide, Gail, about a mono vaccine. And I hadn't really given that much thought before. I mean, has anyone tried to model

what might be gained by preventing CMV mononucleosis in an adolescent boy? That might be a very interesting thing to pursue further.

DR. MALDONADO: Actually another point that Jane didn't bring up today but she's brought up in the past is that CDC's done additional analyses with HPV and depending on how you slice it, you actually gain benefit depending on what the female coverage is as well.

So if female coverage for HPV, for instance, is low and you introduce male coverage, that becomes much more cost effective, even for protection of women. So again, it depends. It's a very -- it's a very dynamic model. It's not going to be static. And I think things will change over the course of -- as many of the current vaccines have, as the epidemiology of the disease changes. And that's what the CDC will be watching over is what happens to disease over time in the population.

Because initially, it may be that male administration may actually be more cost effective if uptake is low initially.

DR. PICKERING: Okay. If there are any other questions -- if not --

DR. LANZIERI: I have an announcement.

DR. PICKERING: Okay. One done --

DR. LANZIERI: No, it's just because I didn't have time to show a lot of the modeling and we've set up a poster outside. And if there is anyone interested, I'll be happy to walk through all the results and have more discussion about it. Thank you.

DR. SEWARD: Just to comment on Florian's comment, I mean, I think -- I think this highlights the, you know, real importance of understanding the epidemiology of this disease as well as we can, you know, how do people acquire it, when, you know, when is -- in different populations, transmission, first pregnancies, second pregnancies, you know, a lot of more -- better epidemiology to be able to guide vaccine policy.

DR. PICKERING: Okay. We have to be out of here very soon. So we'll hear Bob, Mark and then, Phil, if you want to sort of give closing remarks about tomorrow and maybe summarize what the product of this

whole conference will be? So if we can go in that order?

DR. PASS: Okay. Mine's very quick. I just couldn't let the FDA get out of here without a question. So for Dr. Roberts, it was actually encouraging what you said about vaccine studies in pregnant women. Another issue, if one is immunizing women of childbearing age, is the potential of immunizing women who are lactating.

Are there special considerations that would have to be taken there?

DR. ROBERTS: Yes. And in fact, the change to our labeling around pregnancy is called the -- the new regulation will be the pregnancy and lactation labeling rule. So there will be changes with regard to that. And, you know, it would -- it generally follows the same kind of paradigm that the HPV vaccines did.

Those women who were inadvertently exposed, safety data was collected for a whole number of things, including neonatal outcomes and with regard to nursing. So, you know, that's kind of the paradigm going forward for females of reproductive potential.

DR. PASS: If one is doing a study in women who are likely to be lactating or you know that a certain proportion would be lactating, one could expect to have such a study approved with an appropriate safety plan?

DR. ROBERTS: Well, absolutely. And this will be, obviously, very much case by case because you can imagine that we would ask for more extensive transmission and shedding studies for some of the live vaccine candidates than some of the others.

DR. FEINBERG: Mark Feinberg from Merck. This is -- the presentations were great and this discussion, I think, has been really helpful but I do think it's really important to be clear that there are certain things about this that distinguish CMV vaccine development from other vaccines.

And you know that for many years, CMV has been prioritized as a vaccine, yet, we don't have a CMV vaccine. And unlike other vaccines, where there was sufficient, you know, public health need or biological plausibility or the environment with the FDA and the ACIP or maybe a little bit different than they were or

much different than they were previously, I think it's pretty clear that unless some of these issues get addressed and resolved, you know, priority populations, disease endpoints, what would be sufficient for a compelling recommendation, you know, how would you maximize the public health impact, I think it's going to make it very difficult for manufacturers to feel confident moving forward with the major investments they'll have to make to bring a vaccine to market.

I mean, while you saw encouraging presence of five vaccine manufacturers who have an interest in this area, that doesn't mean that five vaccine manufacturers have committed to actually develop a CMV vaccine or that there is a viable path forward for them to do so. So I think it will be great if what comes out of this meeting isn't just highlighting all the challenges, but really coming up with what are the priority issues and how can we address them and solve for them so that the world may soon -- or at least eventually have a CMV vaccine.

DR. KRAUSE: Yeah, just to comment on the session as well, I was very impressed with the

modeling. And it does strike me based on some of these discussions that if a vaccine -- it sounds like the modeling tells us -- even if the modeling may not be right about exactly what the impact of immunizing infants would be, it seems as though the chance to have the greatest impact on congenital disease probably lies in that area because the modeling suggested that it would take a long time to see an impact on congenital disease if one restricted oneself to the adolescent immunization strategy.

So that then sort of leads one into these same kinds of questions that Florian was asking of, "Well, if one has a vaccine and the intent is to give it to infants for the purpose of interrupting transmission of CMV," then, you know, we at the FDA think about, "Well, what is the indication for that? Is that really a licensable indication based on the benefit to the recipient of the vaccine?"

And then, as Jane says and Larry said, the ACIP has to think about, "Is that something -- on what strength of evidence then could the ACIP recommend the use of that vaccine?" At the same time if -- so I do

think it's worth thinking a little more about exactly what data would be needed to get one there if -- because if the modeling turns out to be right, that may be where we all need to go.

So I'll make the other remarks that Larry wanted but I'd be interested in hearing some additional panel reaction to that.

DR. SEWARD: Well, I agree. I don't disagree at all. I think more data, more modeling, you know, including reinfections, which wasn't included in the model, refining models -- models are one way of looking at something. I agree; they're not the only way. But I think -- understanding the epidemiology more and doing some more of this modeling will be very important to inform steps forward.

And I don't think anything should be off the table as far as the -- if a clear strategy stands out as being -- having the great -- by far the greatest impact on public health burden, then, to me that's a pretty logical thing to pursue.

DR. PICKERING: Yeah, and I agree with you. And I think I'll lead into hopefully what you're going

to say next, is that at the conclusion of this meeting, hopefully there will be a publication that will list all of the things at all the different levels because there are like four or five different levels here we're going to have to approach from, you know, the beginning -- through FDA and ACIP.

Hopefully, we'll have those unified so that we all agree with this and then can move forward so that we just don't have this meeting and all go home, but take it as a learning experience where we can move forward together to get this done.

DR. SEWARD: I mean, durability of protection is, you know -- I mean, there's a lot of issues. I think some of these we'll be discussing in more detail tomorrow.

DR. KRAUSE: Sure. Although, at least in Tatiana's model --

DR. SEWARD: Yeah, right.

DR. KRAUSE: -- it appeared as though the public health benefit was relatively insensitive to durability of protection. Although, of course, if durability of protection is short, maybe you'll just

shift infection to older kids and they'll infect their mothers anyway. So, one has those kinds of shell games to worry about as well.

But anyway, so the organizing committee, once the meeting is over, will get together. And the intent is to write a publication that summarizes the meeting, really, very much with an emphasis on where the priorities and real action items should be.

And I'm not sure that this can be done on exactly the number of levels that Larry's suggesting in the -- within the confines of what one can actually get published but I think that that should be an important product of this meeting because if there isn't a record of what we've done, then the information and the discussion's we've had won't turn out to be as useful.

As you all know, because you've been asked to state your names before you make a comment, we have a transcriptionist who's diligently keeping track of what's going on in the corner over there. And so there will also be a transcript available of the meeting which will be, obviously, a record of what everybody has said. And of course, everything that we're doing

now is currently being webcast as well to people who aren't able to be in the room with us.

So hopefully, with all of those measures, there will be enough public dissemination of what's happening in this meeting in order to build and sustain some momentum that will help lead, not only to the discussions that we have, but to things that -- concrete things that investigators can take home with them and write grants to do, the NIH can consider for funding, additional epidemiological studies that the CDC can consider doing, additional modeling that the modelers consider doing and ways of thinking about modeling.

And so I think there will be a fairly long list of those kinds of suggestions and recommendations that come out of this meeting. And in fact, what we hope to do in the final session of the meeting is not just summarize the meeting, but have a real discussion about what those next steps should be and what those priorities should be.

So that's what Session 7 is of this meeting. And so I really hope that -- although, I'm sure

everybody will be tired by late tomorrow afternoon -- that as many people as possible can stay for that discussion.

DR. PICKERING: Thank you and we'll resume tomorrow at 8:00.

DR. KRAUSE: That's correct.

DR. PICKERING: Same place.

DR. KRAUSE: Thank you very much, everybody.

(Whereupon, at 5:22 p.m., the first day of the Development and Evaluation of Human Cytomegalovirus Vaccines workshop concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, NATASHA KORNILOVA, the officer before whom the foregoing meeting was taken, do hereby certify that the proceedings were taken by me in audio recording and thereafter reduced to typewriting under my supervision; that said transcription is a true record of the proceedings; 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.

_____

NATASHA KORNILOVA

Notary Public in and for the

State of Maryland

$

$16 10:6

0

0 306:22

0-12 299:3 304:20

0-5 305:7

09 127:1

1

1 8:20 12:12 13:14,21 26:1 55:12 105:16,19 111:22 117:16 183:8 184:10 236:18 260:3 303:16,18

1,000 183:9 184:10

1:1 220:22

1:45 199:16

10 1:5 14:7 15:4,15 22:6 31:1 40:15 52:17 94:18 107:5 163:9,12 242:16 259:11 263:19 267:15 275:3 295:18 297:14 300:9 302:2 304:8 322:15 323:15 345:16

10,000 238:2,19

10:00 74:4

100 41:17 42:3,6 46:22 47:11,22 48:9 89:15 120:12 170:13 184:22 191:17 227:18 235:17 259:12 283:3 301:8

100,000 33:21

1000 236:18

101 2:16

10-11 299:8 300:8,10 301:18,22

10-percent 125:4

11 112:10 295:18 300:11

11-12 325:17 326:1 328:22 329:16

113 43:12 261:4

118 2:18

12 5:7 35:7 42:2 43:5 45:7 52:2 267:17 282:20 283:12,14 295:18 324:17,19 325:8

1-2 331:16

120 124:22

12-15 325:15

12-16 42:5

12-18 298:20 299:1,2,6,8,14 300:5,13 301:7,17 303:9

122 127:9,17

123 127:8

124 127:8

12-week 56:1

13 107:14 179:20 264:14,16 267:10,18

13.7 290:11

13-15 326:10

13-16 43:12

133 2:20

14 2:7 127:20 266:5 322:17 323:15

140 104:17

1400 260:2 303:11

145 2:21

15 15:4,15 31:1 40:15 77:1 83:3 138:1 163:9 246:7 266:5 333:17 334:8

15,000 293:16

150 275:22

16 41:17 42:3 43:19 49:15 120:20 125:2 212:11 283:10

16.8 261:11

16-week 45:9,17 50:2

17 105:4 244:12 259:21

177 3:4

18 23:20 41:12,18 127:14 136:13 207:7 212:10,12 231:6 263:7 328:8 338:16

18/20 60:4

180-day 139:14

18-24 222:10

19 52:2 280:22 290:13

19,000 283:7

191 3:6

1941 7:6

1962 7:7,18

1963 7:9

1964 244:19

1965 7:9

1969 7:18 280:21

1970s 133:5 324:7

1971 76:22 83:3

1980 101:10

1980s 280:22 322:8

1983 237:5

1984 259:19

1985 5:3

1986 244:11

1988 149:9 281:7

1989 91:20

199 48:7

1990 265:11 294:7

1990s 324:10

1992 21:4 272:21

1993 308:20

1994 254:2

1996 325:18

1999 113:20 153:12 185:11

1percent 85:19 86:7

1-percent 89:4

1-to-3 160:20

2

2 8:20 13:14 23:14 48:3 55:11 65:15 120:13 161:20 243:15 300:16

2.5 140:16

20 26:13 37:11

41:12 46:8,10 79:16 91:2 136:6 183:17 207:21 212:12 248:9 259:11 272:19 273:2 277:1 284:6 295:14 297:1 298:11 300:1,17 301:13,19 302:1,9 303:10 304:5 331:17

20,000 7:10 312:12

200 263:11

200,000 237:6

2000 5:5,10,13

2001 86:22 295:20 334:2

2002 111:10

2004 5:14 263:3 333:17

2005 27:10 179:16 326:2

2006 21:10 87:1

2006-10 326:11

2007 24:18 254:6

2008 126:19 187:3

2009 15:21 127:1 188:1 333:18

201 3:7

2010 24:18 250:10

2011 48:11 160:19 250:15

2012 1:5 202:13

2020 301:6

207 3:8

20857 1:10

20892 1:8

21 46:10 261:1

212 3:8

215 3:9

21st 5:5 127:3 294:7

22 256:4 260:18,19 268:4 275:14

220 3:9

23 43:9 105:4 250:19 256:5

23.78 263:17

24 44:14 261:3

24,000 311:10

24/25-week 56:14

240,000 14:1 87:20

244 3:13

24-percent 120:19

24-week 50:12

25 25:18 102:7 118:2 122:9 263:20 277:2,3 290:12 300:16 303:5

259 3:15

26 126:2

26.5 43:14

27 127:15

27.3 43:16

279 3:17

28 29:15,16,18 261:6 263:21 264:8

28,000 303:8

28-percent 29:14

29 43:8 127:5

295 3:18

3

3 8:21 18:16 25:1 48:3 55:11 79:11 126:22 243:16

3,000 183:10 195:7

3.4 43:10 100:21

30 16:16 27:11 49:16 76:5 79:16 86:5 90:22 94:7 108:1 127:18 246:21 259:11 263:10 264:8 267:11 299:17 301:8,13 303:13

300 196:22

3000 235:18,20

3000-5000 236:4

3000-fold 227:18

30-100 306:21

308 3:20

31 120:14

322 3:21

3253 259:21

33 149:13

33.3 44:12

336 3:22

34 260:20

35 52:6 303:22

35,000 13:19

350 304:1

3500 304:9

36 125:14

37 119:12 120:21 127:16 141:2

38 26:13

38,000 283:5

381 43:1

38A 1:7

39 297:14

4

4 23:14 50:4,5,11 65:16 111:22 125:14 203:19 210:12 252:16

4.3 100:18

4.6 105:3,11

4:00 277:2,3

40 2:9 14:13,15 16:14 104:19 117:15 120:22 125:1 248:9 282:10 299:22

40-percent 86:5

41 261:12

41.9 26:8

42 136:10 261:21

43 264:14,18 267:10

44 47:21 127:19 141:7 259:22

45 122:10 127:17 299:21 300:16 311:17

450 171:19

45-50 324:1

47 119:12

49 334:13

5

5 2:4 13:10 23:15 24:22 25:4,12 26:4 105:15 126:2 163:14 175:21 238:2

271:15 298:11 299:14
5.7 26:6
5:22 365:9
5:30 74:9 277:11,20
50 2:10 14:15,16 22:8 36:13 37:8 51:20 87:1 116:13 120:7 179:21 220:5 230:6 276:2 292:14 329:14 334:8,9 335:8
50/50 288:21
500,000 240:20
50-percent 136:10 160:22 161:1
511 260:19
56 260:2
5600 1:10
59-percent 21:21
5-percent 125:4
5-year 301:11

6

6 44:5 46:7 47:7 55:12 123:2 125:13 126:5,11,15 260:18,19
6.1 105:4
6:00 277:22
60 14:13 16:14 22:10 41:20 87:1 292:14 295:20
60-70 324:8
60-plus 18:1
60s 156:1 261:18
6-12 343:5
62 141:1
63 299:16
64 7:10
644 106:16
65 7:10
66,000 33:21
66,452 24:19
68 36:12 37:7
69percent 86:12

7

7 13:10 23:15 87:1 100:19 184:4 364:21
7.7 152:7
70 16:17,21 43:7 47:21 259:12 298:9 299:15 301:9 304:6
7000 303:7 311:18
70s 156:2 273:21
71 141:6 334:21
75 2:14
761 311:15
77 263:16
772 46:18
786 262:13

8

8 46:7 105:15 126:11 260:22 290:14
8.5 334:22
8:00 9:6 365:5
80 259:12
8000 303:14
80-percent 125:3
80s 100:18 156:21 261:18 324:7
8169 109:1 110:5,14 111:3
81-69 103:3
84.7 42:6
85 331:13

9

9 26:3 120:15
9.4 25:4
9.8 22:7
90 14:10 16:22 28:13 79:20 126:12 259:12 298:10 299:15,21 301:10 306:21 330:11
900 262:12
9000 1:7
90s 91:2 172:4
92.8 42:3
920 260:22
9-26 311:11
93 27:14 170:17
93.8 47:2
94 47:6
96 24:16 164:10
97 27:15 104:15
97-percent 51:18 52:3

A

A&M 260:22
a.m 9:7
AAFP 325:18 330:8 349:10
AAP 32:9 245:20 325:18 330:7 349:10 350:12 351:2
Abel 160:19
ability 59:10 112:14 177:6 184:19 238:19 271:9
able 6:19 8:1,11 19:20 22:9 58:10 65:5 68:9 130:4,16 138:4 146:16 176:19 185:3 195:9 198:2 204:10 209:6 213:5 260:4 286:13 337:11 341:12 346:8 356:17 364:2
abnormalities 14:7 46:13 80:13 115:12 120:17
abortion 197:6 340:12 342:1
absence 63:11
absent 338:10
absolute 60:2 145:18
absolutely 9:17 75:21 79:9 86:19 120:18 230:14 277:15 338:22 358:6
absorb 109:13,19 110:3
absorbing 110:17
absorption 110:14

academia 199:1
Academy 245:19 253:22 254:1,5,9
accelerated 177:17 178:8,18 179:3,7,8,14,21 180:2,13 192:4,7
accept 194:9 195:9
acceptable 201:20 240:5
acceptance 201:15 328:21 332:7 333:15 335:21
accepted 82:1 245:3 291:16
accepting 330:6
access 242:16,22 251:11 270:15,19,20 271:3
accompanied 83:1
accomplish 8:1,19
accomplished 6:22
Accomplishment 272:15
according 61:20 108:14 119:6 122:22 202:12 205:5 312:13
Accordingly 1:17
account 20:13 102:11,12 344:18
accounted 29:16,18
accuracy 1:18
achievable 216:8,14
achieve 10:18 11:8 57:9 63:19 67:21,22 69:18 159:11 186:16 209:1 267:5 296:12 301:4,15 324:12 329:22
achieved 63:15 127:14 301:12,14,19 302:2 304:18 335:18
achieving 186:15 207:18 322:4 325:12 330:11
acid 211:22
ACIP 3:12 204:20 205:1 206:5 239:4,5,6,12,18 240:3 241:2 243:19 244:3,4,19 245:2,5,10,12,14,22 246:3,4,5,7,12,15,19 247:6,8,11,14,22 248:1,5,8,10,12 249:17 250:6,9,22 251:5 252:1,13 253:12,15,21,22 254:9 255:21,22 256:2,4,20,21 257:2,7 318:8,13 320:13 325:18 348:8,11 349:1,7 352:14 353:10,13,19 358:22 360:20,21 362:6
ACIP-recommended 251:15
acknowledge 336:5
acknowledged 6:14
ACOG 330:8 334:5 351:5
acquire 79:4 104:7 117:14 296:20 345:17 356:14
acquired 52:22 79:12 82:6 101:17 104:2,3,8 116:13 126:1 201:21 260:3 288:2 289:6
acquiring 40:1 284:14 286:5 344:10
acquisition 18:5,9 19:9 20:17 22:21 32:1 59:2 78:6 102:13 134:4 135:3 136:6,11 143:7 272:9
across 25:12 88:10,22 109:3,21 189:16 203:5 205:20 213:22 218:11 281:22
across-the-board 236:7
act 182:19 188:9,15 237:5,7,18 246:1
action 72:20 73:4 363:8 366:9,13
actions 121:7 193:18
activating 154:12
activation 154:17
active 124:17 127:1 155:15 159:3 173:5 193:4 195:20 222:8 275:5
actively 257:19
activity 18:21 19:4,5 20:11 24:5,10 53:7 96:16 110:5 111:22 112:1 118:17 121:9,15 130:15,17 161:10 274:18
acts 91:15
actual 117:20 122:5 124:11 128:4 151:20 241:12 242:5
actually 32:15 36:22 57:17 58:20 62:3 76:9,21 91:2,17 94:12 95:7 96:9 97:14 99:19 100:6 101:9,15 102:10 103:4,7 104:8,10,20 105:9 109:13 110:4 143:22 146:1 147:14 149:9 152:7 162:2 166:13,21 167:14,16,22 172:14 183:15,19 184:21 187:2 207:22 208:7 214:18 227:12 232:4 233:15 235:15 238:19 239:2 241:16 261:18 262:12 268:2 270:21 281:12 283:20

285:13 287:9 303:17,22 306:20 307:12,14,18 319:21 340:17 347:10,11 351:5,20 355:4,7,21 357:5 359:13 363:11

acute 40:12

AD169 207:1 228:15

adapted 298:4

adaptive 90:12 91:1

add 53:14 72:19,20 167:20 219:18 230:8 243:2 322:20 337:8 340:9 342:11 350:17

added 244:17 322:21 323:19

adding 282:20

addition 10:4 20:10 53:22 90:19 122:5 208:8 220:9 266:9

additional 7:13,15 48:5 81:15 93:2 120:16 131:9 158:16 174:15 184:13 188:20 189:12 266:8 304:6 305:2,13 355:6 361:6 364:10,11

Additionally 53:6

address 51:6 57:19 62:15 67:8 68:9 166:7 200:17 206:1 307:5 323:11 338:8 340:1 359:18

addressed 8:17 66:18 89:20 208:12 305:2 317:17 349:9 359:3

addressing 201:10 203:22 278:20

adenovirus 132:15 133:3

adenoviruses 152:19

adequate 207:18 230:7,10 317:19 319:19

adequate-controlled 320:1

adequately 57:13

adhere 11:14

adherence 332:4

adjacent 114:22

adjudicates 338:6

adjust 32:17,18,21 33:3

adjusted 32:12

adjuvant 135:18 138:2 166:17,20 167:10,16,17 187:9 188:1,4 206:20 215:18,20 219:20 220:19 221:1,8,21 231:14 235:10 314:11

adjuvanted 142:11 158:18 186:14 187:4,14 188:3 192:1 206:19 215:11 220:4

adjuvants 148:16 157:19 186:21 187:3,10 191:8,10 236:9

adjuvated 201:5

Adler 20:6 65:2 73:9 118:22 135:12 170:10 171:10 172:6 222:1 242:10 294:1,4 342:19

administer 265:14 266:19,20

administered 5:7 177:4 264:16,21 265:5 268:21 269:5,9,15 273:16 324:21

administering 202:8 333:5

administration 1:9,17 323:5,20 355:21

admittedly 226:2

ado 258:2

adolescence 275:1

adolescent 3:14 28:2,3 136:6 208:2,14 212:11,19 217:8 232:7 244:15 254:7 258:4 259:18 266:14 267:19 270:12 271:10 307:2,7,10 326:9,18 327:1,18 329:21 335:19 341:9 348:5 352:7 355:2 360:9

adolescents 28:6 52:2 195:1 222:14 245:21 249:5 259:6,15,20,21 260:6,17 264:16 267:4 270:16 271:18 273:16 274:14 285:4 325:17,21,22 326:21 327:7,11 328:17,22 334:16 342:9 349:18 351:7,21

adopt 266:11 269:22

adopted 191:2

adoptive 151:14

adult 3:14 124:7 126:1 244:16 247:10 254:13 255:9,11,13 258:5 266:15 271:10 341:5 348:2

adulthood 327:11

adults 2:8 38:21 135:20 179:21 195:1 205:8 207:4 241:9 244:17 257:12 260:17 261:4 328:11 336:15 338:20 350:5

advance 111:5 160:13

advanced 41:4 45:8

advances 185:3

advantage 270:14,17,21

293:13 323:13
advantages 211:21 270:2,9 271:2 325:1,3
advent 36:19
adverse 183:8 184:9,11 187:19 193:16 195:16 289:18 302:12 333:9
advice 194:18 195:4 197:16 244:20
advises 199:2
advisory 185:11 204:8 246:1 252:11
affairs 190:17
affect 27:17 228:17 271:9 272:10 296:14
affected 67:15 266:5 279:17 313:13 335:7
affecting 329:4
affects 334:17
affiliation 29:9 168:6
affinity 60:21 63:8 154:11
afforded 5:21 208:20
aficionados 85:9
afraid 99:14
Africa 13:12 16:20 22:18
African 27:15
afternoon 278:3 294:16 365:1
afterwards 12:1 225:3
against 53:5 65:11 93:6 106:9 109:1,4 111:11,13,20,22 134:17 136:5 142:11,15 150:18,20 152:21,22 154:20 157:4,5 158:2 159:9 163:6 170:12,20 171:1 173:2 182:4 208:17 209:16 210:14 216:6 229:14 291:19 305:4 318:9 326:17 343:1
age 5:7 16:10 17:10,13,20 18:1,3,16 19:6 20:17 23:11,19,20 25:18 32:4,18,22 33:3,5,9 35:5,21 51:20 52:2 69:2,4,11,15 92:18 108:15 179:21 182:15 189:16 193:1 205:13 212:11,12 214:15 216:22 232:1 242:8 251:17 255:13 258:11 259:7,8,13,21 261:11 262:2 263:1,7,14,16 264:3,8,12,16,18 266:13 267:9,17 268:9 270:9,13 272:8 282:20,22 283:10,12,14 284:6 290:12 293:14 295:12,17 296:10 297:9,17,22 298:14 300:3 301:21 302:5 304:13 305:1,7,8,12 311:11 322:9 323:5,7 324:18,21 326:4 327:21 328:8 329:12,16,17 330:20,21 331:1 335:6 338:16 341:3,14 344:2,3,4,13,14 345:3,20,22 346:7 352:13 354:7 357:8
agency 319:4
agenda 8:19 9:15 224:2
agents 245:7
ages 31:17 251:4 260:18,19,22 346:20
age-specific 36:4
age-stratified 290:8
Aggie 260:22 261:1
ago 37:11 58:17 67:9 77:15 91:20 93:1 94:7 107:5 109:12 118:21 143:15 145:22 147:9 151:2,14 167:21 262:6 275:15 276:7 308:15 327:1 335:8
agonist 138:3
agreed 214:1
ahead 63:5 256:10,14 277:5 347:14
Ahlfors 113:6
Ahmed 97:10 253:5
aid 188:13
aids 78:1 93:7 274:2 288:22 289:10 292:1
airplay 340:19
airport 347:19
al 17:11
Alabama 2:6,15 12:18 29:12 85:22 86:22 114:15 116:4 173:18
albeit 291:4
alcohol 15:19 310:1
Aldema 272:22
Alford 101:7
Alistair 147:11
alive 262:11
alleging 337:21
Allergy 4:3
allografting 289:10
allow 63:22 121:17 205:19 218:11,18 227:22 228:2 259:2
allowed 7:13 10:7

147:2 148:1 320:18
allowing 167:1 227:6
allows 188:10 294:8 331:22
alluded 97:4 203:1 245:10
alone 230:7
AlphaVax 211:7
alphavirus 132:17 139:19 142:10,17 211:9,11 220:14
already 12:3 52:3 75:21 77:17,19 78:15 79:1,14 82:12 83:5,18 85:13,16 91:13 96:22 98:20 122:17 125:10 126:8 149:10 150:1 161:15 197:19 216:2 239:7 244:8,14 251:2 259:10 269:20 280:9 300:5,14 301:20 313:10 322:14 332:21
alter 5:20
alternate 330:9
alternative 201:19
altogether 122:7
altruistic 198:8
alum 166:20 167:11,18 188:2
am 37:9 73:7 78:11 124:10 132:19 143:16 149:22 175:1 276:15 366:8,10
amateur 69:9
amazingly 7:17
ambiguous 54:16
ambitious 9:15
amendment 338:11
America 13:12 17:5 22:18 341:12
American 75:5 240:20 245:19 253:22 254:1,5,9,10,11
amniocentesis 46:5 119:7,9,17 125:15 127:13,14
amniotic 46:14,18 47:4,10
among 5:8 15:18 19:2,10 57:8 70:5 77:10 122:3 259:6 309:1,21 322:4 329:12 334:4,8 335:3 344:17 345:2
amongst 34:16 64:11 95:15
amount 11:5 79:4 164:8
amounted 8:2
amounts 159:21
amphiphile 220:21 **ample** 242:4 **analogous** 158:22
analogy 73:12 225:16 274:22
analyses 250:6 265:11 347:7 355:6
analysis 123:20 193:16 205:2 239:7 250:4 251:13 262:13 265:10 271:22 276:18 281:21 288:9 294:9 295:19 345:5
analyze 247:21
analyzed 34:11 128:4
analyzing 316:4
anamnestic 138:15
ancient 109:10
and/or 48:2,16 316:2
animal 144:1,8,20 145:13 147:6 148:13 149:2,4,20 150:10 158:19 162:4,13,14,22 172:10,11 173:7 177:18 178:1 192:20 195:17 212:21 213:13,19 218:14 221:3 225:15 226:14
animals 106:14 112:12 148:10 155:7 158:12 159:20
animistic 230:22
Anna 336:9
Annals 254:12 255:20
announcement 11:11 356:3
annualized 105:4
annually 13:16 14:2 254:15 303:15 304:6,11 325:9
Annunziato 203:20
anomalies 317:6
answer 12:2 31:4,5 34:5 36:2 65:21 66:10 68:12 94:10 144:14 204:3 224:9 257:9,14,21 321:11 338:14
answered 33:22 225:1 246:20
answers 144:19 315:13 349:7
answer's 230:4
antenatal 284:2
antibodies 2:17 39:19 45:20 56:21,22 59:3,15 63:1,18 65:6,10,15 69:22 91:7 95:2 103:5,12 108:18 109:14 110:11,12,20 111:11,12,13 119:1,5 121:19,20 123:13 129:2 131:12 133:8 135:16 136:17,21 137:2 138:8 141:18 143:3 151:8 161:9 198:15

207:6 209:12,14 215:16 219:21 220:7 221:10 227:10,11,14 228:3 231:17 290:10 305:4 323:8

antibody 41:7,8 52:5 62:2,17 71:3,22 73:1,2 91:13,14,18 92:21 94:4,12 103:6 104:3 108:22 109:6 110:22 112:2 118:7,17 120:7 128:19,20,21 129:1,4,16 131:11 136:19 138:6,8 140:5,6 142:1 148:4 151:11 157:2,4,15 158:1 162:5 172:22 173:11 211:18 213:15 225:19 227:19 228:5,7 229:1 232:19 233:1,4 273:1 292:17 293:9 325:8 342:22

antibody-based 73:2 94:16

anticipated 126:8

anticipating 285:13

anti-CMV 42:22

anti-epithelial 143:3

antigen 41:8 142:11 156:20 206:19 213:7 218:18 220:12 221:21 229:10,12 235:11 236:5

antigenemia 83:10,11

antigens 2:12 57:14 71:5 89:21 97:16,17,20 103:14 106:10,18 118:12 133:22 143:6 153:19 157:19 213:2,4,11 323:16

antigen-specific 220:7

anti-inflammatory 121:12

antisera 245:6

antiviral 94:4 108:18 137:10 141:4,6 214:16 245:7

antivirals 137:16

anybody 29:21 62:15 63:7 67:5 226:19 257:18

anymore 234:11 274:4,5

anyone 90:18 164:19,22 239:12 243:9 255:22 294:13 354:22 356:7

anyone's 282:11

anything 10:13 35:15 164:19 226:12 292:5 321:7 361:16

anytime 94:3

anyway 51:2 53:19 61:7 103:14 111:5 117:10 118:15 122:13 129:11 187:18 363:2,4

anywhere 227:17 248:9

AP86 104:4

apologize 131:14

apoptosis 146:14,16

appallingly 322:8

apparent 328:19

apparently 137:19 169:7

appear 108:3

appearance 130:9

appeared 89:2 362:19

appears 1:16 16:7 33:2 67:12 110:10 111:14 112:2 155:15

Applause 29:3 49:5 99:11 116:17 131:15 143:19 163:4 190:3 199:6

applicable 83:11 177:20

applicant's 194:1

application 176:10

applied 147:13 148:8

apply 281:18 309:17

applying 237:18

appointments 276:12

appreciate 66:16 121:3,18

appreciated 94:17 144:6

approach 45:15 50:15 141:9,15 154:10 158:18 161:6,14 202:21 253:2 257:3 287:7 310:7 319:5 342:14 362:5

approachable 81:17

approaches 133:1 201:4,5 202:12 280:10

appropriate 6:5,16 79:4 189:8 238:18,21 316:1,7,13 318:1 321:8 352:5,9 353:1 358:4

approval 177:17 178:7,8,16,18 179:3,6,7,9,22 180:2,13,14 188:22 192:4,7 195:4 201:20

approvals 179:14

approve 32:4 176:22 192:21

approved 177:1 179:8,15 188:11 193:11 250:9 313:6 320:18 358:4

approximately 13:19 31:11 41:11 47:6 52:13

104:17 113:19 311:10 345:16
APRE 95:6
apropos 343:8
area 5:12 17:9 38:12 63:10 73:9 75:11 88:8 148:7 158:19 160:4 201:7 257:13 350:22 359:12 360:7
areas 16:22 70:17 81:7 244:6 261:12 348:10
arena 236:11
arenas 347:17
aren't 69:11 75:21 272:7 352:1 364:2
arguably 148:22
argue 165:7 279:12
argued 113:12
argument 32:2,3 229:4,20 343:13
arguments 94:6
arise 246:20 348:13
arises 317:7
arising 146:20
arm 81:22 93:8 127:19 230:9 322:1
arms 5:22 118:1 127:21 174:15
Arora 44:13
arose 232:18
array 176:16
arrest 348:19
arrive 60:13
article 171:18 252:12 253:11,13 255:20
AS01E 206:20
AS1 167:16
AS3 167:16
Asia 13:13 22:18
Asian 17:3 24:22 25:17 27:14
ASO3 138:2 191:13,18
ASO4 188:1
aspect 66:22 79:2 128:4 202:5,6 240:2 241:10 302:3
aspects 76:11 128:21 129:6 194:7
assay 36:15,19,22 37:21 42:19 47:20 48:5 58:20 61:9 62:1,5,18 63:21 71:3,15,19 72:1,2,10,11,18 73:7 94:21 96:5 103:21 122:8,9,18,22
assaying 96:10
assays 37:12 61:17 70:20 71:6 72:8 75:22 94:15,16 96:3,6 102:3,9 118:12 123:4 129:12
assess 75:2 125:16 295:1
assessed 42:11 73:1 119:22 148:18
assessing 189:13 213:21
assessment 216:19 250:12 253:3 310:5
assigned 78:13
assignments 205:22
assist 247:9
associated 14:12 17:20 18:12,19 19:1,4,5,8 22:20 23:9,17,22 57:15 81:21 83:15 118:19 149:14 180:17 185:15,19 189:20 279:5 290:18 291:9 292:13 302:7 340:11
associates 136:4 137:7 139:22 141:9
association 291:11
associations 290:22
assume 172:16 288:21 344:1
assuming 189:10 190:2 297:4 299:14,20 301:11 344:8
assumption 65:10 279:4 280:1
assumptions 294:10 298:9 300:9 303:4
assure 242:17
astonishing 123:9
asymptomatic 15:9,15 26:7 28:9,14 30:18,19 47:8,9 263:18 264:1,9
asymptomatics 15:2 28:8 282:14
atherosclerosis 272:8 292:18 293:9 354:18
Atlanta 2:14 5:11 256:6
Atlantic 281:22
attack 233:18
attempt 224:8
attempts 141:20
attend 247:8
attended 319:3
attending 19:17 20:3
attention 49:4 84:7 118:15 128:20 140:3 162:19 199:5 306:13
attenuate 155:16
attenuated 84:4 132:8 133:5,9,12 142:13 151:7,18,20 154:3,6 155:7,20 156:20 158:5,12 159:12 162:8 185:9 186:2,4 196:16,17 228:16 291:4 312:19
attenuates 159:4

attenuation 152:3 162:7 185:13,14
attitudes 329:10 334:1 336:1
attorney 366:11
attract 89:13
attractions 287:7
attractive 152:14
attributed 172:6
attrition 125:5
audience 10:19 102:4 105:10 108:8 111:4 112:7 114:13 118:4 124:9,15 145:10 211:8 279:9 290:20
audio 366:5
auditorium 1:6 11:13 12:4
Australia 13:9 17:1 18:2 89:3 330:10
Austria 124:3
authentically 279:11
author 59:19
authorities 194:15 210:20
authorized 124:12
authors 118:4 121:6 152:12
autoimmune-related 187:19
avail 74:21
availability 4:12 7:13 8:18 350:7
available 10:5 28:4 46:1 59:20 74:8 79:13 94:13 96:13 104:20 119:14 120:5 122:18 124:8 127:9 130:19 143:11 187:6 194:11 205:8 234:5 253:12 259:17 260:9 261:2 294:14 311:7 318:18 319:15 332:15 347:22 363:20
average 248:9
Avid 91:13
avidities 122:13
avidity 41:5,6,8,13 42:1,8,11,13,16,19,22 43:8,9,13,15,22 45:17 49:15 54:21 55:20 58:19 59:3,13,14,20 60:6,7,11 61:7,17,18,21 62:1,9 65:9,18 71:9 91:14 93:3 118:18 121:9,15,16,21,22 122:6,8,9,10,11,18 123:1 129:11 138:10
avirulent 158:12
avoid 75:11 193:13 252:18 311:12 332:1
avoided 284:7
awards 253:7
aware 42:7 45:11 93:17 116:10 123:5 124:10 132:19 149:16 211:8
awareness 209:3 242:11,12,13 332:1 334:3,7
away 88:6,20 239:17 316:15 319:4 320:15 350:9
awful 274:3
awhile 249:8
Azevedo 295:11 298:4 302:10

B

babies 37:19 51:21 52:19 68:7 101:12 104:18 107:13 108:9 114:16,18,22 115:7 116:2 127:7 173:20,22 217:14 263:2,4 264:7,12 283:7
baby 23:19 24:1 71:17 101:17 107:6,18 109:17 110:9 127:4 280:3 333:10,12 335:4
baby's 109:5
BAC 111:3 147:9,18 154:2 162:9
BAC-engineered 155:19
backbone 111:3
background 2:2 8:21 12:13 244:18
backgrounds 16:12 27:21
BACs 168:18
bacterial 213:3
bacterium 213:2
bad 256:8
balance 192:14 198:9 210:8 317:11 323:5
balancing 195:12 238:9
ball 257:22
ballpark 236:17
band 101:18
bands 101:16,19
bank 104:19,20
banks 72:21 73:6
bar 25:12 327:4
barely 234:8
barrier 89:7,8 265:17
barriers 309:12,13 323:21
Barry 160:11
bars 326:7 327:3
base 220:20
based 16:4,11 27:21 52:5 57:6 64:14 70:12,20 75:17 86:10 101:6 102:21 103:20 107:16 126:7 139:18 161:7 176:8 177:1 178:9,21 192:15 193:11 215:10 217:9,20 234:4 267:9

275:14 360:1,17
baseline 305:20
basic 5:19 85:10 86:14 157:13 224:11 237:9 313:8
basically 32:22 70:20 71:3 83:21 97:5 177:2 237:5 257:9 314:7 336:20 337:11 345:12
basis 8:8 81:8 182:20 188:22 203:15 318:18 353:14,19
Bate 17:11
Baylor 3:15 258:3 261:5
B-cell 152:10
B-cells 138:13
bear 279:4,13
became 311:16
become 76:17 80:17 81:4 82:5 88:16 96:15 208:7 216:18 242:3 288:1 297:2 332:6
becomes 63:3 80:15 156:12 213:12 355:11
becoming 130:19 244:15
beg 175:10
begin 9:6 231:15 283:2 314:16
beginning 70:10 135:12 151:21 254:16 266:21
362:5
begins 18:6
behalf 293:3
behave 130:4
behavior 40:4
behavioral 266:18
behaviors 18:22
Belgium 124:3
believe 97:1 101:10 105:6 201:6,16 202:10 203:3,11 240:10 258:19 267:22 269:7 287:8 303:5 338:2
believed 182:2
belonging 305:19
Benedict 37:3,4,12 38:4
beneficial 93:22
benefit 93:11,13 178:15,17,19,22 179:5,10 180:5,8 182:5 192:14 195:12 207:17 208:5,19 214:7 217:3,5,18 218:2 235:12 239:6 265:8 269:8 271:13 287:4 294:9,14 318:18 328:18 340:15 353:11 355:8 360:18 362:20
benefit/risk 198:8
benefit-risk 310:5
benefits 159:14 204:12 205:13 251:21 279:22 291:12 296:1
332:20
benefitted 285:3
benign 289:22 290:3,4
Berkeley 298:5
Bernstein 62:14,21 70:18 139:21 211:9
Bernstein's 65:3
best 34:20 48:15,16,18,21 49:20,21 55:10 101:21 106:5 157:18 158:2 170:1 193:20 201:1 202:21 209:21 221:21 229:12 295:16 319:8
betaherpesviruses 145:3
Bethesda 1:8
better 37:1,12 53:16 57:9 66:2,5,10,21,22 67:2,8 69:5,16,17 72:7 99:20 161:12 162:2 169:3 184:11 186:17 188:12 194:16 218:3,16 258:8 295:2 305:8 306:8 315:4 325:5 356:17
better-recognized 309:22
bewildering 213:17
beyond 53:14 214:4 315:19
Bialek 11:2
bias 115:8 171:16,22 172:1 173:2
bible 289:5
bifida 15:20 53:17
bigger 124:5
biggest 171:4 305:9 307:1 351:19
bilateral 21:18 22:3,9,14 52:19
Bill 58:14 60:6,16 63:16 99:17,19 115:21 151:3 160:9 163:21
bind 95:10
binding 146:3 338:7
binds 41:7 95:7
biological 75:12 185:10 201:6 358:20
biologically 147:14
biology 77:11 85:4 88:4 100:10 149:1 152:1 165:5
biomedical 309:6,8
Biotest 120:4 123:22
Birmingham 2:7,16 12:18 23:12 29:12 101:5 113:16 173:18
birth 13:21 14:6,9 16:3 25:8

26:2,5,8,10,12 28:14 29:14 30:12 47:8 49:17 55:3 78:14 79:11,12 80:2,11 85:14 119:14 120:21 127:15 156:14 263:5,22 264:7,9,12 266:4 324:2

births 13:11,14,16

bit 4:21 28:20 74:16 83:21 84:11 85:7 122:19 128:7 145:17 150:15 155:4 177:13 191:10 208:16 244:2,18 245:11 251:5 252:17 259:15 261:9 287:6 311:2 316:16 319:22 344:22 345:9 358:22

bivariate 290:22

BLA 247:19

black 23:13 24:21 25:14 32:19 139:2 298:15 324:16

Blacks 18:13

blame 163:22

blocked 65:6 91:18 146:16

blocks 92:21 154:4

blood 33:17 44:4,8,18 45:21 47:12,16,19 48:22 49:21 79:5 83:4,8,12 84:21 107:20 129:8 174:12 220:18

blot 148:3 158:8

blue 140:22 298:18 299:5,7 301:20 327:3,5

board 350:10

Bob 29:11 62:21 67:8 70:14 91:21 136:4 161:2 173:17,18 217:2 220:3 225:22 230:5 342:12 343:19 356:20

bodies 132:21 141:10

Bodo 141:9

body 44:17 83:11 108:2 141:8 162:15 165:11 245:16 251:22 252:3

boldly 279:8

Bologna 2:9 38:20 42:18 46:9,17 56:8 124:17,18

bone 288:20

Bonnie 32:8

book 245:18 258:15,16

boost 109:6 139:17 164:16 232:2,15 275:6 342:22

boostability 208:10 231:20

boosted 109:9

booster 268:5 270:15 299:8 301:18,22 325:10,16 335:16 342:14

boosters 53:1 218:10 231:22 267:8 268:2

boosting 155:3 274:15 275:5

boosts 137:2 142:22 164:8

Boppana 11:6,17 12:9 29:6 34:6,9 36:3,6 38:5,18 48:10 49:6 50:22 53:10 54:1 56:17 57:4,17 58:14 60:16,20 63:5 64:10 66:8 67:5 68:1 70:9 73:8,22 102:21 118:16

born 13:6,17,19,22 15:14 22:11 52:20 57:11 114:18 125:18 173:21,22 196:22 197:8 234:2 263:12,18 283:8 304:11

BOTE 281:21,22 295:19

bother 274:17

bottom 81:19 137:10 140:7 141:22 248:17,21 250:8 313:3 327:4

bouncing 238:9

Bouty 122:9

boy 279:12 327:12 355:2

boys 31:14 279:3,7 280:2,4,9 281:14 282:19 288:16 291:19 292:4 327:16 329:18 353:8,10,11 354:16,17

Bradford 151:4

Bratcher 157:3

Brazil 13:18 17:7 22:4 34:20 104:12 116:1 164:10 169:5 282:9 295:11 302:17 303:16 304:11

Brazilian 22:5 28:19 51:18

break 10:13 74:1,5 200:1 258:22 276:21 277:1 308:10

breaks 10:5,8,10

breastfed 37:19

breastfeeding 20:11 27:22 51:22 249:21

bridge 217:10

bridging 181:11,12,19,22 182:14 189:11,15 214:17

brief 53:12,22 175:2 206:18

briefly 24:12 51:12,15,16 124:21 129:10,15 149:19 188:6 313:19

bring 7:3 78:12 166:17 267:1 282:22 283:20 285:4 298:22

355:5 359:9
bringing 11:12 200:9 288:15 292:11,20 347:3
Britt 2:15 58:15 61:4,11,13 63:20 85:17 99:17,20 100:4 115:22 118:16 151:3 160:9 164:21 165:4 167:20 169:13 171:15
broad 29:19 69:20 204:9,20
broader 54:5 276:20
broadly 316:20
brought 51:7 232:14 281:1 292:15 325:2 355:5
Brune 146:13
Brussels 21:20
buddies 95:12
budge 205:2
buffer 54:15
build 364:5
building 1:7 199:10,11 277:19,22
bullet 315:14
bulleted 26:20
bunch 213:11
burden 12:14,21 21:1 22:19 28:11,12,21 30:10,12 51:12 53:12,15 68:9 70:5 164:11,18 171:4,12 173:19,20 174:2 194:3 204:13 205:4 208:5 218:1 251:7 271:16 279:22 303:3 306:13 335:10 361:19
burdens 279:11
business 66:4 94:8
busy 127:22
button 168:11
bypass 278:5

C

cafeteria 10:9 74:3 199:9
calculations 257:4 298:5
California 89:3
Canada 13:9 16:13 17:2
canarypox 132:13 138:20 139:6,13,15
candidate 88:15 132:7 143:11 158:15 186:19 206:19 207:5 211:6
candidates 7:19 145:14 154:3 189:17 358:10
Cannon 15:21 51:5 53:13 67:7,22 113:3 116:5 171:18
capacity 109:4,9 179:17
Capital 1:12
captive 331:6 332:8
capture 237:16
card-carrying 12:19
cardiac 348:19
cardiovascular 290:14
care 19:10,11,14 20:1,2,4,5 27:22 31:10,16 32:4 170:17 204:11 216:18 257:12 266:7 270:22 294:11 315:20 332:6 348:20
careful 42:10 166:11 270:20
carefully 88:13 192:2 268:22
cares 19:17
caring 23:20 24:2
carrels 261:9
carried 117:17 334:10,11
carry 77:22 88:10 288:5
carrying 78:4 119:18
cartoon 211:13
case 5:10 7:3 35:3 40:2,13 41:3 48:21 73:15 80:14,15,18 104:2 107:22 135:7 139:16 148:18 166:9 168:21 178:8,11 182:11 193:20 195:19 203:3 205:17 228:4 230:14 234:16 280:5 281:19 316:8 338:9 340:2 341:6 348:19 358:7
case-controlled 23:17
cases 7:10 42:16 43:22 47:4,14 56:9,12 60:7 86:18 142:2 171:19 183:22 186:8 188:18 217:13 224:9 241:9 262:12,13 283:5 284:15 285:12 287:15 303:7,11,14 304:1,6,9,10
cataracts 274:3
catch 335:21
catch-up 325:19 326:5,8 330:21
categories 169:20 251:15 312:14 316:21 319:10,14 320:6,16 333:3
categorized 252:3
category 251:16 287:22 312:16 319:5
Catherine 10:22
cationic 220:20,21
causal 291:11 293:11 333:8
cause 22:16 77:3 84:18 148:10 162:16 164:16 187:10 290:17 331:8,11 340:18
caused 180:18

337:14

causes 4:15,16,17,18 7:4 16:2 309:21

causing 53:2

Cavia 145:8

CD 263:3

CD4 207:6 220:12,16

CD4+ 91:5,9 96:14 112:5 133:18 137:4 138:16 142:18 167:2

CD45RA 130:10

CD8 220:12

CD8+ 90:22 96:14 112:4,14 133:19 142:18 152:9 155:17 167:2 168:1

CD8+'s 91:10 152:11

CD8-positive 220:16

CDC 3:13,18,21 4:3 34:14 51:5 100:21 164:5 239:13 243:14,18 244:21 245:3 248:6 253:4,15 254:5 262:6 263:3 272:16 282:6,12,15 305:11 330:4,19 334:5 336:5 337:3 346:18 355:17 364:11

CDC's 355:6

cell 56:22 81:7 90:22 91:2 92:12,15 93:5 94:6 95:18 110:4 133:18 137:4 140:15 141:11 142:15,18,20 143:3 146:7 150:11,13 153:16,17 154:15,17 155:16 158:11,22 167:3 196:6 214:14 215:15 230:19 231:18

cell-associated 83:14

cell-free 73:4

cell-mediated 128:22 130:1 131:11 151:13 160:7 172:21

cells 65:7 88:8,9,15 89:22 90:7 91:5,10 94:20 95:6 96:14 97:8 109:19 130:9 146:2,5,18 147:3 152:9 155:17 207:1 215:17 220:8 227:21,22 228:2 229:14

cell-to-cell 72:11 129:7

cell-type 89:8

cellular 90:11 91:6 92:12 97:12,21 98:5,7 117:20 133:8 139:4 141:18 142:4 151:14 219:19 230:9

center 1:6 74:8 104:14 124:17,18,19 126:21 170:17 256:6 286:4,10

centers 11:1 19:10 20:2 31:10,16 80:11 82:14 124:2 125:6

central 80:12 107:6

century 5:5 283:20 284:8 294:7

cerebral 13:8 14:18

certain 64:14,15 83:2 84:8 169:2 247:16 258:12 315:13 352:16 358:3,15

certainly 9:19 63:20 66:16 69:21 78:14 80:12 82:1,4,9 83:8 88:7,15,22 89:10 90:7,11 91:19,22 92:7 93:5,12 99:7 105:21 145:13 181:7 185:13 186:10 187:11 188:5 191:3 213:7,22 234:17 239:4 259:11 283:22 307:6 344:3 347:20 352:19

CERTIFICATE 366:1

certify 366:4

Cervarix 187:22 233:12 311:5,8 312:3 313:2 332:17

cervical 44:18

cetera 291:2 294:12

chair 9:18 11:17 223:11

chaired 248:4

challenge 30:9,15,21 77:16 83:5 145:16 148:21 150:19,21 152:18,21 154:20 157:11 159:20 162:20 170:14,15 287:3

challenged 148:17

challenges 8:17 189:5 202:14 316:3 323:16 324:4 327:16,17 328:14 333:5 335:20 359:16

challenging 45:14 80:15 329:3

chance 40:5 169:3 229:15 280:3 344:10 360:5

change 35:21 84:9 85:10 115:17 171:2 176:14 298:17 350:7 355:15 357:12

changed 77:18 238:20 254:7 258:20 281:7 321:15 353:6

changes 27:6 181:17 352:9 355:17 357:15

changing 17:12

27:16 36:14 284:10 334:1 336:1

chapter 258:14,18,19

characteristics 30:19 64:6 262:16

characterization 7:14,15 203:6

characterize 184:11 313:16 314:19,20 315:5

characterized 314:13

charge 270:2

charged 144:7 259:3

Charlie 101:7,18

charter 245:5

check 283:21 285:21

cheek 82:9

chief 12:11 135:15

child 30:22 82:2 197:15 205:14 244:14 264:9 275:22 279:18 280:8 284:11,12 286:3,4,9,11,12, 14,17 288:3 324:18 343:11 350:14

childbearing 17:19 20:17 51:20 192:22 205:13 216:22 258:11 259:7,8 268:4,9 270:9 283:19 285:10,20 308:17 330:20 331:1 357:8

childcare 284:14 325:11

childhood 16:1,5 18:1,5,6,10 247:10 249:5 254:6 255:9,12 335:17

children 3:16 13:6 15:9,18 18:16,22 19:12,14,17,19,2 0,21 20:3,5,7,8,11 23:21 24:3,9 26:14 27:19,20 30:7,15,17,20 31:19,20 32:5 35:2,10 53:18,21 57:11 67:15 69:10 87:20 91:9 191:17,20 205:10 216:7 222:5 234:2 245:20 257:10,12 260:17,19 263:11,15,16,22 266:5 268:6 274:2 276:11,16,22 278:20 279:2 281:8 282:16 283:17 285:8 288:6 291:15 295:21 296:2,4 304:19 305:9,11,15,16,1 7 322:5 324:7,17,21 325:10,14,19 326:10 328:8 334:16 336:15 337:4,7 338:4,18,19 339:2,8 343:15 344:17 345:19 346:21 347:2,22 349:4,5,18 351:21

Children's 324:1 328:9

child's 286:5

chimera 153:13

chimeric 147:9,15 148:9 185:9

CHIMES 24:13 26:6 29:14 32:10 33:15 81:11

chimpanzee 146:9

Chinese 206:22

CHIP 123:17 124:13

Chiron 135:17 136:5

CHMP 190:21

choice 83:6 98:1,2 199:12

choose 15:1 71:14 215:19 266:12

choriomeningitis 133:3

chosen 6:6 126:16 259:16

Chris 37:4 153:5,9

chromium-release 168:1

chronic 165:10 284:2

Cincinnati 62:14

circle 76:12

circling 79:15

circulating 64:11

circumstances 282:3 **cite** 202:11 **citizens** 184:22 **civilian** 245:1 **claim** 192:22 194:1 337:10

clarification 29:13 170:11 217:17 277:9 308:13 349:1

clarified 218:2 340:4

clarifies 338:12

clarify 167:9,10,13,15 319:21 321:7 336:17 342:7 344:7

clarifying 11:22 256:12,15 292:9

clarity 8:9 201:8 249:19

Clark 101:7,18

class 158:7,9,21

classified 312:13

cleaning 37:13

clear 31:4 38:14 77:2,19,22 107:1 150:11 159:4,14 174:4 199:2 203:2 253:8 280:17 306:15 309:9 317:3 339:14 353:11,15 358:14 359:2 361:17

clearance 130:19,21

154:18
clearances 253:14
clearing 130:17
clearly 61:5 66:19 78:2,7 86:6 88:17 92:22 102:14,17 108:5 112:1 113:7 143:7 169:18 170:11 172:1 186:19 198:2 202:16 203:1 204:6 208:15 279:17 281:13 288:22 320:11 323:13 330:12 352:2
clinic 28:3 114:20,21 173:4 221:12 238:8
clinical 2:5 6:2,3,13 9:9 12:16 13:1 14:10 39:12,13,16 45:11 56:9 68:14 80:6 96:18 119:2 120:1 132:8,10,13,16,18,19,20 143:6,9 144:10 161:2 170:3 178:12,15,17,22 179:5,10 180:4,8 181:10,12,18,21 185:19 187:13 192:17 193:3,21 194:1,2,6 196:12 201:15 203:7,11,16 204:6 207:11 208:21 210:2,3,8 214:1,7 218:15 221:14 225:2 242:2 251:18,19 275:14 281:13 306:20,22 307:11 308:18 310:3,6 311:4,9 313:4 314:13 315:3 318:2 332:14 352:5
clinically 133:1 140:20 141:16 143:6 162:21 178:10 257:15 280:6 289:7
clinics 14:22 19:2,3 24:17 102:17 273:22 274:1
cloned 154:13 168:18,22
cloning 154:16
close 10:20 71:20 145:4 168:13 184:21 191:20 205:16 235:2 277:18 298:19 319:10
closed 127:6
closely 101:15 113:20 114:14 145:7
closest 161:17
closing 272:12 356:21
CMI 2:17 69:22
CMS 246:18
CMV 2:17 3:10,18 4:8 5:1,5,6,17,20 6:9,12 7:1,2 8:4,18,22 9:4,8 12:14,20 13:5,10,13,18,20,22 14:1,3,5,8 15:2,4,11,14,15,22 16:1,8,9,10,14,16,21 17:3,5,8,12,13,14,16,18,20,22 18:2,4,5,8,11,17,20 19:1,9,20,22 20:2,4,8,12,16,19,21 21:1,21 22:6,12,16,17,19,21 23:1,3,4,6,10 24:2,10,11,14 25:3,10,15,19,22 26:2,12,14,22 27:2,5,12,15 28:9,12,16,21 29:15 33:16 39:8,15 41:10 42:12,14,20 43:2,6,13,19 44:17 45:2,5,13,16,21 47:5 48:1,2,6,15 52:5,8,9,12,20 53:1,7,15 54:6,12 59:16,20 64:11 71:12,17 72:2 75:3,5,12,17 77:2,3,9 78:5,14 79:18,22 80:5,7,16,22 81:14 82:8,18 83:1,6 84:10,17 85:3 87:3 88:12,17,21 89:21 91:9 92:4,16,20,21 93:6 95:10 97:6,17 98:1 99:4 100:11,17 101:3,8 106:8 108:9 111:9 112:8 114:14,21 116:13 117:15,21 119:3,6 123:2,11 125:7 127:13 128:18 129:8 131:6 132:2 133:13,22 134:3 135:1,4 136:5 138:14,18 140:21 141:19 142:8,11,21 143:14,17 144:1,8 145:4,7,8,16 146:10 147:11,18 148:6 149:1,5,7,11,14,17,18 151:6,17 152:5 154:10 155:13 156:5 158:7 159:19 160:8,12,21 161:11,18 162:17 164:8 165:5 166:8 171:4 176:5 177:19,22 180:10 182:4,9 185:7,9,20 186:2,16 187:1 188:4 189:5 190:18 191:2 196:3,8 200:11 201:1,3,13 202:1,13 204:13 206:15,18 207:15,17 208:17 209:4,16,17 210:1,15 211:6 213:1,5 215:4,6,9 216:6 219:22 220:4,5 221:3,5,12 222:4,9 223:20 225:15 234:3 237:11 239:8,10 242:14,17,20

243:16 244:5,7 246:9,10 247:12,15 248:11 249:3,7 251:1 255:4,8 257:11,13,18 258:14,15 259:6,10,18,22 260:1,3,7,15,16,20 261:2,5,13,15,19,20 262:1,3,5,8,10,16,17,20,22 263:3,4,9,12,18 264:1,7,9,13,15,17,20,21,22 265:4,5,8,14 266:2,8,9,12,14,16,19 267:6,10 268:8,14,17,19,21 269:4,7,11,12,14,18,22 270:4 271:8,10,12,14,15,16 272:1,2,5,9,10,14 273:15 274:5 276:10,11,16 278:21 279:5 280:3,4,8 281:17,19,20 282:4,16 283:6,9,16 284:5,11,18,19 285:6,7,14,18 286:5,10 288:2,3,4,13,16,18 289:3,6,9,22 290:8,9,16,18,21 291:3,6 293:8,21 294:9,19 295:1,6,15 296:1,5,8,9,13,16 297:8,12,20 298:8,12,15 299:9,11,13,17 300:1,4,8,15 302:6,11,14 303:5,10,12,18 304:1,8,10,11,15,20 305:5,10,12,14,22 306:2,5,6,11 308:9 309:19,22 315:9 316:8 317:16 328:15 331:9 339:4 340:11,19 343:11 345:10,17,20 350:21 351:7 355:1 358:15,17,18 359:13,19 360:15

CMV-culture 260:11

CMV-infected 156:17

CMV-positive 21:22 23:19

CMV-related 14:19 15:17 53:21

CMVs 102:18 226:14

CMV's 16:5 289:13

CMV-seronegative 222:3

CMV-seropositive 222:14

CMV-specific 39:19 45:20 47:18 94:11 120:6 133:18

CNS 14:7 107:10

co 323:19

co-administration 323:18

cocktails 213:3

coding 139:7 142:21

Coen 148:4

cofactors 32:15

coffee 10:7,8 74:2

cofounders 32:15

cognitive 13:8 14:16 15:6 68:14

cohort 24:17 25:2,4 26:12 29:15 33:2 263:17 324:2

COID 349:15 350:18

coincident 333:8

coincidental 333:7

collaboration 85:18 158:6 211:7 309:5 346:15

collaborations 287:12

colleague 203:20

colleagues 22:4 28:19 44:14 49:1 91:3 148:15 151:19 152:5 154:1,9 159:1 160:12 202:1 233:16 241:22 275:17 290:7

collect 286:3 312:4

collected 34:11 312:22 357:19

collecting 81:3 305:11 346:17

collectively 273:9

College 3:15,16 149:8 254:10,11 258:3 261:5 278:19

colonies 160:14

column 134:10,11,14 141:20

combination 43:21 103:15 141:4 165:8 167:1 188:2 213:9 322:18 323:13,17

combinations 103:16 153:8

combine 60:12 211:20 341:9

combined 42:19 45:17 60:14 131:10 135:5 271:17

combines 219:16

comes 94:21 96:3 106:5 178:4 179:4 248:12,14 280:7,20 288:14 332:17 337:16 359:15

coming 54:11 63:9 169:7 194:7 205:21 267:19 284:11 285:8 288:10 325:14 359:17

commend 292:11,20

comment 28:19

30:5 31:2 34:21 35:1 36:7 37:4 51:12 53:11 62:22 67:7 69:19 72:13 74:11,13 98:1 170:10 173:19 224:14 226:18,20 227:2 231:3 232:6 234:20 235:8,21 237:20 239:13,15 240:14 242:10 257:18 341:14 343:8 346:10 353:3 356:10,11 359:21 363:17

commentary 309:14 310:11

commented 152:13

commenting 321:19 322:2

comments 65:2 223:16 224:1 234:14,19 256:9 342:19

commercial 59:20 120:4 123:4

commercialization 203:10

commerical 1:16

committed 92:16 215:8 359:13

committee 10:21 11:4 39:2 124:13 153:22 185:11 188:8 245:17,18,22 246:1,6 249:20 252:7 257:10,20 259:3 279:1 363:4

Committees 246:3

common 14:15 15:18 86:9 232:2 309:22

commonly 310:9 323:3

communication 188:21

Communications 256:5

community 8:1 82:18 215:3 281:12 282:22 285:11 288:12,20 310:10

community-level 342:14

companies 237:1 243:12 323:19

company 1:12 123:22 215:8 237:15

comparable 129:13 342:17

comparative 193:4

comparator 193:8

compare 52:11 118:11 125:17 158:4 170:2 181:20 263:2

compared 23:14 43:1 52:14 61:17 66:13 101:11 117:16 119:13 120:22 130:7,18,22 134:10 158:17 181:15 208:22 264:1,2 311:18 334:21

compares 31:16

comparing 56:20 137:10 297:16

comparison 42:22 140:18,19 167:8 218:11

compartment 159:16 165:17,18 297:18

compartments 108:2,5 165:11

compatible 221:19

compelling 155:21 240:6 359:5

compensable 336:21 338:5,13 339:19

compensation 205:12 240:11,12 241:4,11,12 309:16 336:14 340:16

competition 87:8

competitor 188:11

complete 45:10 126:22 255:2

completed 123:20 248:13

completely 21:7 84:3 308:18

completing 329:6

completion 329:4

complex 8:6 75:12 95:17 96:11 118:8 135:9 143:4 252:21 322:13,19 323:17

complexes 95:14

complexities 88:4

complexity 201:11

compliance 332:5

complicated 54:21 71:4 77:13 79:21 119:3 204:1 244:14,16

complications 77:15

component 107:9 215:12 219:19 229:18

components 117:22 167:16 273:3

composed 220:20

composition 70:21 209:11

comprehensive 29:7 271:22

comprised 71:1

concentrate 352:6

concentrated 136:12

concentration 42:15 222:5

concept 192:21

conception 197:17 217:15 266:2

concern 307:6 328:7 335:3 339:21

concerned 36:18 61:8 120:1,7 121:21 122:20 128:19 129:1 130:2,12 186:8

326:14 341:17 345:9
concerning 226:14
concerningly 326:13
concerns 175:3 187:10 195:17 200:5 240:10
concerted 8:2 243:4
conclude 141:17 143:13
concluded 365:12
conclusion 43:18 45:6 48:14 62:6 131:1 141:17 155:5 198:18 243:10 289:15 362:1
conclusions 9:13
concrete 364:8
concurrence 206:3
condition 313:15
conditional 192:4,8
conditions 17:9 37:18 53:16,20 168:19 169:2,4 255:15 257:15 293:10 308:22
conduct 315:1
conducted 136:3 140:14,15 263:19 309:1 311:4 315:21
conducting 210:2 346:16
conference 58:21 161:20 207:3 222:22 357:1
conferred 147:21 152:3 158:16
confident 143:16 359:8
configuration 221:17
confines 75:16 363:11
confirm 82:15
confirmation 148:3 226:3
confirmatory 179:9 203:17
confirmed 76:7
confirming 158:8
confirms 261:17,20
conflict 293:2 320:13
conflicts 246:14 294:20
confounders 77:9 291:1
confused 236:22
confusing 252:17
confusion 114:8 252:19 254:6
congenic 111:20
congenital 4:17 7:5,11,16 9:8 12:20 13:4,10,13,18,20,22 14:3,5,8 15:17,22 20:19,21 21:1 23:1,6,10,13 24:2,14 25:3,10,15,19,22 26:12,22 29:15,16 30:8 43:2,9,13,15 47:5,7 48:1,6,15 52:9 53:14,21 71:18 75:17 77:3,8 80:5,16 81:2,10 82:17,18 88:17 99:5 100:11,12,17 101:1,3 105:16 107:14 108:9 109:16 114:14,20 117:21 120:22 123:15 125:3 127:13 131:5 144:2,8 149:1,5,12 150:4 156:9 171:4,11 182:9 196:3 201:3,13,16 202:19 204:5,13,16,17,19 205:18,19 206:2,3,4,18 208:17 209:4,16,17 210:15 212:4 214:9 216:5,13 217:14 223:1 234:21 237:11 260:7 262:5,7,16 263:9,12 264:7,17 267:5,9 272:1,14 276:11 280:11,20,22 281:2,9 282:4 283:6 284:18 285:6,14 294:19 295:6,15 296:9,13,16 297:12 298:8 299:11,13,17 300:1,4,8,15 302:6,11,14,21 303:8,10,12,18 304:1,7,10,11,15 305:10,22 306:2,6,11 307:4,15 309:19,21 317:5,16 331:14 360:6,8
congenitally 79:13 104:18 107:6,14 109:17 110:9 170:3
CONGENTIAL 2:17
congratulate 351:11
conjugate 312:17 326:1
conjugated 322:11
cons 350:2
consciousness 6:7
consensus 70:2,4,11 161:21
consequence 96:8
consequences 76:14,15 79:22 80:9 84:12 97:13 155:10 165:15,16 169:16
consequential 54:9
conserved 150:8,9
consider 46:4 48:4 56:15 79:3 82:14 146:12 164:10 180:9 181:11 182:5,9 202:15,18 208:20 216:1 217:5 247:22 256:21 271:14 281:19 286:1

288:17 289:2 291:5 302:3 335:16 346:17 354:1 364:9,11,12

consideration 126:7 187:13

considerations 3:4,5,12 174:22 175:1 184:1 243:19 308:15 315:13 316:1,17 319:4 357:10

considered 28:22 43:4 55:15 153:14 186:3,11 201:20 225:9 230:7 240:5 246:9 324:18

considering 22:17 118:11 122:7 138:14 231:2 292:3 299:18 300:13 301:6 303:4 326:20

considers 251:1 301:17

consisted 125:5

consistency 249:19 250:2

consistent 30:11 177:12 205:19

Consistently 23:11

constant 222:4 298:2 343:22 344:7

constituents 141:13

constituted 249:7

constrained 297:8

constrictions 125:21

construct 110:1 153:18 207:10 251:5

constructed 226:1

constructs 112:17

consult 207:22 265:22

Consultant 2:20

consultation 197:13

contact 284:11,14 345:2

contacts 345:6

contain 112:9 141:12 283:15

contained 106:18

containing 95:15,16 138:20

contains 8:6 84:3 138:2 188:1 191:13 313:4

contamination 115:15

contemplated 237:12

contemplating 269:10 310:13

contemporaneous 136:20 276:9

contemporary 261:16 265:11 271:22 276:4,18

content 120:6

context 7:1 49:10 146:13 147:11 157:6 164:9 171:6 184:20 186:1,3 201:14 205:14 210:5 251:10 319:22

continue 6:15 50:4,5 74:3,7 99:8 185:4 207:7 231:9 327:7 345:20 352:21 354:7

continued 177:9 263:10

continues 264:18

continuing 77:10 246:12

contraceptive 19:3 28:3

contract 126:19

contracts 280:7

contraindicate 268:17

contraindicated 196:18 312:20

contraindication 197:5 241:20 268:12,13 320:9

contraindications 197:2

contrast 284:4 341:4

contribute 20:16 200:22 218:19

contributes 13:5 15:22 78:7 90:10 91:22 156:8

contribution 34:3 77:21 91:5,7 101:2 165:9

contributions 76:18

contributor 105:7

control 11:1 35:3 57:16 63:9 88:9 89:17,18 90:9,10,12,20 91:9,17 92:20 97:15 104:22 122:2 139:14 140:22 142:2 156:17 163:6 187:1 201:1 229:11 280:11 281:20 283:1,21 285:13 286:16 342:10

controlled 57:13 77:6 93:2 121:5 123:12 124:1 193:5 194:9 252:4 281:4 291:3 317:20

controls 91:16 105:10 263:20 264:2,6

controversial 266:22 316:12

convenient 94:21 222:3

convening 319:1

conventional 107:17 111:7

convert 72:1

converted 134:1

converting 167:3

convince 76:2 204:8

convincing 198:16 229:21

convoluted 109:11

coordinating 126:21

copies 154:16

cord 238:9,10
corner 363:19
correct 49:13 56:6 73:7 171:10 240:22 242:12 333:2 339:17 365:6
corrected 1:15 4:7 168:22
correction 333:1
corrective 193:17
correctly 129:5
correlate 63:14 136:14 179:2 180:19 181:6 182:1,2 213:19 218:9 220:1 225:14,18 226:2,5,7 233:1 274:20
correlates 2:11 73:6 84:5 87:10,12 88:10 89:14 96:20 98:4 144:12 180:11,14 181:2,4,9
correlation 61:21 63:8,13,17,22 292:18
correlative 233:18
cost 205:3 237:16 239:6,11 257:3 265:9,10,16 270:10,14 271:21 275:13 276:2,17 294:2,9,10,11,13 323:21 353:18,20 355:12,21
Costa 64:3
cost-benefit 335:15 **costs** 266:8 **counsel** 366:8,11
counseled 116:11 242:2
counseling 45:10 46:7 60:13
counter 164:20
counterintuitive 100:13
counting 322:18
countries 13:13 16:20 17:3,22 18:4,6,8,15 20:15 28:17,22 34:15 35:13 81:14 197:4 275:21 315:22
country 16:17 17:7,9 38:13 55:6 164:10 243:7 248:8 349:12
couple 6:10 49:7 77:12 87:21 186:14 188:13 206:12 239:3 249:20 252:13 256:10 289:4 322:6 345:13
couples 223:3
course 4:19 5:2 36:14 52:5 79:7,14,19 80:9,21 81:3,20 86:18 94:15 128:1 131:9 135:8,13 141:21 155:11 165:4 168:19 177:8,21,22 178:2 184:10,22 186:6,7 187:22 189:9,19 192:4,16,21 217:16 219:21 222:12 232:17,21 234:5 237:7 238:6 241:5 242:1 245:7 255:16 269:22 274:10 285:11,17 324:22 342:17 350:16 355:15 362:21 363:22
court 338:6,10,11 340:2
cover 266:8 267:11 307:3 330:16
coverage 97:18 207:18 208:4 298:10 299:12,15,22 300:19 301:10 304:14 306:22 307:1,13 322:4,9 323:1 324:6,11,13 325:12 326:9 329:22 330:7,8,11 334:8 335:18 336:3 339:21 355:8,10,11
coverages 333:17
covered 185:1 205:14 313:10 328:10 332:11 336:15,16,22 338:13,21 339:7,16
covering 276:21 321:17
covers 324:1 338:16
Cox 290:14
cranial 80:13
C-reactive 290:10
creating 19:12
creative 204:2
criteria 125:22 126:7 283:4
critical 89:19 96:15 112:13,15 144:13 159:8 166:18 171:8 176:15 182:17 207:13 212:1 219:21 249:20 250:4 275:12 277:17
critically 70:7 200:10
criticism 123:3 225:3
cross 317:8
crossing 286:15
cross-species 146:15
crowd 199:9
crucial 91:1 131:3 231:19
crude 62:2 127:20
crystal 257:21
CSF 107:8
CTL 56:22 133:19 138:22 139:2 142:15
culture 7:8,13 82:12 83:1

141:11 146:7 158:11 260:10

cultured 7:7,18

curiosity 340:10

current 8:14 88:20 94:8 200:17 202:12 234:4 271:12 276:4 286:6,7 312:11 326:3 355:16

currently 61:18 143:4 153:10 188:14 207:10 221:13 227:17 306:6 320:4,7 364:1

curve 136:8,12

customers 204:12

CV 207:17

CVS 348:4

cyto 168:1

cytogam 124:7

Cytogam 227:11

cytomegalovirus 1:4 4:6,12,14 5:12 8:15 145:3,9 146:2,15,18 147:2,10,17,19 150:16 153:6 156:2,12 160:14 161:8,17 176:16 178:1 198:19 200:18 203:10 292:12 365:11

cytomegaloviruses 145:11 148:12 150:11

cytoplasm 146:5

Cytotac 227:10

Cytotect 120:5 127:19 174:7

cytotoxic 167:3

cytotoxicity 130:14,17

cytotrophoblasts 90:1,3

D

Da 64:3

damage 22:16 44:21 80:3 286:6

damaged 280:3 289:13 340:16

dams 158:17 220:17

dark 327:3

data 15:21 16:4 17:11,12 22:15 24:13 27:3,6 28:3,4,8,10 29:22 32:9,10,12 34:10,20 36:4,7,10,11,14 37:7 43:16 48:10 56:12,19 57:3 58:21 60:9,14 61:20 62:12 63:8,17,20 67:18 68:5,8,10 69:11 70:13 78:11 81:3 87:17 93:12,19 99:4 100:17 101:6 108:8,15 113:6,14 114:9,10,11 116:1,2,9 121:17 123:20 130:19 132:16,19,21 136:16 151:1 157:7 171:17,18 173:12 174:16 176:9 185:1 189:11 193:3,9,21 194:6 195:17 196:14,21 207:9 208:12 211:16 217:19 224:10 226:14 231:2,5 234:5 238:13 239:9 251:8 261:16 262:22 265:9 269:9 271:12 275:2 276:4 282:5,12 290:7 292:2 293:13 295:11 297:20,22 298:1,16 302:11,18 305:7 312:1,2,4,6,21,22 313:5 316:4 318:18 319:15,16,18 320:19 329:9 344:19,20,21 346:5,8,17 347:8,12 351:22 353:1 354:4,10 357:19 361:2,9

database 183:3,6,11 192:1 195:6,10 217:9 236:2,10 242:4 315:15

databases 183:2,16 184:16,19 185:2 236:2

date 127:5 144:21 159:10,18 161:4 196:17 256:2 321:4

dated 36:11

dating 42:15

daughter 279:20

Dave 65:3

David 62:14 70:18 139:21 211:8

day 19:10,11,14,17,22 20:2,4,5 27:22 31:10,16 82:13 170:17 273:2 296:17 365:9

daycare 222:2,5 225:22 286:4,9

days 40:15 83:7 106:16 161:21 274:1 311:17

deal 30:21 163:1 195:20 198:11 209:5 245:4,8,12 246:17 340:21 346:4 351:2

dealing 196:2 217:7 329:5

death 290:13 340:11

debate 82:17 282:11

Debbie 153:4 166:12 167:9 232:3 293:1

Deborah 129:5

debut 19:6 35:5

decade 215:10

decades 27:3 75:4 77:15 80:5 85:11 262:6 276:7 301:2 304:21 328:19 331:18 333:16

December 187:2 250:19

decide 240:7
decided 252:7
decidual 89:22
decision 75:17 176:14 251:19 338:10 347:16 348:3 349:3,4
decision-making 176:7,20
decisions 75:15 176:8 224:20 251:19 348:6 349:2
decisive 273:10,12
declined 325:8
decrease 164:18 302:19 323:14
decreased 353:14
dedicated 117:2
deep 108:8
defects 78:14 310:2 331:9
defend 193:7
defense 75:6
defer 35:22
deficiencies 249:13 255:19
deficient 152:10 154:7
deficit 79:19
define 57:22 69:22 70:1 71:14 118:6 159:8 197:17 222:16 226:2 238:10 262:17 308:21 310:12 313:11 314:17 315:4 317:4
defined 62:4 70:16 103:5 104:11 160:6 203:16 237:4
defining 12:21 225:13
definite 235:16
definitely 34:1 71:6 77:14 271:21
definition 6:3 25:6,7 65:5 80:14,16,18 131:7 145:12 216:3 218:15 226:5 238:2,4,5 324:17
definitions 178:11 203:3,4 205:18 313:9
degree 41:8 156:21 159:22
delay 235:5 271:11
delayed 59:2 65:18 130:6 216:11
delays 212:10 269:21
delete 153:20
deleted 154:4
deleterious 155:10
deletion 152:6 158:9,10 162:10
deliberations 257:7
delicate 59:13 317:11
deliver 20:18,22 127:4 322:16 350:11
delivered 23:19 24:1 104:5,17 109:17 260:6 349:14
delivering 20:20 23:6,9 233:10 270:3
delivery 16:18 17:10 22:5 23:16 25:11 27:17 38:14 54:14 56:16 62:9 109:3,6 120:13 122:1 151:10 265:13,18
demise 340:18
Demmler 256:16 258:2,6,8 273:21 274:7,11 275:6,9 276:3 308:6
demographics 259:13 266:4
demonstrable 155:2
demonstrate 14:2 162:5 177:16 182:5 208:18 210:9 217:3,18,20 236:11 337:13
demonstrated 22:4 102:15,16 105:5,11 143:5 146:1 148:19 149:11 177:10 178:3,5 233:2,3 268:10
demonstrates 204:19
demonstrating 148:4 210:1
demonstration 185:12 201:13
dengue 108:11
dense 132:21 141:8,10
Department 1:9 49:2,3
depend 42:13,14 76:3 195:8 222:18 238:3 268:3
dependent 79:17
depending 16:17 17:8 18:17 70:21 71:13 170:14 175:22 222:21 302:15 314:10 355:7,8
depends 43:22 55:5,11 229:8 236:8 355:13
deplete 109:13
depletion 152:11
derivative 167:12
derive 132:4
derived 297:21 319:19 320:20 344:20
described 148:14 167:15 219:11 331:15 334:5
describing 14:21
design 9:7 170:19 187:13 210:5 218:5 222:7 295:7 318:2
designated 188:14 245:22
designation 188:10 238:17
designed 8:19 177:8 237:8

241:8,12
designing 70:7 306:20
desirable 205:16 273:17
desire 200:22
desiring 197:15
desk 199:21
despite 166:7 226:13 306:3
detail 88:19 147:5 158:5 178:6 197:19,20 211:17 332:12 362:14
detailed 26:21 195:2
details 118:5 129:21 311:7
detect 6:7 39:19 42:2 44:3,5,7 62:18 78:17 79:6 106:12 130:16 183:8
detectable 80:2
detected 15:10 33:16 53:19 89:21 120:20
detectible 166:9
detecting 79:11 82:19
detection 47:18 81:17 82:10 166:6
determinant 305:21
determinants 110:18
determination 26:16 47:16 178:14 179:4 321:1
determine 36:16 79:8 181:17
determining 68:3 129:3 180:15 269:6
detoured 118:17 121:20,21
develop 30:7 62:3 71:2 85:15 138:10 201:2 227:7 234:3,11 247:22 282:13 296:22 352:22 353:17 359:13
developed 7:8,21 65:14 111:12 132:7 135:17 136:1 138:22 139:2,19 149:15 151:4 188:3 228:13 321:3
developers 200:21
developing 6:8 13:6 137:22 140:13 200:18 205:17 215:9 232:13 234:22 252:14 304:22 315:10,22 352:10
development 1:3 4:5 8:4,10,16 26:18 53:4 65:6 96:19 132:3 148:8 160:2 181:12 188:5,13 189:12 194:11,15,22 201:17 202:4,13,17 203:9 204:4 206:1,15 207:11,15 210:1 219:10,15 221:13 227:22 228:2,18 237:16 244:4 247:1 250:12 253:9 310:6 311:3,9 313:21 314:14,18,20 316:21 317:5,22 358:16 365:10
developmental 314:6 316:14
develops 80:2
devices 276:15
devoted 11:4
diabetes 250:17
diagnose 45:15
diagnosed 126:13
diagnosis 2:2,8 7:14 9:1 12:14 16:8 38:21 39:4,5,6,8,11,12,13,16,18 41:4 43:6,18 44:2,22 45:2,3,4,6,8,10,11,12,13 46:3,4,5,6,10 47:3,17 48:6,14,20 62:16 125:8 126:10 131:6
diagnostic 6:8 44:1 45:22 216:11
diagram 76:4,9,16,21 88:2 90:2
diaper 82:8
Dick 146:8
Diego 221:6
differ 21:2 329:5,6
difference 4:11 32:2,6 34:10 35:12,15 36:17 60:17 62:12 66:12 91:15 94:19 109:2 113:12 114:2,5 115:3 118:7 119:1 122:3 127:21 130:11,14 134:12 137:15,16 139:11 141:5 166:15 174:4,10,11 178:4 179:1 263:21 314:2 335:2 344:4 345:10
differences 27:21 32:9 64:7 111:18 121:22 129:19 228:15 252:18 254:4 257:6 352:20
different 17:16,18 18:17 23:10 24:7 27:14 31:21,22 47:16 51:12 57:14 59:10 61:17 65:15 68:7 72:17 73:1 97:9,11 103:15 107:10,15,17,19,20 108:2,4 111:6,8 112:17 114:12 115:6 118:12,13 123:5 150:5,6 155:4 156:6 161:6 165:11 169:3,7

170:2,3,5,7,18,19 181:16,20 182:7,10 183:17 198:11 203:5 208:21 211:21 214:13,15 218:11 221:3 226:11 227:12,15 228:10 249:1 252:15 254:8 262:1 264:10 282:22 295:5 298:3 304:13 313:20 322:17 326:13 329:12 344:15,22 345:2,3,6 346:20 347:17 356:15 358:22 359:1 362:3,4

differentiate 33:17

differently 130:5

difficult 8:5 15:1,12 29:22 30:20 42:16 63:4 79:2 117:7 118:11 121:3 128:16 145:12,16 156:9 159:11 173:4 186:15 193:6 194:9 196:11 197:4 201:14 208:2 286:20 312:9 330:22 331:2 332:19 359:7

difficulties 57:21 68:3

difficulty 10:10 81:2 186:18

diligently 363:18

Dimes 243:9

direct 158:20

directed 232:5

direction 62:7 273:8 319:9 352:10

directly 73:7 181:15 342:17

director 244:20 245:3

disabilities 14:19 15:3,16,17

disability 13:7 21:6 53:15,22 174:4 309:21

disadvantage 270:14,18

disadvantages 270:3,10 271:1

disagree 169:17 291:18 361:8

disagreement 80:20

disappeared 281:10

disbanded 248:11,14

discharge 332:3

disclaimer 315:8

disclosures 258:9 294:21

discordant 223:3

discover 236:19

discriminate 37:22

discuss 9:4,7,11 59:21 80:19 176:4 189:6 210:17 224:22 244:1 262:7 270:2 276:20 315:16 317:13

discussed 5:4 6:10 51:8 185:10,22 187:5,11 189:9 196:9 197:19 198:20 203:19 206:13,20 207:3 208:16 209:5 216:12 217:12 225:11 340:20 348:2 352:15

discussing 225:8 296:17 362:14

discussion 2:10,21 3:22 8:22 9:12 10:15 12:1 29:5 51:1,4 78:12 99:15 116:19 144:1 152:12 154:22 161:22 163:9 164:3 185:12 190:5 191:4 199:2,8 201:19 206:14 210:4,12 217:6 222:1 223:6 234:13 239:16 244:1 246:10 263:6,14 272:7 299:1 340:13 349:16 351:12,13 352:8,21,22 354:3,6,7,11 356:9 358:13 364:18 365:3

discussions 4:10 9:21 74:3 161:20 171:7 257:7 277:13,14 285:14 349:19 354:8 360:2 364:7

discussion's 363:15

Discussions 198:22

disease 2:5 3:18 4:15,17,18,22 5:20 7:5 11:1 12:14,21 13:1 14:6,12 15:19 21:2 22:18 28:11,12 30:7 51:12 53:2,12 54:6 68:4,9 70:5 75:18 77:3 78:18 79:14 80:1,16 81:1 83:1,20 85:14 87:14,18 92:20 99:5 102:17 107:7 115:13,18 134:13,18 142:2,5,6,15,20 143:10 144:2 148:10 149:13 155:16 157:4 158:2 159:4,20 162:7 171:12 173:19,20 174:1 178:21 180:17 185:19 188:19 193:20 194:1,2,5 195:14,15 201:1,13 202:20 204:5,17 205:4,19 206:3 208:4 216:6,9,10 234:9 244:17 251:7 256:22 262:5,10 264:17 267:10 272:14 276:11 282:14 290:14 291:7 293:22 295:2,4 303:3 306:4,9,13 316:10 323:9

328:20 329:2 335:7,10 355:17,18 356:13 359:4 360:6,9

diseases 4:3 100:14 244:22 245:18 272:6 318:20 322:17

display 255:2

dissect 94:9

disseminated 14:6

dissemination 364:4 **distinct** 170:8 **distinction** 310:17

distinguish 180:22 358:15

distinguishing 92:8

distribution 31:9 32:11,14 126:3 170:4

diverse 261:7

diversity 64:20 83:20 84:6 97:19 98:19 106:22 108:10,12 169:22

divided 24:20

dividing 316:20

division 107:12

DMORIE 220:21

DNA 33:16 44:3,5,7,8 46:15 83:6,7,15 85:9,20 89:21 131:3 132:19 139:7,8 140:13 142:17,21 153:5,8 160:15 166:8 188:15 219:15 220:6 221:1

DNAemia 44:11,12,14 157:22 158:17

doctor 270:16 276:12 327:7,14

doctors 271:4

document 19:20 22:9 253:15

documents 250:1

Dollard's 282:12

domains 148:12

dominant 91:11

Don 148:4

done 5:17 10:10,11 12:20 21:4 28:20 35:16 51:17 58:7 82:13 88:16 91:3 92:14 98:11,14,18 99:19 102:4 104:13 106:6,8 107:2 111:1 114:16 117:8 145:15 184:12,15 203:15 221:7 239:7,8 249:16 252:9,21 260:12 281:21 290:4,5 295:10 305:13 307:5 314:8 324:11 330:13,18 352:6 355:6 356:4 362:11 363:9,14

donor 134:9,16 137:12,17,21 198:7,12

Dormitzer 3:8 211:1,2 226:21 229:7 230:1

dosage 120:15 125:9

dose 140:7 141:21 207:7 231:6 295:18 301:18,22 326:15 349:20 350:20

doses 138:1,21,22 140:17 173:13 221:11,21 255:5 325:2,4,16 335:17

dosing 181:15

dots 298:15,19

double 177:22

double-blind 123:17 124:6 193:22

doubled 179:16

doubt 236:15 275:15

downstairs 74:2 199:9

DPyPE 220:21

Dr 4:2 12:9 13:4 29:4,6,11,18 30:3,9 31:7,12,14,15,18,20 32:8,16 33:4,6,7,8,12,19 34:2,4,6,8,9,13,14,19 35:4,11,20,22 36:3,5,6,9 37:2,3,9,12,15 38:4,5,7,18 39:1 49:6,9,20 50:1,2,6,9,22 51:16 52:16 53:10,13 54:1,4 55:5,7,9 56:17,18 57:1,4,5,17 58:10,14,15 59:12 60:16,19,20 61:1,4,7,11,12,13,16 62:8,14,21 63:5,6,20 64:2,3,10 65:2,20 66:8,16 67:5,7,21,22 68:1,22 70:9,15 72:4,19 73:8,9,22 74:6,20 87:6 98:4,8,9,10,11,12,14,15,17 99:12,14,16,20,21,22 100:4 115:21,22 116:18,22 117:1,3,4,5,10 128:12,15 131:16,20,22 132:2 143:20 144:3,18 150:2 163:5,8,10,11,13,14,15,16,18,20 164:2,5,21 165:3,4,20 166:5,13 167:9,12,13,14,19,20 168:3,4,5,7,8,9,10,12,14,15 169:13,17 170:10 171:3,10,15 172:5,8,16,18,19,21 173:1,8,9,16,18 174:13,17,18,21 175:7,9,12,13,14

,16,17,20,21 176:3 189:21 190:4,7,10,12,13,15 199:7,14,15,16,19 200:2,7 203:20 206:7,9 210:22 211:2 214:21 215:1 218:21,22 219:1,5 222:1 223:5,9,10,13,15,19 224:13,15 225:4,6 226:21 227:2 228:20,21,22 229:7,20 230:1,2,4,12 231:3,21 232:4,17 233:6 234:12,20 235:14,21 236:13,14,15 237:3,19,20,22 238:1,15,16 239:2,15,19,21 240:1,2,8 241:10,14,15,18,21 242:7,8,9,10 243:1,2,8,14,21 250:5 256:12,18 257:8 258:1,6,7,8,14,20,22 259:19 260:14 263:10 272:20 273:11,18,21,22 274:7,8,9,11,12 275:6,8,9,10,11,12 276:3,19 277:4,6,9,12,13,16,17,21 278:2,9,12,15,17,18,22 292:8,10 293:1,5,6,18,20 294:4,16 306:14,19 307:9,11,17,20,21 308:1,2,6,7 313:10 315:8,16 317:21 318:4,6,11,12,13,21 319:7,12 321:6,14 336:8,11,19 338:15 339:1,4,10,12,13,20 340:4,6,8,9,22 341:1,2 342:5,19 343:8,16,19,20 344:6 345:8 346:1,2,3,10,11 347:15 348:7 349:10 350:12,17 351:9,10 353:3 354:2,13,14 355:4 356:1,3,4,5,10,19 357:3,5,12 358:1,6,11 359:21 361:8,21 362:12,16,18,19 365:4,6,7,8

draft 248:1

dramatic 94:18 157:16 284:18,21 327:15 335:1

dramatically 36:21 116:12 329:14 330:10 334:7

draw 62:6 225:16

DREMMLER 3:15

dried 48:21 79:5

drill 155:8 177:13 259:15

drink 11:13

dripping 273:7

drive 87:3 88:6,7

driven 183:6 184:6

driver 184:2

drivers 204:22

drop 37:5 110:4 116:14

drop-off 327:15

Drs 310:11 343:20

drug 1:9,17 121:4 123:18 124:6 125:9 188:9,10,15 237:5,18

drugs 237:8 317:4,7

due 14:20 15:4 22:19 26:12 28:8,12 57:12 67:13 70:5 71:21 156:14 163:5 164:12 191:1,14 194:5 275:21 296:3 302:6,14,22 303:6,10,12,18 304:1,8 306:2,11

Dumas 3:9 214:22 215:1 218:22 234:20

dunk 353:19

durability 94:14 167:5 232:7 294:11 362:12,21,22

durable 167:2 232:15 325:4

duration 60:20 143:2 189:14 212:7,8,16 214:12 230:13,16 234:5 235:5,9,13 267:3,11,15 274:16 296:11 298:11 299:14 300:12,17 302:15 304:14 346:6

during 7:12 8:12 10:7,10 14:11 17:17,19 20:20 23:18 24:1,4 41:10 42:2,5 44:4,5,16 46:10 47:9 48:3 50:5 62:11 63:15 80:10 92:18 97:13 104:5,9 105:2,12 116:13 117:15 173:21 191:11 215:7 227:5 231:4 234:3 239:16 240:18 246:7 260:3 266:18 267:7 268:11 269:5,9,12,15 270:18,20 286:19 303:6 304:2 308:10 323:9 330:15 331:2,7,9,12,19,20 332:1,11 333:6,15,19,20 334:2 336:2 341:20 350:14

dynamic 355:14

dynamics 279:16 295:2

E

earlier 97:4 130:18 179:18

186:21 189:1 194:16 201:12 211:17 226:13 255:4 295:18 301:16 302:2 315:8 338:3

earliest 269:14

early 16:3 18:5,6,9 20:14 39:10 40:8,22 51:21 91:2 128:21 129:18 131:4 150:16 156:14,21 166:8 172:4 189:17 194:11,15 224:20 273:20 314:13,18 317:22 323:6 328:17 341:22

early-stage 307:8

ease 68:19

easier 63:2 111:2 150:8 233:16,17 245:11 249:18 251:5 255:8 280:15 321:9 328:4

easiest 118:8 221:18

easily 68:16 82:6 141:11 289:21 342:16

East 16:19

easy 71:2 96:16 97:19 166:7 193:7 267:12

EBV 188:16

EBV-CMV 271:17

echoing 317:20

economic 205:1 250:4,6 251:12

economically 171:4

Ed 2:13 11:6 33:12 54:3 74:22 98:8,10 99:15,22 100:7 106:21 117:5 144:3,11

Edington 149:8

edited 1:15

edition 258:16,17

editorial 272:21

educated 242:21

education 204:11

educational 246:12 291:2

effect 5:22 67:3 73:15 84:18 121:10,12 166:4 177:7 181:17 182:3 189:14 265:9 291:3 298:14 299:12 300:3,12 321:5

effective 4:12 77:7 86:19,20 152:7 162:9 177:11 186:19 200:18 202:22 209:19 226:16 227:15,18 239:11 244:22 265:16 270:10,14 275:14 276:2,17 323:7 325:12 342:10 353:18,21 355:12,21

effectively 200:16

effectiveness 178:13 183:5 205:4 210:19 217:20 251:8 257:3 271:21 281:11 294:2 305:6

effector 73:3 97:8 130:9 150:14 229:1 230:21 231:1

effects 80:7 160:17 177:4 185:17 279:18 332:10

efficacious 182:12 204:18 235:4,7 301:10

efficacy 47:15 68:20,21 75:2 87:14 119:5,21 121:2,4 125:16 129:14 132:9,10,12,21 136:4,20 140:14 156:22 161:1 177:14,16 178:5,12,21 180:20 182:21,22 183:4,5 184:7 187:18 189:10 203:8 210:9 212:9 216:4 218:14 226:7,8 251:8 269:18 272:10 283:3 295:21 296:11 298:10 299:12,15,20,21 300:20 304:13 307:13 313:4 314:20 315:2 316:5,7

efficient 79:6

efficiently 158:11

effort 8:2 11:5 12:11 82:3 123:11 144:6 219:7 243:4 272:18

efforts 81:16 135:14 156:1 317:3

egress 96:2

eight 244:11 246:16 269:16,19

either 51:6 56:21 63:16,21 76:14 77:20 78:19 82:5 86:11 95:5 139:13 155:15 156:14 189:20 190:9 222:21 223:1 242:15 255:9 266:17 281:22 284:12 314:1 322:10 333:4,10 337:13 340:1

elaborated 191:8

elapsed 128:5

elderly 97:7

elegant 151:5

elegantly 219:11

element 197:12

elicit 220:15

elicited 138:17 142:9,16 228:9

eligible 178:19 309:8

eliminate 165:13,14 298:21 304:20

341:13
ELISA 121:20 157:14 158:15
ELISPOTs 96:17 140:8
else 31:2 36:1 71:4 308:12 344:21 345:15 348:15
elution 61:13
EMA 3:6 190:14,22 194:21
emergency 8:3
Emory 2:13 33:13
emphasis 162:14 363:7
emphasized 178:11
empirical 230:5
employed 366:9,12
employee 366:11
EMs 146:3
enable 186:22 201:17 227:4
enacted 250:8
encephalitis 139:19
encoded 94:22 112:10 146:22 158:7 161:11
encodes 219:17,18
encoding 148:17 154:15
encourage 317:18,22
encouraged 199:1
encouraging 202:1
357:6 359:10
endogenous 169:15 283:9
endorse 239:12
endothelial 89:22 95:18 209:13
endothelial/ epithelial 65:7
endpoint 71:13 81:5 127:9,13,14 178:21 179:2 180:6,7 181:21 201:16,21 210:15 216:4,12,14,20,21 217:2 222:11 234:12 235:3 240:5 315:4 316:7,11
endpoints 6:3,5 159:19 160:1 178:10,12,13 180:3,4 181:5 189:8 197:18 198:10 201:19 203:11,12 204:7 208:21 210:7 214:1,6 223:1 225:8 314:21 352:9 359:4
engaging 317:22
engine 247:20
engineered 141:14 154:11
engineering 162:9
England 76:22 101:9 108:19 122:21
enhance 209:22
enhances 95:17
enriched 14:21
enroll 124:22
enrolled 24:19 125:8 127:2,8
enrollment 19:21 122:1
ensure 177:9 348:21
enter 18:10 283:13 285:9
enters 211:14
entirely 71:21 168:13 169:8 352:6
entity 75:12
entrance 199:11
entry 56:21 65:6 94:19 95:8,18 135:16 215:16 325:11
enunciated 77:17
envelope 94:22 95:3 96:1 141:12 150:9 156:20 215:13 282:1
environment 358:21
enzyme 101:8
epidemic 7:9,12 191:16
epidemiologic 30:6 203:6
epidemiological 224:11 364:10
epidemiologists 12:19
epidemiology 2:2,5 6:12 9:1 12:13,20 13:2 26:19,22 115:17 271:8 294:19
295:3 304:15 309:20 355:16 356:13,17 361:13
episode 69:8,15
episodes 140:21
epithelial 56:22 94:20 95:18 209:13 215:17
epitope 103:2,4 104:7
equal 53:20 85:14 343:13
equally 24:20
equations 346:5
equine 139:18
equipment 348:18
equity 182:18 251:10
equivalent 31:11 120:7
eradicate 295:22 299:4
error 125:4 168:21
especially 6:13 12:21 41:17 51:13 80:1 81:11 236:9 266:3 329:18 335:20,22
essentially 158:12
establish 184:7 186:7 187:17 212:16 218:9 222:13 233:17 269:1 318:1
established 78:9,10 82:21,22 136:15 221:18 222:15 227:8

244:19 262:15 268:20 312:4

establishes 185:18 309:5

establishing 316:1,7

establishment 152:13 155:1,9 160:13 204:2

estimate 15:1,13 25:13 26:11 30:1 105:13

estimated 87:19 282:6 297:16,22 303:16 344:21

estimating 282:10

et 17:11 291:2 294:11

ethical 194:6 308:14 309:5

ethically 193:6 309:10

ethnic 17:15 18:18 27:21

etiologies 29:22

etiology 16:8

EU 191:9,22 194:8,17 197:3,4 238:1 275:20

euro 275:22 276:2

Europe 2:6 3:5 13:3,9 16:15 17:2 38:8 120:5

European 123:21 190:17 224:18

evade 112:14

evaluate 54:14 73:3 89:10 145:12 186:9 345:4

evaluated 87:19 90:4 186:11

evaluation 1:3 4:5 129:14 166:11 177:19 182:19 189:17 195:11 250:13,16 365:10

evaluations 26:15 333:6

evasion 8:7 112:9,12,21 155:20 158:22

event 195:16 236:18 241:3 302:12 333:9

events 183:8 184:9,11 187:20,21 193:16 195:18 333:7

eventually 69:6 91:9 99:6 118:19 130:7 285:5 359:19

everybody 10:18 33:19 123:4 190:15 191:2 277:6 278:4 342:15 344:10 351:11 363:21 365:1,8

everyone 59:9 74:10 253:19 277:4 279:19,22

everything 10:2,10 71:4 199:18 242:17 274:10 344:21 363:22

everywhere 350:5

evidence 52:4,7 67:15 71:12 106:4 108:20 110:21 112:5 133:16 142:1 158:20 165:1 250:22 251:20,22 252:3,5 253:4 257:2 265:4,7 280:20 289:14 291:17,19,21 293:8,9 360:21

evidence-based 250:7,8 253:10

evidentiate 123:1

evolution 138:13 140:4

evolve 185:4 351:6

evolves 176:13

ex 246:16

exactly 33:4 61:8 154:1 166:1 184:14 187:12 275:9 277:3 307:20 339:3,9 354:2 360:4 361:1 363:10

examination 46:6 187:19

examined 118:12

example 36:12,19 38:16 104:3 129:7 170:1 196:18 202:11 208:21 213:1 233:11 275:19 281:11 283:11 286:4 341:9 346:13,18 353:8

examples 179:13,14 180:1 291:22

exceed 332:20

Excel 294:8,14

excellent 306:15 311:1

except 114:6

exception 323:11 326:19 335:8

exceptional 124:15

exceptions 324:22 332:17

excess 291:8,9 292:1

excise 337:7

excited 4:9 219:9 224:15

exciting 184:15 185:2 223:20

exclude 42:4 169:8

excluded 308:18 332:13

excludes 47:4

exclusively 341:3

exclusivity 188:10

excrete 112:19

excreting 106:17 134:3 284:11

excretion 19:17,18 133:15

excuse 147:21

exercise 195:11,12

exhaustive 35:16

exist 73:6 257:6 269:10 320:7

existing 72:21 178:20 193:8 251:10

exogenous 169:14

expand 108:15 230:8
expanded 184:17 223:2
expansion 184:19
expect 76:13 85:9 209:18 231:13 253:7 284:18,20 288:7 311:21 358:3
expectation 217:16 231:10 314:3,7 315:1
expectations 76:7 205:3,5
expected 28:1 178:14,16 179:6,11 217:19 220:6 281:9 298:17 300:10 314:12,16
expensive 324:3 353:17
experience 36:18 42:18 56:8,11,12 59:17 126:10 214:10 281:11,18 296:22 322:2 327:21 330:16,17 331:6 332:7 362:10
experienced 36:2
experiment 109:12 147:16 149:9 160:4 281:17
experimental 106:4,19 145:20
experiments 152:3 173:2
experts 176:16 189:7 229:17 248:7 252:11
explain 121:6
explains 255:21
explanation 122:16
explant 228:11
explants 227:9 228:10
explicitly 166:2
explore 118:8 295:4 304:12
explored 129:7 146:6 201:4
exposed 134:3 135:4 357:18
exposure 18:22 19:13 20:12 24:10 35:9 52:4 53:6 63:10 73:13,16,17,18 164:7 222:4 311:21 313:1
exposures 24:7,11 27:22 332:1,18
express 109:19 148:5,6 154:11
expressed 206:22 211:9
expressing 110:2 147:10 152:17,20 220:14
expression 96:8 157:20
extended 104:12
extensive 358:8
extensively 156:19 191:13
extent 57:11,20 309:13
external 309:2
extra 154:16 265:20 279:18
extracellular 102:5
extraneous 177:5
extraordinary 144:6
extrapolate 198:3 212:18 238:13
extrapolation 16:4 198:5
extreme 195:18
extremely 145:11 353:20
eye 144:9 151:11

F

fabulous 228:4
FACA 245:22 246:2
facilitate 8:18 206:15
facilitating 210:20
facility 10:16 11:12 177:8
facing 244:5,7
fact 27:10 37:18 66:18 76:16 77:12 85:18 101:17 116:7 119:7 121:4 122:17 123:8,9 141:1,10 146:5 149:13 155:1,3 170:22 179:18 183:22 184:18 186:2 188:13 191:1,19 209:19 212:3 225:14 226:6 232:18 289:8 308:21 313:14 326:18 329:1 342:10 357:12 364:16
factor 23:6 33:8 329:19
factored 340:13
factors 5:20 18:19 19:4 20:10,16 22:20 23:9,17,22 32:18,22 34:16,17 35:9 153:20 170:16 286:16 329:4
facts 218:4
faculty 260:13
fail 213:8
failure's 273:3
fair 74:22 77:14 225:5
fairly 5:8 10:5 106:19 117:12 184:6 221:15 229:21 308:7 349:11 364:14
fall 138:8 350:22
false 37:6,13 40:12,17
familiar 211:12 253:20 290:9 309:20
families 19:11 20:8 279:17 291:22 328:3
family 27:22 254:1,10 265:22 268:3 279:16,19 284:8 327:5

329:13 343:11,15 346:21 347:4
family/adolescent 327:18
Faruque 253:5
Faruque's 253:11
fascinating 88:8
fashion 32:13
fast 174:9 188:17,20 190:19 352:3
faster 100:5 235:3
father 99:2 279:13,20 343:12
fathers 279:14
favor 86:17 265:2
favorable 206:5
favored 83:7
favorite 95:3
Fc 94:4
FDA 4:2 153:12 177:12 187:3 188:21 189:22 240:4 245:13 246:17 247:18 251:3 256:21 308:3,16 319:3,17 320:14,22 333:1,3 351:22 353:1 357:4 358:21 360:15 362:6
FDA/CBER/OVRR 2:4 3:20
fear 307:2
feasibility 210:8 251:9 304:22
feasible 126:16 143:8,11 194:6 197:13 203:18 271:17 298:22
feature 152:14 161:19
February 254:17,22 256:4
Federal 246:1
feeds 340:15
feel 200:14 315:7 359:7
Feinberg 3:7 30:3,4 200:5,7 239:21 240:2 241:10,15,21 242:8 256:18 306:19 307:11,20 308:1 358:11
Feinberg's 33:14
fellow 260:13
felt 308:10
female 18:20 34:7 163:22 266:15 278:10 279:21 288:21 329:11 355:8,10
females 3:14 258:5 265:5,8,21 270:8,12 271:10 279:3 291:6,13 310:18,21 311:11 312:8 314:1 327:2,6 353:14 357:22
fetal 2:5 13:1,2 15:19 39:5 46:3 47:12,16 65:11 79:3 88:1 156:4 159:16 218:17 228:2 271:20 310:1 315:18 316:21 317:5 339:21 340:18
fetal/neonatal 44:21
fetus 22:17 41:16,22 58:2 72:2 78:19 93:9 95:22 119:9 126:10 143:9 151:12 156:3 159:6 165:18 172:12,15,22 173:6 214:3 229:15 241:17 269:8 286:7 288:14 331:11 337:22 338:1 339:15 340:16
fetus/newborns 127:17
fetuses 2:8 38:22 47:8,11 50:19 119:19 125:18 126:12 127:15 149:12 309:17
fewer 329:16
fibroblast 56:21 209:12 215:16
fibroblasts 90:1 94:20 95:5 109:13 110:2 118:18 135:16 146:9,11
field 73:12 111:5 143:14 172:2 203:5 229:17
Fields 289:5
fifteen 85:13 290:9
fifth 9:8 284:7
figure 101:9 154:14 180:22 236:17 240:7 282:11
figures 283:7
filed 247:17,18,19
files 337:10
filled 6:20
filter 82:8
final 26:17 34:11 210:16 243:9 272:3 364:17
finalized 321:2
finally 17:5 24:12 26:11 28:15 111:16 116:5 214:8 221:7 222:18 261:16 316:15
financial 279:18
financially 366:12
financing 205:7
finding 102:22 169:6 293:22
findings 115:3 118:10 294:17
finds 52:21
fine 69:14 99:16 232:16
fingers 99:2,6,7
finish 98:21 128:10,14 143:22 277:7
finished 128:8 256:13 268:4 277:14
finishing 277:10
Finland 276:1

firmly 267:22
first 7:6,7,14,17 11:18 12:17 24:10 27:2 39:4,8,21 41:13,14,19 42:2,5 43:4 46:12 48:3 50:11,17 54:7,9 55:18 60:10 62:11 66:8 69:8 77:1 78:1 80:3 86:21 90:6 101:5 121:14 124:13 126:2 127:2 128:6 132:6 136:13 137:11 141:17 169:10 170:12 175:13 191:8 196:10 203:14 206:12,17 207:15 211:2 212:2,4,13 215:1 216:3 222:20 223:7,16 225:7 227:5 228:1 232:11 235:6 238:11 243:17 244:10 249:3 251:3 253:20 254:2 255:16 258:9,16 259:5 265:19 269:16,19 280:12 284:12 296:3 304:16 305:19 306:22 307:2 312:10 315:14 331:12,17 336:21 342:6,14 349:20 356:15 365:9
Fishers 1:10
fit 59:9 223:14 255:7,8
fitted 297:20 298:2 302:17
five 52:13 183:12 189:10 197:9 207:8 224:16 232:15 237:1 240:17 243:12 247:9 255:5 277:2 297:22 302:20 304:5 333:13 359:11,12 362:4
flat 338:12
Florian 35:20 63:6 233:5 351:10 360:12
Florian's 356:10
flow 96:15
flu 170:7 191:12 334:10,12 347:19 350:4,5,6,9,19
fluid 46:14,18 47:4,10
fluids 44:17 83:11
FluMist 186:10
focus 12:15 113:16 128:20 129:17 217:13 219:15 222:22 259:14 322:3 324:10 330:16
focused 12:12 285:15 317:5
focusing 330:5
folks 74:6 86:1 88:18
follow-up 28:10 33:14 50:4 60:8 127:7 131:8 187:14,18 197:7 207:9 263:11 290:11 316:13
fond 192:6
food 1:9,17 11:13
foot 200:3
force 87:7 164:13 248:18,21 298:3 343:21,22 344:1,4,7,12,16, 17 345:21
foregoing 366:4
foresee 127:6 210:19
forever 302:19
forget 194:19 195:11 275:16
forging 308:11
forgive 143:12
forgot 191:6 192:3 194:19
form 48:16 157:9 210:1 262:14
formal 195:9
formalin-inactivated 150:17 153:9
formally 127:5
format 140:11 254:6
formed 247:16 248:13
formulated 219:20
formulation 167:18 181:15 206:22 220:20 231:14 238:21
formulations 189:15 **forth** 165:22 **forties** 268:6 **fortuitous** 102:22
Fortuitously 7:7
fortunate 70:22
Forty-four 127:12
forum 210:4
forward 78:13 155:7 173:4 175:6 200:11 201:8,18 206:12 211:5 218:19 225:15 238:10 243:11,12 271:12 357:21 359:8,14 361:15 362:8,11
forwards 206:16
foundation 204:11 319:1
foundations 243:6
four-minute 231:4
fourteen 260:2,6,8
fourth 7:20 9:5 218:6
four-year 246:8
Fowler 2:6 12:17 13:4 29:4,18 30:9 31:12,15,20 32:16 33:6,8,19 34:4,13,19 35:11,22 36:5 37:2 38:7 51:4 52:16 100:7 303:19
Fowler's 86:10
fragmented 214:12

fragments 102:5
frame 337:16
frames 77:12
Framework 253:9
France 59:18 116:15
free 83:14,15 177:3
freedom 177:5
frequency 88:22 170:14
frequent 52:4 53:6 73:16,19 88:13 89:6
frequently 7:3 63:18 93:10
front 4:7 12:4 66:18 100:1,2 199:11,20
fronts 167:15
Fruh 160:10
frustrating 352:15
full 194:22 248:1 270:17 276:6
fully 93:16 146:9 180:18 313:17
function 62:3 68:19 69:4 95:6 156:7 225:19 226:8 244:2
functional 131:12 198:15
functionalities 129:2
functions 8:7 96:2,9 112:10,13,22
fundamental 179:1 203:4,12
funding 364:10
funds 251:11
funny 212:17
fusion 95:7,11,13 139:22 211:10
future 9:11 81:11 89:9 94:3 143:17 144:22 145:6,21 148:7 160:5 176:20 215:5 224:17 254:17 262:20 266:15 273:9 274:5 279:6,14 280:3 286:14 287:4,10 295:9 297:7 304:17 328:11
fuzziness 93:12

G

Gag 112:18
Gail 3:15 256:11,16 258:2 273:18 274:9 343:4 354:20
Gail's 258:4
gain 355:7
gained 355:1
gaining 293:2
gains 301:12
Gall 310:11
games 363:2
gamma 93:20 94:7 154:12,16 221:10 233:2
ganciclovir 147:20,21 148:2
gap 217:7 220:20 271:11
gaps 5:16 6:20 8:17 12:15 26:18 200:17 206:1 207:13 212:1 216:1 219:10 224:1 271:7 276:8 295:3
Gardasil 233:12 311:5 312:2 313:2
garner 204:20
Gates 319:1
gateway 214:9
gather 247:21
gathered 15:21 249:12
gB 91:21 95:3,12 107:16,21 109:19 132:11 135:14,22 136:5 137:3,6,19,22 138:11 139:6,7,13,15,22 140:10 142:9,10,19 148:12,15,18,19 152:17,20 161:3 166:15 167:22 206:19 207:1,10 211:9 215:11,17 219:17,21 220:3,8 226:18 230:6 232:10
gB-specific 138:13 151:8 228:4
gels 101:20
gender 31:11
gene 138:20 147:10,17 154:15 162:18
general 15:8 28:5 61:22 72:13 73:4 75:1 78:3 84:9 118:15 173:3 179:11 248:20 249:9,14 251:9 257:17 290:6 314:22 331:1
generalities 124:21
generally 17:13 248:11 257:14 309:3 312:21 313:17,22 314:12 357:16
generate 59:10 106:9 154:2 287:9
generated 91:7 101:7 107:4 169:22 172:22 231:5 354:10
generation 186:22
generations 186:21 284:1
genes 64:15 84:3 138:19 146:21 153:18 154:5 158:9,10 162:11
genetic 16:2 64:11 108:11
genetically 64:8 141:14
genetics 111:3
genome 85:6,7 147:11,18 154:13 158:8 169:18
genotypes 64:14 107:15,17 111:7,20

gentlemen 143:13 200:2
geographic 16:11 32:11
geographical 222:16
geography 259:13
geriatric 272:8
Germany 59:18 120:4 124:2 168:16
gestation 41:18 42:3,5 43:5,12,20 45:8,9,18 46:9,10,12 50:3,12 56:2,14 125:15 126:2 128:2 269:17
gets 169:22 212:12 240:4 247:12 270:7
getting 10:10 67:18 69:2 88:1 124:5 197:16 230:6 251:12 284:5 307:7 328:3 335:2,19
gH 103:21 107:16 152:17,20
gH/gL 95:9,14
Gibson 172:8,18,21
girl 212:11 266:13 279:4
girls 31:14 136:6 204:21 208:2,14 232:7 258:11 261:14 280:2,5,9 281:14 282:19 283:13 288:16 291:19 292:4 329:7
given 12:17 36:16 37:17,18 93:11 117:6 118:16 119:6,10 120:2 121:4 123:8 125:4 135:21 136:7 138:1 140:18 172:11,13 174:18 177:7 186:15 216:2 251:4 253:4 279:2 280:9,14 282:19 283:4 288:17 295:21 300:9 303:3 304:22 313:17 318:8 325:7,9,10 328:12 338:20 339:6 341:20,21,22 342:17 347:17 348:9 354:21
gives 192:11 230:15 231:15 255:13,14,16 281:11 304:4 313:15 342:8
giving 11:21 12:13 144:11 173:3 206:10 266:4 286:4 287:1 342:11 349:1
gL 95:15
glance 66:9
gland-adapted 154:20 159:21
GlaxoSmithKline 136:2 137:22 206:8
Glezen 309:15
glimmer 259:18
global 14:4 87:18 256:5 335:9
globe 14:22
globulin 93:16,21 94:7 119:5,11,12,20,22 120:2 121:1,8,10 122:15 124:8 125:17 227:6,10 233:3
globulins 227:16 245:6
glyco 111:22
glycoprotein 71:2 95:4 96:1 103:2,11 104:4 109:11,14 110:2,6,19 111:1,6,11 135:15,22 142:10 148:8 156:22 157:10 158:18 219:17
glycoproteins 94:22 141:12 150:9 227:15
gM/gN 96:1
gN 107:8,16,19 111:22
gN1 111:7
gN2 111:7
gN3 111:7
goal 75:1 216:5,8 272:15 319:13
goals 2:3 3:3 8:13,20 9:3
gold 48:1 82:11
gone 75:4 97:2 112:11 114:16 128:9 132:12,20 182:21
goodness 128:15 129:20
gospel 346:12
gotten 163:7
government 10:21 74:17 246:16
government-funded 324:2
gp350 188:16
grab 100:2,3
GRADE 250:11,16 252:14,20,22 253:2
grades 252:7
grading 250:11
graft 198:9
grant 107:4
grants 188:12 364:9
graph 25:9 138:6 140:2 141:3 299:18 302:13
graphed 183:14
graphically 291:20
grateful 144:16 233:16
gratefully 6:14
gray 350:22
Grazia 2:18 36:8 58:7 60:22 97:1 116:20 131:19 151:1 157:7
great 10:16 38:4

64:21 69:11 70:19 71:22 88:19 90:19 91:5 92:7 93:13 118:3 123:11 229:7 230:5 274:5 322:22 326:19 343:16 358:12 359:15 361:18

greater 16:21,22 21:6 25:22 59:3 73:17 84:8 115:10 121:2 122:10 147:5 159:12

greatest 202:19 264:17 360:6 361:18

greatly 16:11

Greek 296:19

green 183:20 298:21 299:2 326:7 327:5

grew 102:5

grey 42:17

Griffith 92:3 343:21

Griffiths 11:6 86:21 137:7 278:3 295:18

Griffith's 343:9

GRIFFITHS 3:16 278:17,22 293:1,6 342:5 343:16 346:11

grind 260:9

ground 204:10

group 18:18 25:15 43:4,11,16 48:11 62:10 86:22 104:16,22 105:1 107:13 111:8 119:8,15,16,17,21 120:11,13,19 121:2,11 122:2 134:21 135:4 136:9 137:11,13,17,18 140:19,20,22 141:5,6 147:12 170:21 195:20 197:15,22 198:3 246:4,6,15 247:15,16 248:4,10,14 249:6,7 251:17 252:11 253:1 260:18,22 261:3,7 272:22 278:20 285:6,18 296:10 297:17,22 305:7,12 317:10 322:9 327:22 329:16 330:22 331:2 341:3,19 345:22 346:18 347:4 348:5 352:13

groups 14:21 17:15 22:2 43:4,17 59:18 114:2,6 119:6 122:2,4,14 129:19 130:5,11 140:3,4,7,8 174:5,11 182:15 189:16 196:5 214:15 225:10 247:7,15,20 248:3,8,10,15,17,18 249:5 251:8,9,14 258:5,10,12 260:18 270:5 272:18 282:22 291:8 321:18 329:12,17 330:21 335:6 341:14 345:3 350:11

group-specific 110:12,18,20

grows 213:12 266:14

growth 156:13 314:19

Gruber 235:21,22 236:14 315:16 319:7,12

GSK 3:8 166:15 167:21 173:12,16 191:12 206:18 207:9 241:22

guard 199:22

guess 31:4 33:7 51:10 57:10 172:19 256:19 340:1 342:19

guests 11:15

guidance 198:19 244:20 249:21,22 250:4 314:5 315:9 321:3

guide 202:22 295:9 332:2 356:17

guided 87:14,15 240:3

guideline 192:11

guidelines 50:14 191:1,2 192:5,9 309:5,6

guinea 145:9 146:1,5 147:13,18,19,22 148:2 149:18 153:10 156:11,15,18 157:9 158:7,14 159:2 160:4 220:15,17 230:11

guys 65:22

Gynecologists 254:11

Gynecology 49:3

H

H1N1 184:20 334:2

half 46:12 55:22 228:1 246:11 279:21 283:7 293:3

half-hour's 256:1

hallmarks 2:5 13:1

halting 316:2

hamster 206:22

hand 63:18 142:3 237:13

handful 118:2

handled 205:11

handling 249:14

handwaving 287:6

hangover 191:10

Hansen 112:7 161:15

Hansen's 106:7

happen 12:11 78:21 87:4 242:5 255:6 282:3 292:14 301:15 346:13 353:16

354:3
happened 114:7 127:4 311:3 345:12
happens 84:22 90:6 97:5,6,13 98:19 109:20 233:14 242:19 290:6 306:21 337:8 355:18
happy 129:3 190:1 224:8 356:8
hard 15:11 68:17 70:1 79:4 187:11 234:9 254:18 270:15 348:5
hardly 36:13
harm 307:18
harmed 241:17 292:22
harmful 177:3 265:3,6
harmonized 247:10 253:20,22 254:2,13
harms 251:21
Harpaz 34:14 164:5 165:3,20
hatch 327:4
hate 172:2
haven't 31:3 33:22 164:6 252:21 290:4
having 7:8 24:3 25:5 30:22 33:10 37:20 169:6 190:6 191:5 208:21 216:1 279:8,18 280:3 283:14 285:9 315:9,10 326:19 333:2 351:12 361:18
Havrix 184:5
hazards 290:15
HCMV 111:5
HCT 196:6 197:22
HCV 172:3
HD 140:3
head 308:11
heads 274:2
health 1:6,9 8:3 123:19 126:22 202:22 204:11 205:1 207:18 210:20 233:7 234:21 252:11 266:7 270:22 295:9 312:5 328:10 341:11 348:20 358:20 359:6 361:19 362:20
healthy 4:16 24:16 75:15 166:6,10 207:4 313:18 314:14
hear 10:17 82:14 93:17 176:3 189:7 210:10,13 211:1 214:22 226:12,17 234:13 235:14 236:16 276:16 341:14 356:20
heard 57:6 75:21 77:17,19 78:15 79:1,14 82:12 83:18 85:16 150:1 157:7 164:6 201:11 223:17 226:10,18 229:2 234:15 235:17 236:1 244:8 251:2 259:10 333:2,12
hearing 12:22 13:7 14:15 15:5 16:1,2,5,6 21:14,18,19 22:1,3,8,11,14 25:7 26:2,3,5,8,10,11,15,16 29:14,16,19,21 30:22 52:17 67:12,17 68:15,19 79:19 80:1,7,17,18 85:21 114:6 115:11 116:3 160:2 174:3 201:18 274:2 340:2 361:6
hearings 153:12 154:1
heart 198:5 238:6
heartened 351:14
hearts 212:5
heavily 330:5
height 136:20
heightened 334:3
help 87:11 90:9 104:12 218:4 252:18 259:17 279:19 281:20 294:2 295:2,4,7 321:7 364:6
helped 212:14 336:6
helpful 30:4 256:18 321:9 340:8 346:14 358:13
helping 4:11
helps 42:11 222:6
hematopoietic 81:7 94:6 140:15 196:6
hemodichorial 156:6
Hepatitis 250:17
hepatosplenomegaly 115:5
herd 202:10
hereby 366:4
Here's 271:14 287:13
hereto 366:12
heroic 156:1
herpesvirus 145:8 188:14
herpesviruses 95:12 168:18
he's 99:18 278:10,19 347:10
heterogeneity 6:1 64:11,20 85:8
heterogeneous 118:10 197:22
heterologous 106:10,13,18 112:20
HHS 244:21
Hi 64:3
high 10:19 16:21 17:3,5 18:3,8,11,14 20:15 22:17 23:4,14 28:16,21 34:15 35:6,13

41:16 45:17,18 50:18 59:2 64:8 67:12 69:21 92:15 115:14 121:8 122:10,13 138:10 140:6 154:11 157:14 158:15 173:6 223:20 234:1 275:18 286:22 303:20 306:2,5 322:4 324:12 325:12 335:18,21 342:2 346:22 352:3

high-avidity 65:10,14 66:4 173:11

high-dose 140:3,8

higher 13:13 15:8 18:12 19:16 20:2 23:2,3,13 25:16,19 30:12 31:8,9,17 32:20 52:14 81:8 83:8 103:20 105:18 130:17 139:16 184:3 231:15,16 233:19 236:12 300:19,20 302:7 344:16

highest 19:18 25:10,20 299:9 300:18,19 304:18 344:17

highlight 216:1 244:5 322:15

highlighted 322:8

highlighting 359:16

highlights 17:7 32:11 356:11

highly 51:13 130:10 147:20 154:5 158:12 159:19 162:8 207:5 222:18 335:9

high-risk 251:7 265:17 270:13

high-titer 136:18

Hill 1:6 11:12

hint 62:7

Hispanic 24:22 25:17 32:21

Hispanics 18:13

histograms 264:6

histology 156:6,16

historical 37:6

history 6:12 115:18 123:14 132:3,5 203:7 295:4

hit 70:18 114:9 282:21

HIV 73:12 78:1 84:16 85:3 102:17 170:3,7 221:3 225:16

HIV-infected 84:18 85:1

HLA 97:19

hold 64:19 219:3

holding 307:7

Holger 253:4

home 236:4 288:15 328:13 349:13 350:2 351:7 362:9 364:8

homes 349:12

homologue 157:10 161:8 220:15

homologues 158:7,21

honestly 267:13

honor 39:2

hope 4:10 6:15 10:17 81:10 89:9 90:8 117:7 143:12 161:19 176:19 206:13 328:9 364:17,22

hoped 6:17

hopeful 11:8 262:19

hopefully 6:18 8:11 76:1 211:4 274:4 338:14 361:22 362:2,7 364:3

hopeless 226:6

hopes 211:20

hoping 286:8

hospital 114:17 126:20 332:4

host 66:14 85:8 88:9 90:7 97:11 170:1 289:6

hour 199:14

Houston 3:15 258:3 261:4 263:8 273:21

HPV 221:20 241:1 242:1 250:15 274:15 310:22 312:5 326:5,13,15,19 327:16 328:14 329:7,11 330:6 335:20 349:16 350:21 353:7 354:1,5 355:6,10 357:17

HPV-1 330:1

Huang 101:7

huge 11:5 72:21 115:3 155:11

human 1:4,9 2:11 4:5 87:2 92:15 97:3 103:6 145:2,8,13,14,16 146:2,9,11,18 147:2,10,16,17 148:5,14,15,19 155:11 156:7,16 161:2,18 178:1 214:10 227:3,9,11,21 228:8 312:21 315:4,5 332:16 365:11

humanize 162:13

humanizing 148:6

humanly 149:3

humans 77:22 144:10 195:17 221:11

humoral 90:11 117:20 131:11 150:13 155:14 159:2

hundred 65:17 77:12 87:21 259:22

hundreds 135:19

Hungary 124:3

hurt 212:14

HUVEC 129:8

hygiene 40:4

hygienic 266:18

hyperimmune 93:16

119:5,11,12,20,22 120:2 121:1,8,9 122:15 124:7 125:17 227:6,10,16

hyperimmunoglobilin 216:17

hypothesis 90:4

I

I&D 194:17

i.e 34:16 264:22

I'd 74:9 93:10 206:9 211:2 219:5 227:2 258:8,9 267:10 272:12 273:13 316:15 330:4 336:5 341:14 353:3 361:6

idea 54:7 63:10 73:6 90:9 97:10 114:3 147:15 162:17 173:5 184:18 192:11 237:9

ideal 194:4 267:13

ideally 203:4 205:21

ideas 72:14

identification 6:4 20:1

identified 5:16 26:4,6 77:15 78:1,2 114:17 119:6,16 146:19 151:21 169:20 263:18 327:17

identifies 16:8 47:10

identify 5:16 8:16 9:13 28:9 29:8 41:15,20 58:10 70:17 74:10 180:19 184:9 207:16 260:4

identifying 12:15 17:3 26:14 189:7

ides 271:14

IE1 139:7 140:9 141:15

IgG 39:19,21 40:6,10,16,18,20 41:11 42:1,7,11,13,15,16,18,22 45:16,20 54:20 59:3,14,19 60:6 290:10 293:8

IgM 39:19,22 40:7,10,12,17,21 42:12,19 43:21 45:17 47:18 49:15 54:20 60:10

ignorance 73:10

ignoring 292:13

II 3:2 6:14 87:13 123:17 210:5 222:12 225:13,20,21 314:9

III 3:10 6:16 9:7,9 87:16 96:17 124:6 189:8 210:3,7 218:20 222:17 226:4 295:8 297:21 314:22

IL10 161:8,10,11

I'll 34:21 54:1 67:7 81:18 84:7 92:13 98:21 99:10 100:4 116:16 145:4,9 149:19 152:15 168:9 174:20 190:19 259:4 294:16 304:16 308:14 309:4 310:19 311:2 318:16 321:17,19 322:2 323:11 326:20 330:15,16 331:3 342:5 356:8 361:5,22

ill-defined 70:3

illness 334:4

illustrate 111:16 114:13

illustrates 76:9,16 100:10 105:22

illustrious 258:19

I'm 30:4,10 31:12,18 32:7 33:12 34:9 35:22 36:3 38:6 58:4 63:21 64:10 68:9 69:8 70:11 72:16 74:22 75:22 76:4 78:12,15 83:19 93:18 98:11,14,18 99:14 103:13 109:15 110:14 113:1 115:22 116:22 125:20 131:22 133:10 144:15 149:16 164:19 170:16 173:7 175:9 176:4 183:1,18 190:1,2,18,21,22 198:6 200:19 201:9 206:17 207:12 210:10 224:15 233:16,21 235:11,12,18 236:22 238:4 240:1 241:1 243:14 257:5 281:21 296:19 298:7 299:5,10,19 301:3 303:1,4 318:7 327:19 335:10 336:10 351:14 354:20 363:9 364:22

imagine 163:18 286:20 342:20 343:2 358:8

imaging 80:11

immature 289:14

immediately 55:21 122:21 246:20 329:22 331:3 341:10

imminently 214:4

immune 5:22 8:7 73:21 79:18 84:5 85:1,2 87:10,12 88:10 89:7,14 91:1 93:8 94:13 96:13 97:12 98:7 112:9,12,21 118:1,8 128:18,21,22 131:4 133:8 138:4 145:14 150:12 154:18 160:7 161:12 162:10 169:14 173:22 180:16,19,22 181:4,5,6,9 186:15,17,20,22 209:10 211:14 218:9 226:8 228:9 232:20

245:6 249:13 255:19 289:13 316:22 317:12 323:7 325:5

immunity 21:6 22:6 23:3 53:8 57:9,15 58:1,5 59:8 66:14,21,22 67:3,20 69:5,6,14,17,20 70:1 91:6 93:5 97:21 117:11,18,21 130:1 131:10,11 139:4 141:18 142:4,5 150:10,14 151:13 153:3,7 155:14,17,18 159:2,5,10 160:5 161:3 162:1,3 164:8 166:19 172:21 181:3 202:10 212:7,16 213:17 214:12 272:4 285:16 286:12 294:11 295:14 302:9 325:4 343:6

immunization 3:12,19 65:16 69:16 106:16 155:15 157:11 158:14 159:3 161:6,8 172:20 173:5 202:21 204:12 237:13 243:20 244:4,11,16 247:2,10 249:2 253:18,19 254:13 255:10,11,17 264:22 265:2,3,15 287:14 308:4 309:18 310:6,9,13,16 317:18 319:2,15 321:8 330:3,14 337:17 342:15 348:14,16 352:7 360:10

immunizations 249:12 269:3 337:20 347:21 348:4,22 350:15

immunize 233:8 270:8 279:2 281:8 284:16 320:11 345:19 349:4,5 351:20

immunized 148:16 283:14,18 285:9

immunizing 189:20 208:8 232:6,7 285:15 343:14 357:7,9 360:4

Immunoaffinity-purified 156:22

immunocompetent 102:19 107:3

immunocompromised 107:2 150:3 196:4 209:18 289:4,17 290:1

immuno-depression 198:1

immunogenic 135:20 140:11 207:5

immunogenicity 180:3,6 182:14 198:14 217:10 222:13 314:12,17 315:5

immunoglobulin 120:3 150:20 172:17

immunologic 106:2 150:7

immunological 75:20,22 170:16

immunologist 229:8

immunology 9:1 92:4 97:4

immunomodulation 162:19

immunomodulators 206:21

immunomodulatory 121:12 154:5

immunoresponse 41:10

immunosenescence 4:21 354:17

immunosuppressed 133:17 142:14

immunosuppression 214:16

immunotherapeutic 94:11

immunotherapy 151:15

impact 27:8 157:16 165:21 166:2 169:12 202:19 205:2 233:7 259:7 264:17 271:9 276:10 294:18 295:1,5 296:8,13 297:12 298:7 299:9,11 300:5,18,20 304:8,18 305:5,9,22 340:21 345:5,21 351:19 359:6 360:4,6,8 361:19

impacts 296:15

impairment 13:8 14:17 15:6

imperfections 351:16

implement 240:7 247:3

implementation 193:17 204:9 205:6 244:7 270:5 295:8

implemented 250:14 335:8,15

implementing 335:11

implications 213:1 257:1

imply 53:3

importance 5:4 6:1 20:7 26:14 135:13 137:20 138:16 139:3 143:3 178:10 203:4,12 220:9 225:13 289:9 317:1 356:12

important 5:2 9:21 23:5 24:9 33:7 34:2,3 42:8 45:9 50:16,19 51:6,8 55:4,17 59:22 60:1,9,12 70:7 72:9 79:22 85:16 90:10,12,21 91:1 95:6,19 99:8 131:4 132:4

134:6 137:1,3 146:21 150:10 154:15 155:6,18 156:4 159:17 160:9 161:16 162:21 176:6,11,21 178:13 180:12 181:11 185:6 200:10 213:18 234:6 246:9 257:1,15 264:4 282:16 285:17 289:3,13 291:6 302:3 305:21 310:17 312:1 313:16 315:21 316:6 317:10 327:12 334:16 335:16 339:22 347:6 350:16 351:8,13 352:8 358:14 361:14 363:12

importantly 100:15 104:1 138:12 152:8

imposed 337:7

impossible 226:21 231:22

impressed 97:3 359:22

impression 122:12

impressive 120:18

improve 142:22 162:1 208:3,4 330:8 346:8

improved 6:8,11 144:22

improving 324:10

inactivate 161:9

inactivated 167:6 196:14 312:17 322:10 333:22

inactive 161:7

inadvertent 269:3 311:21 313:1

inadvertently 189:21 193:1 196:21 268:21 357:18

incidence 23:1 85:21 87:22 115:14 174:14 194:5 201:3 281:2 282:4 344:2

incidences 195:15

include 25:6 84:11 95:3 187:14 188:4 194:22 314:1 320:19

included 81:20 95:1 171:19 185:12 319:16,20 321:1 349:20 361:10

includes 124:2 282:7 312:16

including 2:12 4:21 6:3,11 8:22 9:10 64:18 88:18 146:8 151:18 153:6 154:4 160:16 179:14 185:13 186:4 187:9 188:15 229:3 231:14 246:3 291:1 294:10 309:20 335:16 357:20 361:10

inclusion 125:22

income 100:19,20 261:14

incompletely 160:6

inconsistent 131:8

incorporate 297:6

incorporated 116:10 297:10 344:14

increase 45:20 147:6 164:17 166:16 174:1 222:6 295:14 302:4,10,21 303:2 304:3,5 306:1,11,12 307:4,15 332:4 334:6

increased 19:9 36:21,22 154:17 162:19 179:17 334:3,7

increases 17:17 18:3 41:9

increasing 17:13,14 18:3,20 19:5 66:1 69:2,5 110:3 162:15 302:6 309:2

increasingly 322:12 326:14 327:8

incredibly 214:12

incubation 138:14

indeed 42:4 62:6 71:21 91:8 104:7 119:1 123:16 126:9 129:15 132:20 134:14 136:8 137:19 139:10 140:5 191:8 224:15 230:22 258:21 274:20 341:11

independent 183:3

index 42:16,19 43:22 61:19 122:9

India 13:21 14:2

Indian 87:20

indicate 22:15 49:18 130:20

indicated 205:8,12 279:7 313:18

indicates 76:6,12 86:12 130:20 299:2 301:21 346:22

indicating 26:13 77:20 139:3

indication 82:2 195:8,10 204:18 208:13 209:1 212:4 214:9,10 217:11 222:20 223:2 238:14 256:22 308:9 313:6 318:20 320:4 360:16,17

indications 3:11 9:5 196:3 243:17

indicative 39:22 40:9,11,16,19 41:2 45:18

indicator 44:19

indirect 313:12

indirectly 313:13

indiscernible 41:7 68:7 168:2 211:22 215:6,14,19 233:6 236:2,9 283:22

individual 85:2,3 111:10 117:13 131:11 134:16 170:5 202:8,9 228:3 241:17 251:18 261:10

individually 353:12

individuals 4:16 76:13 78:2 79:21 83:17 84:19 85:6 89:12 92:13 93:20 102:19 134:1 135:12 136:22 185:16 207:9 289:16 290:1 296:20 297:2,3,14,17 314:18

induce 138:4 173:11,13

induced 53:8 133:8,19 143:4 153:8 155:14 158:15 159:3 221:10

inducer 135:15 142:18

induces 161:9 168:1 172:14

inducing 110:19

induction 146:14 230:19

indulgence 259:1

industry 199:1 272:17 275:17 314:6

inevitable 268:20

infance 323:9

Infanrix 184:5

infant 23:9 79:8 81:4,21 104:5,6,10 197:11 220:18 235:1 314:19 316:10,13 318:19 322:1,10 323:8,18 324:13 326:17 335:17 336:16 339:5 341:5,10

infants 13:22 14:1,5,8,12,13,17,22 15:3,10,11,14,15,18 21:5,7,12,15,16,17,22 22:7,10,12,13 24:19,22 25:1,5,14,17,20 26:3,5,7,9 27:19 28:9 38:22 53:2 79:16 103:19,22 108:1,4,14,15,21 159:20 195:1 245:20 257:11 302:10 307:16 314:18 315:6 321:21,22 322:15 323:4,14,22 324:19 336:14 341:7 345:16 360:5,14

infect 110:2 112:12 165:18 288:15 331:9 363:1

infected 14:1 20:12 26:3 34:17 44:13 46:18 47:8,10 51:21 69:2 78:2 79:9 81:5 85:6 87:20 88:17 97:22 103:18 104:10,18 107:6,14 109:13,17 110:9 119:10,19 125:18 126:12 127:17 129:8 149:10 151:6 169:9,22 173:6 212:12 214:3 220:13 222:5 229:10,14 288:3 297:18 331:12 343:11

infecting 287:5

infection 2:5,8 4:20 5:21,22 6:7 12:14 13:1,2,5,10,13,18,20,22 14:3,5,8 15:22 20:14,19,21 21:1,2,3,5,12,14 22:12,22 23:2,7,10,14 24:1,2,8 25:4,5,7,10,15,19,22 26:12,14 27:1,18,20 28:12,16 30:8 35:17 38:21 39:5,6,9,15 40:2,5,9,12 41:3,11 42:2,6,15,20 43:1,2,7,9,14,15,19 44:4,6,7,11,17 45:2,5,14,16,19 46:3,8,11,12 47:5,7,17 48:2,6,15 49:19 50:16 51:19 52:7,20 53:1,5 55:20,22 56:5,10 57:9,16 59:16 60:14 62:10,19 65:11,12 66:3,6 67:14 70:4,5 71:9,12,18 72:3,12 76:10,15,19 77:5 78:8,19,20 79:22 81:11 82:2,17,18 83:17 84:2 86:3,6,8,18 87:7 88:17,21 89:1,5,11,14,17 92:4,9,10 93:9 95:20 96:5,10 100:12 105:16 106:1,3 107:15 108:10 109:16 113:13,17,18,21 115:1 116:8 117:12,15,16 118:14,20 119:3 120:22 123:2,11,14,15 125:1,3,7,8,14 126:1,6,12 128:2,5,18 130:7 131:5 134:12 135:1 136:6 137:13 138:14 141:19 142:3,12 143:8 144:8 146:1,15 150:5,18,21 153:1 155:16 156:4,8,10,15 157:5,13 159:6 161:13 164:11,14,16 165:8 171:13 173:21 174:2 180:17 187:1 196:8 198:13 201:3,16,21 202:12,19 204:16,20

205:18 206:2,4 208:20 210:15 211:15 212:10 216:5,13,22 217:1,4,14 218:16 219:22 220:5 222:10 223:1,4 231:8 232:9 233:22 234:1,2,21 256:22 259:9 260:7 280:7 281:6 283:1 284:5 285:7,14,18 286:18 287:15,21 289:6 291:9 294:19 295:6,15,22 296:5,9,13,16,21 297:4,5,14 298:3,9,12,21 299:4,11,13,17 302:5,6,7,15,22 303:6,10,11,12,19 304:1,2,10,15 305:5,10,14,17,22 306:2,6,8,12 307:4,15 316:9 331:11,13,15,17 343:21,22 344:1,2,5,8,11,13,17 345:21 363:1

INFECTION/ DISEASE 2:12

infections 19:8 20:20 21:8,9,11,15,16,17 22:1,16 23:5,18 24:4 27:9 28:13,17,18 33:11 52:10,15 55:8 57:11 58:17 59:2 71:21 83:20 100:16,22 101:1 102:11 105:7,18 111:9 113:5,8,10 164:18 171:11 229:11 260:5 271:16 284:20 300:2,4,8,15 302:11,14,22 303:2,6,8,18 306:11

infection's 14:3

infectious 4:3,17 82:20 211:15 245:17 284:17 286:11 296:4,21 346:6

infectiousness 288:6

inferred 158:20 161:10

infiltrate 156:18

inflammation 160:18

inflammatory 187:20 293:10 317:1

inflation 97:7

influence 38:1 83:20 135:1 158:3 304:12 334:14

influenced 116:12

influences 88:21

influenza 179:15,17 184:21 221:3,8 245:8 318:17 325:9 326:5 330:16 333:16,21 335:2

inform 144:10 295:9 329:9 361:15

informal 74:4

information 12:13 26:21 58:3,4 72:15,16 75:14 81:15 90:17 150:1 153:16 159:16 160:10 173:7 174:9 184:15 201:12 228:6 247:22 249:11 262:4 266:17 269:2 281:16 293:17 294:1,5 319:15 332:14,16 363:14

informative 75:22 81:22 211:4 320:17 347:10

informed 40:4 318:8

infrastructure 328:7

infusion 95:9 120:12,14

infusions 120:16

inhibition 154:16

inhibitory 241:7

in-house 58:19

initial 72:12 131:2 267:17 307:11

initially 7:19 329:6 353:9 355:20,22

initials 144:15

initiate 345:11

initiating 314:8

initiation 329:4

injection 133:14 136:18

injections 196:12

injured 337:11,18,22 339:15

injuries 338:4,5,12 339:19,21

injury 205:11 241:11 309:15 336:14,21 337:1,14,15

innate 90:10 131:10 138:4 155:21 162:20

innuendo 54:19

inoculation 133:12 138:11 160:6,18

inoculum 272:10

insensitive 362:20

inserted 147:17

insight 305:19,20

insights 145:19 304:16

instance 35:7 102:6 104:3 105:14 107:19 115:4 181:3,13 184:4,20 246:9 249:3 351:3 355:10

instead 72:5

Institute 4:2 5:3 282:18 291:15 294:6

Institutes 1:6

instructed 100:8 311:12

insufficiently 148:10

insurance 328:8
insurmountable 26:20 186:1
integrated 239:22 244:14 323:2
intended 222:19 313:22 314:8,15
intensely 65:13
intent 360:13 363:5
interest 3:12 146:12 151:8 180:15 181:13 216:2 223:20 243:19 246:15 257:18 279:19 293:2 359:11
interested 210:13 212:6 226:22 255:22 260:14 282:12 294:13 356:8 361:6 366:13
interesting 116:9 128:4 132:4 136:16 149:2,7,9 150:22 151:22 152:4 153:15 157:6 161:13 173:5 211:4 226:14 255:13 307:21 313:11 355:2
interestingly 23:1 133:21 134:19
interests 280:2
interface 88:5,11 90:8 92:6 94:1,5
interfere 216:19
interferon 221:10
Interferon-gamma 96:17
intermediate 42:17 287:22
intermittent 44:9
internet 187:7 242:16,22 334:12
interpret 42:11 78:13
interpretation 160:22 193:17
interpreted 101:20 309:17
interpreting 42:7 181:5
interrupting 360:14
interstitial 151:15
intervals 267:20
intervene 126:14
intervention 116:6
interventions 276:14,15
intrauterine 44:20 156:13
intrigued 354:20
intrinsically 147:19
introduce 11:16 256:11 258:2 283:10,11 342:16 355:11
introduced 106:10
introduction 2:3 131:17 219:12
intussusception 184:1
in-utero 339:19
invasive 46:5
inventive 275:18
investigated 131:3
investigation 133:2
Investigational 194:20 195:5
investigators 21:20 364:8
investments 359:8
invite 224:17,21
invited 190:16 194:18
inviting 200:12 321:15
involved 77:5 116:20 180:3 184:21 284:13
IOM 5:5 239:7
IQ 115:11
IRCCS 2:18
Ireland 27:13,15
Irish 27:11
irrespective 122:13 123:8
isn't 57:16 166:7 171:3 177:18 181:6 328:19 359:16 363:13
isolated 67:17 107:7 108:9
isolates 101:8,11
isolation 19:22 20:4 46:14,17,20 48:2,8,17,18
isothiocyanate 61:13
isothiocynate 61:11
issue 57:20 68:9,13 84:6 116:6 121:14 146:6 147:4 150:8 155:8,11 156:7 161:21 163:1 166:5 168:13,17 171:13,15 173:9,14 191:22 192:8,16,17 209:4 234:22 241:16 242:12 274:14 312:9 315:7 316:12 338:11 340:4,15 348:12 350:19,21 357:7
issues 9:9 26:21 51:7 68:14 70:9 76:11 185:21 186:1,3 187:5,12 189:19 191:7 201:9 232:14 244:5,7 251:13 266:22 270:1 321:19 351:6 359:2,17 362:13
Italian 123:16,19
Italy 2:9,18 36:12 37:8 38:15 46:9 50:9 124:3
item 72:20 73:5
items 185:12 363:8
it'll 233:12 350:8 351:4
it's 7:2 8:6 15:5,7,11,12 27:6 29:22 30:1,20 31:22 32:3 33:2,3,10 34:11 35:8,17

36:13,21 37:5,8,15 38:2,10,12,13 40:13 41:3 50:16,19 51:20 55:13 59:22 60:1,4,6,9,12 63:2 69:7 70:6 72:12 74:22 79:2,3 80:20 81:1 82:6,22 83:10 84:2,4,15 85:2 87:14 88:12 89:7,15 91:2 92:10 95:3,6,11 96:16 97:19 98:2,20 99:8 100:18,21 102:15 105:15 110:18 115:8 116:3 124:5 128:16 131:3 136:15 137:1,3 142:6 146:12,14 149:2 151:8 153:15 159:4,14 164:21 165:3,7,8 166:20 167:3,16,18 170:13 171:1,7 173:5 177:20 178:13 179:11 183:12 187:11 191:16 192:8 199:11,20 200:9 206:19,22 207:1 211:4,12 213:1,2 214:12 217:5 218:6,13 221:18 223:19 225:9,21 226:21 229:7,12,18 230:14 231:10 232:6 234:9 235:8,10,21 238:9,18 239:6,11 240:17 241:2 246:12 247:18 249:7,22 252:21 253:8,21 255:21 256:1 262:10,11 265:3,17 267:13 268:12,16,17,18, 20 269:8 270:12,14,15 271:15 275:2,3,6 276:18 277:14 280:2,15,16 283:19 284:1,20 286:20 290:3 293:15 295:19 297:11 303:3 305:20 308:11 309:9 310:9 313:11,16 316:9 317:3 319:8 322:19,20,22 328:20 329:1,3 330:17,21 331:5 332:8,21 334:16 338:13 340:10,20 343:2 347:7 349:3,17,18,21 350:6,8,19,20 353:16,18,20 354:15,16 355:13,14 356:5 358:14 359:1,6 361:1

I've 11:10 76:5 83:5 98:19 100:5 117:6 128:8 144:7 163:7 173:1 183:14 205:20 219:3 235:15 258:7 259:16 263:10 281:20 289:4 291:10,21 292:6,7 297:18 300:21 302:1 310:8 311:7 317:12 321:15 340:10

J

Jacobs 336:9,10,18,20 338:22 339:3,9,11,17 340:3,5,7

Jane 3:21 243:14,21 256:9 321:11 354:15 355:5 360:19

January 1:5 254:18,20

Japan 17:2

jaundice 115:4

Jeff 318:6 332:11 333:2

Jeffrey 3:20 308:3

Jennifer 11:3

job 75:19 230:5 245:10

John 166:22

join 283:18

Jolla 37:4

Jonjic 151:3 154:8 159:1

Journal 76:22 101:10 108:19 289:20

JR 2:13

judgment 236:8

June 127:1

justification 218:18

justified 354:16

justifies 310:5

justify 121:10 213:4

K

Kaplan 136:7,11

Kappler 166:22

Karen 2:6 12:17,18,22 29:6,12 34:10 38:18 51:4 53:14 67:8 86:10 87:19 100:7,9 113:3,15 303:19

Karen's 79:20

Karin 113:6

Katz 243:2,8

Kaufman 110:15

Kawasaki 195:19

kb 152:7

Kenney 3:9 140:18 219:2,5 230:4 238:16

Keros 59:18

key 148:11 149:21 150:7 166:18,19 185:12 189:4 204:4 206:1 208:11 210:9 225:9,14 244:5 296:14 339:22

Khanna 148:14

kick 12:7 269:18

kidding 278:6

kidnapped 99:3,4

kidney 134:8,16,20 137:7 198:5 214:18 238:4

kids 33:18 195:1 196:22 284:13 285:19 329:17 345:12 363:1

killed 269:11

kilo 120:12

kinds 360:12 363:2 364:15

kinetics 42:13 90:5 129:16

King 273:14

Kingdom 3:17 280:19

kiss 286:5

kit 42:13 43:22 59:22 122:20

kits 42:14 59:20

Klaus 160:10

Klause 112:6

knew 119:18 153:17 272:4

knowledge 5:19 8:14 12:16 26:18 70:18 162:16 295:3

Knowles 27:10

known 4:7 20:12 27:19,20 28:4,15 30:6 53:16 75:7 76:2,17 80:5 85:11 90:22 108:5 127:11 143:6 195:13 225:19 261:17

knowns 75:7,15 76:2

KOB 111:19

Kornilova 1:11 366:3,19

Koszinowski 154:1 168:4,7,9,12,14,15

Koszinowski's 147:8 152:18

Kowalik 85:5 108:7

Kowalik's 107:1

Krause 2:4 3:4 4:2 57:5 70:16 98:8,10,12,15 99:14,22 144:4 163:8,11,14,16,18 175:12,14,17,21 176:3 190:7,12 199:14,16 200:8 223:9,19 237:3,20 277:9,13,17,21 313:10 317:21 339:13,20 340:4 359:21 362:16,19 365:6,8

Kroger's 348:15

Kumar 259:19

L

La 37:4

lab 40:15 49:2 60:1 93:20 111:18 145:22 147:8 152:19 218:7 227:3 228:16

label 102:8 312:2 313:4 319:20 320:3,14

labeled 320:8

labeling 319:17 320:17 321:2 357:13,15

labels 313:2

laboratory 42:9 178:14 181:10 182:22

lack 8:9 26:21 28:9 152:13 156:4,8 212:21 213:13 218:13 273:6 298:1

lacking 112:21 191:1

lacks 96:7 211:12

lactating 357:9 358:2,3

lactation 357:14

ladies 143:12 200:2

lag 271:1 283:12

Lampe 261:10

landed 256:8

Lane 1:10

language 338:6

Lanzieri 3:18 293:20 294:16 307:9,17,21 341:2 343:21 344:6 346:1,3 356:3,5

lapsing 328:8

large 17:7 24:15 114:20 154:4 157:20 159:21 176:16 210:2 220:13 237:15 281:4

largely 85:19 163:5 164:12 170:5 240:3

larger 47:14 76:18 93:2 141:21

Larry 3:13 243:15,17 256:13,19 258:1 360:19 361:5

Larry's 363:10

laser 183:18

last 29:13 39:6 40:20 47:17 50:12 56:15 75:13 86:4 94:18 118:2 127:2,4 130:13 162:4,12 179:19,20 183:17 190:18 193:14 218:13 219:1,7 221:6 250:15 253:17 254:12,16 256:7 258:13 285:17 289:20 290:5 305:18 310:12 311:16 334:11,12 346:15 348:8 349:15 350:18 354:14

lastly 134:19 141:8 205:10

lasts 302:19

late 16:7 50:20 56:6 130:18 131:14 163:12 164:1 263:13 322:8 341:21 365:1

lately 124:3

latency 76:12 133:16 152:13 155:1,9 165:10 185:18 186:7

296:22

latent 76:15 77:21 155:4 283:15 298:12

late-onset 16:6 21:19

later 69:10 80:20 86:22 93:17 111:12 145:5 168:22 191:3 203:19 208:6 209:5 232:2 273:2 274:15 297:5,14 299:1 323:12 328:19

Latin 13:12 17:5 22:18 341:12

latter 73:19

Laughlin 11:1

Laughter 58:13 61:3,6 74:19 87:5 98:3 117:9 128:11,13 144:17 163:17 175:11

Laura 172:7,8

laws 177:2

lawyers 240:20

lax 74:17

Lazzarotto 2:9 38:20 39:1 49:20 50:2,9 55:5,9 59:12 60:19 62:8 64:2 122:17 124:16

lead 10:9 81:15 155:10 164:17 199:2 345:6 361:22 364:6

leads 24:7 66:19 258:19 360:11

learn 5:19 81:10 228:21 281:17

learned 2:19 3:21 142:7 145:20 185:7 195:22 269:2 321:12

learning 176:18 362:10

least 34:6 37:11 51:20 57:21 61:19 65:12 67:15 70:12 73:10 91:22 93:11 117:12,15 120:14 127:10 130:16 140:10 142:2 146:20 159:9 175:2 183:10 186:9 194:2 195:7 207:2 221:15 225:18 229:3 230:17 241:9 242:12 248:4 262:22 265:10 290:12 301:8 312:11 314:13 337:6 348:1 359:19 362:16

leave 116:18 190:5 199:17 246:12 272:12 273:13 277:11 278:7 315:15

leaves 101:21 321:11

lecture 39:3

lectures 253:1

led 254:5

left-hand 134:10 137:12 138:6 141:20

legal 342:3

legislation 340:2

length 166:16 316:13

Lenore 88:3,16,19 227:3 228:22 260:7

less 21:9 23:20 25:1,18 35:5 37:11 55:1 67:10 69:13 73:19 80:1 83:4 86:7 93:10 107:3 117:17,21 118:21 141:21 150:11 166:9 207:21 236:18 237:7 263:7 282:15 284:17 295:21 296:2,4 303:14 315:13 327:21 328:7 329:17 345:19 353:18

LESSON 3:21

lessons 132:4 142:7 145:20 321:12,17 353:5

lethal 150:19,21 152:18,21

let's 16:9 33:16 37:16 49:15,16 72:6,7 75:8 105:14 130:2 131:20 163:8 167:13 169:3 177:13 237:1 262:1 275:3 276:19 280:1 281:19 283:2 284:6 285:21 298:22 299:21 308:2 321:21 336:6 338:17 343:1 348:4

letters 296:20

leukocytes 129:9

leukocytic 156:18

level 10:19 35:21 77:16 91:22 170:6 171:5 198:1 217:4 223:20 231:7,12,16 234:1 257:7 281:1,3,10 285:5 293:9 301:8 327:18,20 328:6 348:6

levels 69:21 138:7 227:13 292:17 329:22 362:3,4 363:10

leverage 206:14

liaison 246:21

licensable 360:17

license 189:3 245:14 256:21 318:20 351:22 352:13

licensed 7:19 143:17 177:12 179:17,20 182:18 186:4 187:22 191:9,11 245:12 272:3 313:4 318:7 320:4 332:15 352:17 353:2,7,8,9 354:5

licenses 245:13 251:3

licensure 179:12 180:2,10 181:7 183:2,11,16

184:9 203:15 204:17 206:5 208:13 217:20 234:4 236:20 240:5 251:6 311:10,22 326:1

lied 162:12

lies 360:6

life 5:8 16:3 20:14 48:3 77:13 80:3 208:6 232:2 262:11 284:10 288:2

lifelong 185:17 295:13

lifestyle 259:13

life-threatening 178:20 195:14,16

lifetime 19:7 78:10 230:17

ligand 154:11,12

light 150:22 157:7 183:20 327:5 354:14

likelihood 63:14 69:2 352:3

likely 8:10 20:13 21:18 24:8 30:13 33:16 51:20 67:10 96:18 118:19 174:3 178:22 179:4,7 180:4,7 212:13 220:1 239:11 261:15 263:5 271:12 358:2

limit 53:7

limitation 131:5 159:18

limitations 251:22

limited 83:12 85:5 237:14 269:13 291:13 312:22

limits 42:12 146:14 218:14

line 81:20 298:21 299:2,7,18 300:6,7,14 301:20 313:3 324:16

linear 103:2

lines 274:13 298:18 299:6

link 206:2

links 250:20

Lion 273:14

lipid 188:2 220:20

liposomal 167:18 206:21

list 5:9 221:4 362:2 364:15

listed 24:19 26:20 224:3 243:3 317:12 321:20 337:15

listening 191:5

Lister 1:6 11:12

literally 135:19

literature 14:20 35:12 37:6 54:7 56:9 69:9 89:2 114:14 166:8 280:11 289:12 291:21 292:16 311:7 320:22 331:15

little 4:21 28:15,19 63:2 68:22 72:7 74:16 79:10 82:7 83:21 84:11 90:14 98:13 100:5 111:2 117:19 128:6 145:17 150:11,15 155:4 177:13 178:6 191:10 211:13 236:22 243:4 244:2,18 245:11 251:5 252:15,17 261:9 264:11 266:13,21 310:16 311:2 313:7 315:10 316:16 319:22 332:14 337:19 344:22 345:9 348:8 358:22 361:1

live 13:11 63:3 65:4,19 84:4 132:7 142:9,13,16 151:17 154:3 155:6,19 156:20 158:4 159:12 162:8 185:5,9 186:1,4 196:16,17 226:13,15 232:18,21 268:17 276:11 312:19 324:20 325:5,15 331:8 358:9

lived 133:20

liver 137:7 198:6

living 191:22 194:4

load 44:7 131:2 144:13 148:18,19,20 153:2 157:12,17 158:3 159:8 160:17 162:6 220:19 286:22

local 133:13

locations 222:16

log 158:16 160:20

logical 361:20

logically 143:8 341:22

logistical 269:14

London 3:16 149:8 278:19

long 4:19 5:1 55:12 60:5 69:10 91:20 93:1 96:6 109:12 122:22 126:9 132:3 138:15 167:21 183:7 197:7 230:16 233:4,20 248:16 249:1 252:17 272:13 275:2 285:16 296:12,17 301:3 305:15 308:15 333:12 360:8 364:14

longer 33:3 130:22 187:14 258:18 275:3 276:12 300:17 331:12 345:14

longitudinal 263:9

longstanding 332:7

long-term 28:10 155:10 162:14,16 185:20 208:9 216:11 231:1 263:11 272:4 309:21 333:11

long-time 56:11
lose 170:22 175:21
loss 12:22 13:7,8 14:15 15:6 16:1,2,5,7 21:14,18,19 22:1,3,8,11,13,15 25:7 26:2,5,8,10,11 29:14,17,19 30:1 31:1 52:17 67:12,17 68:15,19 80:2,8,17,18 85:21 114:6 115:11 116:3 136:18 160:3 174:3 271:20
lot 54:7,18,19 58:7 64:5 68:4,5 69:10 78:11,15 87:8 88:2 91:13 106:22 114:1,21 144:18 145:15 184:15 185:7 201:11 219:7 223:22 228:7,21 229:13 231:19 247:13 248:2,7 249:18 251:2 252:22 254:5 269:6,14 285:15 316:7 328:15,16 330:7 331:6 348:12 350:3,13,19 351:6 353:22 356:6,16 362:13
lots 64:13 70:11 91:3 96:9 216:2 221:2 222:1 290:22 333:7
Lou 160:10
Louis 106:6
low 17:21 18:5 35:13 43:7,9,13,21 44:8 52:17 64:9 69:15 100:19 122:6,10 194:5 209:3 261:6 263:5 281:1,9 291:1 322:8 330:6 333:14 355:11,22
lower 18:21 37:20 52:12,15 138:5,12 261:14 299:20 300:6 326:16 328:22 329:14 331:16
lowering 37:17
low-level 165:10,15
low-passage 135:6
luck 192:6
lucky 256:3 286:21
luminaries 76:7
lunch 175:8 190:5,19 199:8,13 200:1
lung 198:6
lymphocytes 112:4
lymphocytic 133:2

M

M112/M113 146:22
M137/M141 152:6
M94 154:7
Mac 99:18
macaque 145:4 149:18
macaques 106:10
MacDonald 152:4 155:5
Mach 102:22
Mach's 111:18
Madonna 298:6
magnitude 157:17,22 160:20 195:6
main 125:22 177:19 216:1 246:5 270:7 335:2
mainly 121:10 322:2
major 95:3 96:1 105:6 129:19 131:5 136:19 138:21 139:3 141:12 160:12 169:12 177:15 178:4 196:2 197:14 215:12 270:22 288:13 323:10 359:8
majority 14:9 118:3 220:13 312:15
mal 207:4
malaria 221:4
Maldonado 32:8 350:17 355:4
male 69:19 128:10,14 176:1 219:3 223:12,14 225:5 271:19 277:19 278:7,14,16 279:21 288:21 289:1 318:22 347:14 354:6 355:11,20
males 250:16 288:18 291:6,8 292:2 327:2
manage 331:22 332:1
management 193:10
manager 256:3
managing 330:13
mandate 190:21,22
mandatory 40:2,13 41:3
manifestations 14:10
manner 177:12
MANUFACTUERS 3:2
manufactured 120:3 177:11
manufacturer 177:2 240:15 248:15
manufacturers 9:2 175:1,2,6,19 189:18 190:8 200:4,12 209:22 210:11 223:18,21 226:10 231:2 234:19 235:19 239:3,13 242:11 339:22 342:2 352:1,10,22 359:7,11,12
MANUFACTURER'S 3:7
manufacturing 177:7 181:14

323:16
mapped 151:21
mapping 101:8
march 127:3 243:9 273:8
Maria 2:18 36:8 58:7 60:22 116:20 151:1 157:7
Marion 235:22
Marisa 28:19 34:21,22 51:5,11,13 53:10 100:7 104:12,14 113:3
Marisa's 116:1
mark 3:7 11:7 30:4 33:14 143:22 163:18,21 166:18 172:9,10 200:5 206:7 210:13 220:13 230:9 239:14 256:17 303:17 356:20 358:11
marker 24:5 42:20 83:5 84:1 92:7 129:4 159:6 179:5 189:1
markers 19:4 57:22 58:11 78:18 189:13,16 194:10 218:8
market 8:10 122:18 227:17 237:6,15 359:9
marketing 237:17
Markus 147:8
Marrack 166:22
marrow 288:20
Martha 260:14
Mary 259:19
Maryland 1:8,10 366:21
mass 96:16
Massachusetts 172:9 **massive** 97:6,7 **matches** 171:12 **material** 199:17
maternal 3:19 21:3,5,8,22 22:22 23:8,11,19 26:22 28:17 32:18,22 33:9 39:4 46:8,11 49:18 65:11 86:6 88:1,11 89:17,18,22 100:11,16 113:4 118:13 128:5 157:12,22 158:3 159:7,14,15 160:1 216:22 220:18 223:1 262:2 263:1,14 264:11 273:1 302:14,22 305:4 306:7,12 308:4 309:18 310:6,8,12,16 315:18 316:9,22 317:11,17 319:1 323:7 325:7 337:16
maternal-fetal 88:5 94:1
mating 157:11
matrices 298:4 345:2
matrix 347:6
Matteo 2:18 126:20
matter 30:14 37:15 71:9 177:5 217:6 235:10 345:13
matters 93:3
Matthias 151:13
maturation 41:10,11 59:14,16,19 60:4,6,21 61:21 65:18 118:18 123:1
maximize 359:6
may 10:9 14:5,18 16:5 17:8 22:16,19 26:14 32:15 36:6 42:14,15 44:17 59:8 62:21 63:12 66:9,22 67:16 69:12 73:11,13,16 85:3 93:17 94:10 95:10,19 105:6 138:15 142:5,6,22 150:5 155:3,17,21 156:7 158:21 159:12,19 169:15 173:14 175:21 176:5,13,14 178:15 182:14 186:20,21 187:18 199:9 202:14 204:1 208:3 214:9 216:13 219:13 230:8,16 233:15,17 234:14 237:15 240:13,22 246:9,10,11 248:14 249:3,4,7 252:18 253:7 262:19 275:12 279:6,13 287:3 288:4 289:12 292:12,13 293:2 296:22 308:22 316:19 323:1 328:4,15 329:5 353:7 355:20,21 359:19 360:3 361:3
maybe 31:3,5 36:6 63:14 67:8 68:22 69:6,13,14 72:19 80:20 85:2 93:3 95:1 105:14,15,17 170:15 172:9 191:10,16 195:3 231:3 233:9 266:10 267:2 276:9 277:22 278:12 308:10 333:13 336:16 343:9 351:21 356:22 358:22 362:22
McGregor 147:12
MCMV 146:20 152:20 153:9 154:10,13,14 159:1
MCV 326:12,15
MCV4 326:4
McVoy 158:6
mean 30:16 32:12 33:1 36:1 49:17 64:5,12 66:15 67:19 68:1

70:11,12 73:19 84:21 87:11 99:7 102:11 165:4,19 168:12,18 172:2,16 215:5 217:1 226:22 229:11,12 234:5 259:21 261:11 263:16 264:7 276:19 290:11 292:21 317:6 318:13 319:12,13 330:21 344:1 347:17 349:10 350:3,4 351:17 353:8,15 354:22 356:11 359:10,12 362:12,13

meaning 31:12 310:16

meaningful 63:22 178:19

meaningfully 200:22

means 120:12 122:10 135:8 143:9 177:3,5 183:9 244:22 301:1 303:14

measles 322:7 324:9 341:13

measure 28:10 71:3 81:4

measured 68:16 95:5 105:1

measurement 122:7

measurements 182:14

measures 40:4 94:13 96:13 180:22 311:15 364:3

measuring 82:4 83:15

mechanism 94:2,3 121:7,18 166:21 183:4 210:18 218:3,16 229:1

mechanisms 8:8 108:16

mediated 133:19 150:12,14 152:9 155:17 317:7

mediates 95:7

mediator-related 187:21

mediators 317:1

medical 171:20 188:18 195:14 208:15,19 276:14 279:17 310:10 317:16 328:13 340:14 349:12,13 350:2 351:7

medically 90:21 147:14

medications 332:10

Medicine 3:15 5:3 106:7 258:3 261:5 282:18 291:15 294:6

medicolegal 309:14

MedImmune 135:5

medium 60:3

meet 10:1 177:8 288:7

meeting 2:3 5:11,13,15 6:15 8:12,13 9:14 10:1,12,14,22 11:8,18 12:8,12 70:16 72:5,13 75:1 175:5 176:15,18,21 182:8 185:11 187:6 189:6 200:8 205:21 209:6 210:17 211:3 215:2,7 219:6 224:2 246:19 247:8 248:3 250:15 256:4 277:17 319:3 348:8,11 349:1,15 350:18 359:16 362:1,9 363:5,6,13,20 364:5,16,17,18,21 366:4

meetings 246:7

Meier 136:8,12

mellitus 250:17

member 153:22 248:5 260:14

members 11:4 67:6 163:20 188:7 246:7,11,13,15,16,18 247:7,8,14 284:8

memory 97:7,8 130:9 138:13 153:17 167:2 230:19,21 231:1,18 232:21 325:6

mening 328:1

meningococcal 326:1

menstrual 311:16

mental 14:17

mention 78:21 92:13 141:8 188:6,8 191:6 192:3 234:9 293:7 313:12

mentioned 31:7 104:14 106:22 122:17 185:8 212:22 217:21 231:4,9 234:8 238:16 242:11,14 250:5 255:4 312:20 343:4

Merck 3:7 30:5 200:6,20 358:11

message 236:4 243:5 352:2

messages 334:6

met 262:6 273:21

method 42:10 45:22

methods 6:6,9 65:15 73:2 81:17 83:9 214:20

MF59 135:18 136:5 166:15 220:4

MHC 158:7,21

mice 148:16 151:6,10,12 152:10 154:19 168:1

Michael 102:22 111:17 243:1,8

micrograms 136:7 138:1

microphone 10:17 34:7,8 168:11
mid 18:5 35:14
mid-1990s 322:5
middle 16:19 100:19 134:11 246:10 280:22 287:21
mid-gestation 228:1
midranges 16:14
migration 27:13,16
migrations 27:7
Mike 15:21 51:5,11 53:11 68:2 113:2 116:5 158:6 171:18
mild 280:6 288:18
milk 92:22
millennium 261:19
milligrams 140:16
million 184:22
mind 37:21 38:3 51:14 68:18 90:5 258:20
Mine 100:4
Mine's 357:3
minimal 105:12 154:18 158:13 323:21 345:15
minimize 193:13
Ministry 123:19 126:22
Minnesota 147:12
minor 101:19
minority 120:15 285:12
minus 122:9
minute 34:22 256:13 331:4
minutes 10:13 49:7 149:19 151:1 163:9,12,14 175:21 187:5 200:4 242:16 273:20 277:1,2
misinformation 348:9
misleading 69:1
miss 265:16
missed 172:10 174:9 329:19
mistake 4:6
misunderstood 163:15 **mix** 164:12 **mixing** 347:5 **mL** 120:10,13
MMR 196:17 281:8 325:15
MMWR 250:19
mobility 276:15
Mocarski 2:13 11:6 33:4,7,12 34:2,8 54:4 55:7 65:20 66:16 67:21 72:19 74:6,20,22 87:6 98:4,9,11,14,17 99:12,16,21 115:21 116:18 117:1,4 131:16,22 143:20 163:5,10,13,15,20 164:2 166:5 167:9,13 168:3,5,8,10,14 169:17 172:5 173:8,16 174:18 175:7 340:9
modalities 211:21
mode 170:15 272:9
model 145:5 147:13 148:13 149:7,15 150:1,19 151:5,9,16 153:10 155:13 156:5,10,19 157:1,10,17 158:19 159:1,2,13 160:12,13,15 161:19 172:10 178:1 192:20 213:13,20 225:16 228:11,13 230:11 266:11 285:7 291:14,22 296:18 297:4,11,20 302:17 344:9,20 346:9 353:20 354:22 355:14 361:11 362:17
modelers 341:2 364:12
modeling 3:18 148:1 156:9 276:22 282:2 293:21 294:18,22 295:1 296:6 304:12 306:1,21 307:5 342:7 344:14 346:19 351:15,18 356:6 360:1,3,7 361:3,9,14 364:11,13
models 106:20 129:17 130:3,15 144:1,8,20 145:13,21 147:7 149:3,4,20 150:5 152:18 155:7 162:4,15 163:1 173:7 212:21 218:14,17 221:3 227:8 267:1 287:8 290:15 295:10 344:15 346:12 347:13 361:11
moderate 17:21 22:13,14 42:17,19 43:8,10,14,21 47:20
modern 152:1
modes 20:14
modest 157:18 158:2 259:2
modification 162:10
modified 71:1 95:14
modify 126:14
modifying 123:14 207:10
modulation 162:10 **molar** 220:22
molecular 152:1
molecule 71:2 207:1
moment 45:22

47:13 152:15 174:16 286:19 293:19

momentum 336:3 364:6

moms 170:17

money 5:7

monitor 348:16

monitored 323:2

monitoring 47:9 315:19 316:2 322:4 324:11 328:11

monkey 112:8

monkeys 112:16 160:20

mono 271:17 272:5 354:21

monoclonal 103:6 148:3 227:11 228:5

mononucleosis 4:17 271:15 355:1

monophosphoryl 188:2

month 240:17 300:13 301:7,17 303:9 304:20 349:7

monthly 120:12

months 44:5 55:11,12 65:16 123:2 135:22 136:10,13 207:7 212:11 219:8 222:10 231:6 232:11 243:7 252:13 266:1 295:13 296:21 298:20 299:3,6,8,14 300:5 323:4 324:18,19 325:9,16

month's 289:20

Morello 153:5,9

Moreover 42:15

morning 9:6 12:9 13:4 39:1 104:14 161:22 164:6 190:15 196:1,9 197:19 206:20 208:16 215:19 217:22 236:3 259:10 303:20 325:3 336:12,13

morning's 70:17

mortal 259:2

mortality 150:18 156:14 157:5,12,17 159:10 160:1 162:16 220:18 290:16,17 291:10

Mossman 3:8 167:14 173:9 206:8,9 231:3 243:3

mostly 11:22 38:21 73:2 194:11 306:7

mother 21:13 53:2 79:17 101:17 214:2 217:5 279:6,20 284:17 286:11,17 288:15 303:19 318:19 331:11 333:10,11 343:12

mothers 20:5,13 21:15,16,17 22:11 23:4,12 25:21 52:11 57:8,12 101:12,14 103:21 118:9 125:18,19 130:20 134:3 135:3 173:21,22 222:3,9 234:2 263:6,15,17,22 264:8,12 266:4 276:15 287:3,17 296:5 315:6 363:2

mother's 92:22 286:15

Mothers 35:4

motivation 273:6

mouse 147:11 150:15 151:17 152:5 153:6 154:10 155:13 156:2,5

move 38:5 51:3 99:13 155:7 165:17 169:21 173:4 174:19 221:22 225:15 259:1 293:20 320:15 362:8,10

moving 188:22 201:8 206:15 218:19 240:9 243:11,12 262:11 271:12 319:4,9 321:2 359:8

MPL 138:2,3 166:20 167:10,17,19 206:21

MS's 90:15

mucosal 160:5

muffins 10:7

multicenter 123:18 124:1

multinational 124:2

multiparameter 96:15

multiple 24:11 77:22 78:4 83:20 86:1 108:3 168:20 169:6,9 341:14,18

multi-race 25:1

multivalent 41:7,8

multivariate 32:13

Mumbling 62:20

Munich 168:4,16

murine 145:7 147:2 149:18 151:6 156:10

muromegalovirus es 145:7

Mussi-Pinhata 35:4 51:5,16 56:19 57:1

mutant 146:20 147:1 152:5,6 154:7

mutants 151:19,21

mutated 161:7 168:22 169:2

mutation 147:20 154:7

mutations 151:20 152:2

MVA 132:14 139:9

myriad 349:8
myself 225:7 272:20 333:2
mystery 92:19

N

N2 111:11
Naf-expressing 112:18
narcolepsy 191:17 195:19
nasal 186:10
Natasha 1:11 366:3,19
Natcher 199:10
national 1:6 4:2,3 5:10 11:2 205:11 263:3
native 156:22
natural 6:12 57:9,15 59:8 66:2,5,21 67:2,20 69:6,14,17,20,22 72:22 73:13 86:2,17 96:5,10 115:18 117:12 123:14 162:1,3 203:7 208:20 231:8 295:3
naturally 52:22 97:22 133:22
nature 7:16 22:9 83:16 106:7 147:16 153:1 309:14
nearly 18:4 222:4
necessarily 32:3 69:17 88:6 181:22 226:2 287:8 320:20 341:4
necessary 8:21 99:8 204:3,7 218:12 233:8 251:1 268:9,13 315:19
Neels 3:6 190:13,15 217:22 224:15 238:1 275:12 315:8 317:21 318:6
negative 39:21,22 40:7,10,16 47:1,4,5 50:3,10 55:15 137:12 198:12,13 288:10
negatives 143:1
neighborhood 87:21
neither 366:8
neonatal 151:5 316:10 357:20
neonate 197:8
nervous 80:13 107:6
neural 151:6 160:2 310:2
neurodevelopmental 162:22
neurologic 113:11 115:11
neuropathology 151:5
neutral 220:22
neutralization 72:10 73:3 94:15,17 95:4 108:22 129:11
neutralize 91:15 110:16,17
neutralized 111:13
neutralizing 94:11 95:2 103:5,12 109:4,6,9,20 110:5,10,20,21 111:12,19 118:17 121:9,15,19 129:3 136:16,21 137:2 138:6,7 140:5 142:8 157:14 158:16 161:11 209:12,13 211:18 215:16 219:21 221:10 231:7 233:1
nevertheless 134:5 236:16 287:4
newborn 14:11 15:10 20:18,20 21:1 23:6 26:3 29:21 38:22 53:18,19 79:4 80:12 149:14 151:12 241:17 263:19 312:5
newborns 2:8 13:17,19 22:21 24:16 25:21 39:7 47:18,19 48:2 50:19 56:5 96:22 120:1,21 125:17 127:15 216:7 217:4 234:10 260:6 303:8 304:10
newer 64:17
news 273:2
newspapers 242:20
next-gen 64:18
NHANES 17:11 290:7 292:2 293:13 297:21 298:16 305:13 344:20
NIAID 10:22
nice 5:14 97:17 231:5 236:16 343:17
night 256:7
Nigro 118:22 125:2,11
NIH 6:12,16 187:3 246:17 272:16 364:9
nil 238:19
nine 259:3 260:8,10
NK 154:11,15,17 158:22
NKG2D 154:12
nobody 126:9 234:11
nomenclature 107:17
nominated 253:8
non 21:7 23:4,22 28:17 44:16 67:13 70:3 77:4 78:19 102:20 113:4 243:16 286:10
non-adjuvanted 187:15
nonclinical 192:17
non-existence 87:3
non-Hispanic 24:21 25:14,16

32:20
non-immune 39:22 93:10
noninvasive 46:5
non-live 268:18 269:11
non-pregnant 265:20 314:14
non-primaries 113:17,22
non-primary 21:3,11,13,16 22:2,12,16,22 24:8 27:8 44:4,6,11 45:5,13,15,19 52:20 55:22 66:2 68:4 70:5 76:19 77:19 78:8 85:15 86:7 92:9 100:16,22 102:11 105:7,18 106:1,3 111:9 113:8,21 116:8 282:7 306:7
nonproductive 146:1
non-replicating 132:14
non-starter 342:4
non-sterilizing 153:1
non-transmitter 118:9 129:17 130:3,15
non-transmitters 58:18
non-transmitting 56:20
non-transplant 3:11 9:5
non-White 18:15
nor 109:21 366:9,12
normal 97:14 197:11 289:6 348:10
normally 289:22 290:3
Notary 366:1,20
note 48:20 81:6 137:1,3 143:13 157:2 178:13 182:16,17
nothing 9:19 109:20 123:10 308:12
noticed 58:21 74:16
notify 348:15,16,17
Novak 103:11
Novartis 3:8 135:17 140:12 211:1,6
novel 154:9 161:13 187:13 188:1,3 314:11
November 126:18 185:11
Ns 111:6 **nucleic** 211:22
numerous 354:7
nurseries 24:17
nursery 15:10 19:14
nursing 357:20
nutritional 276:14

O

obesity 291:1
objectively 68:16
objectives 10:1 11:9 70:15 125:20 144:10 243:22 296:6
objects 19:22
OBs 327:11
observational 2:11 89:1 203:17
observations 53:3 64:13,16 313:19 332:18
obstacle 188:5
obstacles 243:11
obstetrician 266:1 327:9
obstetricians 254:11 327:6
Obstetrics 49:2
obtain 15:12 39:21 40:6,7,16,17,20, 21 45:16
obtained 42:22 43:5,11,16 46:16,21 48:8,11 55:15 89:4 122:12
obviate 142:6
obvious 75:6 80:5 250:21 270:1
obviously 17:20 29:20 30:16 38:10 54:12 62:18 63:3 73:9 82:10 96:14 180:11 202:4 208:8 210:9 216:18 223:19,22 224:8 225:8 233:8,19 237:11 294:10 312:9 313:5 314:10,15 340:17 353:1 358:7 363:21
occasion 124:14 338:8
occur 18:9 28:21 63:10 154:17 155:3 240:21 295:15 297:13 301:1 343:12
occurred 85:17 260:5 311:20
occurrence 52:19 195:18
occurring 9:22 13:14 17:18 23:5
occurs 13:10 15:6 41:11 60:4 106:20 226:4 241:3 306:7 344:17
October 5:10 127:5 250:10,15 254:19
offer 40:3,13 41:4,5 46:3,7,9 334:22
offered 123:10 215:3 280:4 291:16 341:6
offers 334:20
office 4:4 11:3 235:22 244:21 329:21 349:21
officer 366:3
offices 260:20 327:4
Office-sponsored

5:11
official 191:2 245:2
officially 126:18
officio 246:16
off-label 318:14
Offspring 25:18
Oh 31:1 99:21,22 128:15 175:9 229:17 252:20 258:8 307:17 336:11 346:3
oil-and-water 135:18
okay 13:4 35:12 38:16 54:1 55:5,9 73:22 78:11 98:14,17 99:10 117:3,6 132:1,2 163:10,13,15,16, 20 168:12 174:17 175:16,20 176:3 182:21 190:12,15 192:14 200:2 219:5 223:9,15 225:4 230:12 235:14 237:19 239:2,19 240:8 242:9 243:21 258:1,8 275:11 278:2,12,15,17,1 8 287:20 293:18 308:1 321:10 336:18,19,20 339:20 342:5 345:8 349:21 356:1,4,19 357:3
old 27:3 35:7 52:2 62:11 92:18 95:3 116:22 117:1 246:13 292:14,21
older 25:20 288:14,15 293:3 325:9 327:10 328:22 329:17 339:6 351:3 363:1
oldest 264:14
olds 266:5,12 297:14 300:11,13 301:7,17 303:9 304:20
one-and-a-half-fold 157:21
one-page 262:14
ones 95:15 183:21 184:3 213:18 244:8 286:21 287:20,21,22 311:19
oneself 360:9
ongoing 33:20 82:17 123:20
online 294:7,15
onset 44:6 46:8 118:13 125:13 126:6,11 128:5
onto 278:6 291:18 330:3 337:2
onus 291:17
open 29:1 54:1 101:21 102:12 124:1 164:2 198:20 224:19 225:1 338:2,3,13 339:18
operationally 203:18
opinion 49:14 70:12 129:6 142:8 271:11
opinions 70:12
opportunities 19:13 32:5 201:7 326:22 329:19
opportunity 31:22 206:10 215:3 292:6 329:20
optimal 45:22 202:18 221:17 295:12
optimistic 286:1 328:2
optimized 154:3
option 256:14 273:4 343:7
optional 267:21
options 188:7 248:1
oral 84:20 186:12 324:22
orange 298:18
order 10:8 36:16 37:22 40:4 57:7 62:5 108:11 121:6 123:12 125:1 126:3,14 129:12 187:17 267:5 289:15 336:20 337:1 351:17 357:2 364:5
orders 332:4
Oregon 106:6 112:6
organ 81:7 137:8,21 142:12,14 196:7 198:4 214:13 288:19 289:10
organization 193:15 252:12 349:3
organizations 9:10 204:8 243:5 246:17,21 247:1,2,5,9,11,1 4 254:22 272:16
organize 78:16
organized 123:22
organizer 12:12 215:2
organizers 190:16 200:8 206:10 211:3 219:6 321:14
organizing 10:20 39:2 144:5 188:8 215:2 279:1 363:4
original 146:3 169:1 232:10
originally 135:17 153:13 237:8
orphan 188:9,15 195:10 236:21 237:2,3,4,18 238:1,11,14,17 239:1
ostrich 194:16
others 4:22 20:6 80:11 81:12 151:4 160:10 165:7 222:1 240:13 268:2 350:13 358:10
otherwise 85:9 166:3 189:1 225:2 256:16 354:4 366:13

ought 315:7
ours 243:6
ourselves 8:11
outcome 5:20 28:7,15 30:17 68:16,20 81:1 83:21 113:4 119:2,14 120:1 127:11 194:6 203:8 222:22 289:18 328:18 366:13
outcomes 67:19 68:14,17 114:4 162:22 196:21 202:22 205:16 234:9 312:5 316:14,20 317:10,13 323:9 357:20
outreach 347:3
outside 81:16 205:9 328:12 348:10 350:2 356:7
ovary 206:22
overall 6:7 25:3,13,15 26:2 38:13 79:18,20 85:20,21 100:21 114:3 127:16 251:7 261:12 289:1 290:13,16 303:14 304:7,9 306:3 307:14 315:14
overcome 73:13 155:20 209:7
overlap 298:19
overly 285:22
overt 291:7
overview 32:17 75:19 78:22 206:18 253:2
overwhelming 156:15 297:11
overwhelmingly 288:22

P

p.m 365:9
P32-labeled 102:5
package 208:12 233:21 234:4,10
Paediatric 194:19,20 195:5
page 2:2 3:2 256:1
pages 258:17
pairs 316:4
palatable 271:18
palsy 13:8 14:18
pancreas 198:6 238:7
pandemic 84:16 179:18 184:21 191:11,12,15 334:2 335:9,11 350:7
Pandemrix 191:12,18
panel 57:6 67:5 161:22 163:9 164:2 243:10 287:11 336:7 346:15 361:7
panorama 122:18
paper 58:22 61:1,9 67:9 82:8 101:9 103:17 106:7 112:6 114:8 118:16 121:17 122:21 123:3 145:1 146:16 152:4,12 154:22 155:5 157:3 160:19,22 161:5,15 211:8 228:14 272:21 282:6,9 290:2
papers 118:3 146:7 151:18 152:22 153:4
paradigm 357:17,21
paradoxically 164:17
parallel 89:11 326:12 351:21
parameter 80:21 130:8 131:3 181:13,16
parameterizing 347:7
parameters 3:12 47:16 77:6 84:9 94:14 96:14 98:7 106:3 130:4,12 243:19 318:1
pardon 175:10
parent 84:4 110:6 272:17
parenthetically 231:21
parents 19:10,14 20:3 30:21 215:5 271:18 343:14 349:17
parity 18:20
parsed 77:21
participants 6:14 124:9
participate 247:8
participating 125:6 185:16
participation 10:19 124:18 272:15 309:8
particles 133:2
particular 43:20 80:8 90:2 129:13 131:8 132:13 135:21 149:1 152:6,14 157:9 160:19 164:7 180:16 201:10 226:8 274:21 285:6 286:2 291:8 309:4 337:15 351:8
particularly 73:15 80:10 115:14 121:8 123:6 140:6 149:5 150:22 152:22 155:17 157:4 162:15 206:2 218:7 242:6 311:22 313:12 315:21 316:17 337:21 351:14
parties 366:9,12
partner 95:9 221:13 271:19 284:22 288:4
partnered 261:9
partners 19:7 284:9 285:2 288:8 330:5
partnership 206:1
partnerships 204:3
Pass 11:7 29:11 70:15 136:4

161:2 173:17,18 174:17 201:22 217:2 220:3 230:5 342:12 343:20 345:8 346:2 357:3 358:1

passaged 102:7

passed 291:18

passive 92:21 119:5 123:13 150:19 151:11 155:15 157:2,3 159:3 172:20

passively 305:3

Pass's 91:21 226:1

past 32:10 40:9 72:3 132:5 355:6

Pasteur 3:9 136:1,5 214:22 215:8

path 200:11 310:19 359:14

pathogen 289:10 290:1 291:6

pathogenesis 80:22 92:20 95:19 135:1 149:5 228:15

pathogens 180:18 186:18 340:18

pathological 93:21

pathology 151:7

pathway 205:17 317:2

pathways 8:10 177:15 178:3,4 180:10

patient 109:16 110:7 111:19 127:2 149:21 150:6 243:5 334:21

patients 60:5 78:1 107:3 109:21 113:11 124:19 133:17 134:6 137:8 187:16 196:4,5 197:21 198:5,10 212:16 251:20 257:19 288:22 292:1 329:11

patient's 110:13

pattern 17:1 24:7 85:3

Paul 3:16 11:6 86:21 92:3 137:6 278:3,6,16,18 292:8,10 341:2 351:14

Paula 203:20

Paul-Ehrlich-Institut 120:8

Paul's 278:5 346:10

pause 207:14 285:21

pave 4:11 5:17

Pavia 2:18 97:2 124:18 126:20,21

PBS 167:7

PCR 46:15,17,19 47:4,10 48:4,7,12,17,18, 22 83:7 85:20

peak 136:17 274:18

peaking 184:3

peaks 183:19

peculiarity 100:10

pediatric 182:18,19 234:14,16 236:21

pediatrician 327:8,13

pediatricians 257:9 260:19 327:4 329:12 350:9 351:8

pediatrician's 349:21

Pediatrics 49:3 245:19 253:22

peds 352:6 **peer** 290:2 **penetration** 146:4

Pennsylvania 2:20 49:10

pentameric 95:17 135:9 143:4 226:19

people 7:3 31:3 59:9 64:12 69:21 75:9 108:7 114:13 116:11 165:5 172:3 177:21 183:10 185:1 208:1 214:2 215:4 220:13 229:10 235:17 237:6 238:19 248:7,9 249:12,18 250:17 252:21 253:4 255:15 257:11,19 270:21 279:9 287:13 289:11 290:20 313:18 338:16 346:14,16 347:3,9 356:14 364:1 365:2

Peptides 132:18

per 120:9,12 275:22

perceive 207:13 224:1

percent 13:11,14,21 14:7,10,13,16 15:5,15 16:15,16,17,21,22 22:6,7,8,10 23:14,15 24:16,22 25:1,4,13 26:1,3,4,7,9,13 27:11,14,15 28:13 29:15,16,18 31:1 36:12,13 37:7 41:17,20 42:3,6 43:10,14,16 44:12,14 46:22 47:2,6,7,11,21,22 48:9 51:21 52:6,17 79:16,20 85:13 87:2 89:15 104:15 105:3,4,5,11,15, 16,19 108:1 116:14 117:15,17 120:22 125:1,2 126:12 127:12,16,18,19, 20 141:2,7 149:13 164:11 170:13,18 207:22 220:6 230:6 259:12,22 260:2,3,21 261:3,6,13,22

271:15 282:10 283:3 290:13,14 295:21 298:10 299:15,16,17,21, 22 300:1,9,16 301:9,10,13 302:1 303:5,10,13,16,1 8 304:5,9 306:22 307:1 324:1,8 329:15 330:11 331:13,16 333:17 334:8,13,21,22 345:16

percentage 44:12,14 46:22 47:1 92:15 103:20

percentages 13:15 44:10

Pereira 88:3 93:20 227:2,3 228:21

perfectly 75:22 99:16

perform 71:15 184:6 196:12

performance 122:19 181:18

performances 123:5

performed 40:14 47:15 48:3 119:7

perhaps 4:20 57:12 72:7,9,18 149:15 163:12,14 231:14 261:8 265:8 267:16,17 268:5,6 279:10 282:10 287:13 292:6 293:2,4 301:12 309:13 316:4 317:13 318:11 328:7,18 343:15 350:9

perinatal 18:9 305:4,15

perinatally 345:17

period 14:11 18:10 42:4 55:2 71:18 138:14 187:17 191:15 197:17 228:19 230:17 283:12 293:19 305:15 308:11 311:16 346:6

periods 248:16

peripheral 83:4 84:21 129:8 174:12

permanent 13:7 14:14 15:4,13 248:18,19

permission 259:1

permissive 146:9

permitted 320:19

persistence 120:17 207:5 218:10 231:7

persistent 165:8 232:19,20 284:2

person 37:22 113:5 183:12 190:18 248:6 319:8 337:11,18 339:7

personal 9:19 143:13 191:4

personally 230:19 236:17

persons 20:12 169:9 251:17 313:13

perspective 3:3 7:8 10:4 30:6 57:5 144:20 155:12 176:6 190:17 202:20 207:19 308:12 310:15,17,21 313:20 316:5 317:15

perspectives 3:19 8:5 9:3 10:18 176:5 200:13,19 203:21 308:4

pertinent 249:11

pertussis 196:15 318:9,17 333:22

perverse 302:12

petechiae 115:5

Peter 160:11 175:14

ph 272:22 297:10 312:12

Pharma 120:4

pharmaceutical 123:22 272:17 275:17

pharmacist 348:3

pharmaco 193:14

pharmacology 192:20

pharmacovigilenc e 191:14

pharmacy 348:14 349:22

pharynx 95:21

phase 6:13,16 9:7,8 40:12 87:13,15 96:17 123:17 124:5 127:1 128:21 153:14 189:8 194:21 207:3 210:3,5,7,12 218:20 221:7,18 222:12,17 224:20 225:13,19,21 226:4 295:8 314:9,22

phases 313:20

phenomenon 232:2

phenotype 149:13

Phil 3:8 12:10 57:4 70:16 74:1 99:10,12 144:4 175:8,10 190:4 191:5 195:7 199:8 200:8 211:1 214:21 223:7,15 229:2 232:5 238:16 339:14 356:21

Philadelphia 2:20 63:6 351:10

PHILIP 3:4

PHILLIP 2:4

Phil's 58:15 65:21

phospholipid 220:22

phylogenetic 145:2

physical 89:8

physician 208:1 329:20 348:17,18

physician-based 262:14

physicians 251:19 254:1,10,12

272:17 329:10,13

pick 204:7 311:8

picked 111:15 286:10

Picker 106:6 160:10

Pickering 3:13 239:15 243:18,21 257:8 273:18 274:8 275:11 277:4 293:18 306:14 318:4,12,21 321:6 336:8,11,19 338:15 339:1,4,10,12 340:6,8 348:7 350:12 351:9 354:13 356:1,4,19 361:21 365:4,7

picture 54:5 184:12 256:7 345:19

piece 116:9 234:6 294:1

pieces 86:15

Pieter 3:6 190:7,13 217:22 223:10,16 224:13 237:20,21 240:14

pig 145:9 146:2,5 147:13,18,19,22 149:18 153:10 156:11,15,18 157:9 158:7 159:2 220:15,17 230:11

pigs 148:2 149:14 158:14 160:4

Pike 1:7

pillar 176:11 193:14

pillars 192:15 193:12

Pippa 166:22

pivotal 203:16 222:18 315:2 316:8

placebo 81:22 123:18 124:6 127:19 134:10 136:9 137:11 140:20 141:6 174:11 193:4,5 194:7,8 222:9

placebo-controlled 193:22

placed 135:7 171:17

placenta 78:21 88:13,22 90:3 95:22 156:5,6,7,15,16,17 165:18 213:22 227:4,7,9,19,22 228:1,8,11,13,18 286:15 317:8

placental 89:1,5,11,14,17 94:5 159:15

placentas 260:8

places 91:4 174:5 199:12

Plachter 141:9

plan 193:10 194:20,21,22 195:5 266:6 358:5

plane 256:8

planned 266:1

planning 207:21 242:15 265:22 268:3 270:20

plans 9:11 266:7 269:14

plasmid 153:8 219:17,18

plasmids 139:7 142:17

plateau 231:11

platform 106:9 219:8

plausibility 358:21

play 2:12 45:1 69:13 91:10 155:17 158:21 180:12 267:19 317:1 327:11 340:19

played 117:20 185:6

players 95:16

plays 45:4

please 10:12 29:8 34:7 49:8 51:15 74:15 128:10,14 164:3 168:5 223:7 278:4

pleased 235:15

plethora 214:19

Plotkin 2:20 7:21 11:7 49:9 50:1,6 56:18 131:20 132:2 150:2 174:21 175:9,13,16,20 190:4,10,13 199:7,15,19 200:2 206:7 210:22 214:21 218:21 219:1,6 223:5,10,13,15 224:13 225:4,6 228:20,22 229:20 230:2,12 231:21 232:17 234:12 235:14 236:13,15 237:19,22 238:15 239:2,19 240:1,8 241:14,18 242:7,9 243:1,8 250:5 258:20 273:11 274:8,9,12 275:8,10 308:7 315:16 341:1

Plotkin's 258:14,22

plus 214:14 234:5 295:17 299:8 301:18,21

PNAS 166:22

pneumonitis 151:16

point 29:12 36:10 38:11 55:17,22 56:1,4 59:21 72:20 73:11 75:6,13 77:2 82:20 84:7 96:2,22 105:8 108:20 115:13 117:13 125:16 128:17 135:11 152:15 166:1,17 167:4 175:4 182:17 209:21 210:16 218:6,13

225:6,12 226:9,12 230:13 231:18 232:22 234:20 235:9 240:4,9 241:19 274:12,22 286:2 307:21 309:4 310:5 314:19 315:12,14 319:10 337:17 346:3 354:15 355:4

pointed 5:6 62:1 74:2 86:21,22 129:5 166:14 308:7

pointer 183:18

points 78:12 226:13 240:13 259:3 270:7 341:1

Poland 310:11

policies 248:1

Policlinico 2:18 126:20

policy 175:15 194:16 202:22 205:3 244:4 253:18 280:17 295:9 308:20 335:12 356:18

policymakers 240:6

polio 322:18 324:22

poloxamer 140:17

polyclonal 151:7

polysaccharide 312:17 322:12

polysaccharides 196:14

poor 44:19 96:8 142:5 163:5 233:10 291:1

poorly 65:8 335:15

popular 82:6 83:9

populated 143:16

population 13:21 15:9 16:18 17:10 21:20 22:5 23:16 24:15,18,20 25:11 27:9 28:5 31:16 32:21 36:17 38:14 51:14,18,19 52:4,18 59:4,7 64:6 67:4 73:20 76:14,17 78:3 85:20 87:2 96:11 97:19 100:19,20 104:15 105:6,14,16 113:9 114:15,16 115:8,16 125:5 149:22 169:21 170:18,21 181:14 189:11,21 202:5,17,18 204:9 205:6 207:16 208:5,9 212:17,20 214:11 217:8,9,11,18,19 218:3 222:19 233:11,20 235:7,17 236:6 238:2,12 242:21 245:1 260:2 263:20 264:20 278:21 280:12 282:5 283:14 284:3 290:6,8 293:4 303:21 307:1,2,3,8,10,14,19 315:2 331:7 332:8 344:2,11 345:3,7 355:19

populations 3:10,13 6:5 9:4 16:12 23:2,11 24:9 27:7,17 51:13 52:13,15 53:6 67:13 68:6,11 73:16,18 81:9 86:11 97:22 102:16,17,18 115:7,16 150:3,7 170:2 171:2 182:20 189:12 198:21 209:18,20 237:14 243:16,20 258:21 293:12 306:3,5 351:1 352:16 356:15 359:3

Porath 276:6

porcine 146:10 149:7,10,14

portion 12:8

posed 259:5

positive 22:7 26:4 40:7,11,12,17,18,21 42:12,20 45:16 46:21 47:10,11 54:20 60:10 119:18 121:6 125:15 133:21,22 137:12 140:9 198:12,13 220:12 260:11

positive/recipient-positive 137:18

positives 37:6,13

positivity 43:21 83:2 134:1

possibilities 78:16 103:16

possibility 41:5 45:19 55:19 102:13 108:17 114:6 212:15 342:11

possible 4:19 12:6 28:11 39:20 45:15 110:18 118:6 121:7 159:8 164:20,21 190:20 196:13 198:5 265:6 277:18 323:6 343:3 365:2

possibly 4:22 33:9 165:19 211:22 274:15 285:19 329:1

post 332:2

posted 252:1 253:11

poster 356:7

post-infection 181:3

post-licensure 184:13,14,17 217:21 332:18

post-marketing 179:9 192:18 210:18

postnatal 305:5

postpartum 220:4 266:19 271:2,4 310:14 342:12,18

postponing 232:8

post-registration 193:9

post-third 207:7 231:6
postulated 121:13
post-vaccination 82:10 297:19 302:15
potency 177:9
potent 142:18 177:6 231:14
potential 4:21 84:8 129:4 145:6 159:11 173:9 180:9 182:9 185:14,15,17,20 186:9,13,16 187:9,10,19,20 188:21 201:19 207:20 208:4 234:4 241:16 258:5 271:9,13 278:20 295:5 296:1,8,15 303:2 306:1 308:17 310:18,22 312:8 314:2 317:17 332:20 357:8,22
potentially 84:12 165:14 189:13 295:22 298:21 302:21 304:20 350:21
power 125:3 222:6 226:3
powerful 162:9
poxvirus 142:10,17
pp65 138:21 139:3,7 140:7,9,11 141:13 142:16,18 219:18 220:9 226:18 229:3,4,19 230:10
pp65/IE1 140:1
pp65-IE1 211:10
practical 50:7 212:22
practice 242:5 265:22
practices 276:4
practitioners 327:5
pragmatic 306:19 307:6
pre 217:19 311:3,9
precautions 266:18
precedent 265:12 267:13,16 280:5 313:7 315:10 338:7
precise 15:1
precision 63:21 120:16
preclinical 132:17 193:2
pre-clinical 318:2
preclinically 132:15,22
preconception 117:18 197:12
preconceptual 21:6
predict 178:15,17,22 180:4,8 233:4 271:9
predicted 300:22
predicting 8:9 67:1
predictive 46:22 47:1,5,11
predictor 204:4
predicts 30:7 179:5
predominant 161:19
preemptive 81:9
preexisting 23:3
pre-exposure 91:21 92:2
pregnancies 101:12 109:2 265:17 266:6 267:22 271:6 311:18 356:16
pregnancy 20:20,22 23:18,21 24:1,3,4,5 28:2 40:8 41:2,13,19 44:16 49:12 50:5,10,11,13,15 ,17,21 54:13 55:2,10,11,14,16 56:6,11 60:8 76:10 80:10 92:14,18 93:8 97:5,13,14 104:5,9 105:2,12 109:5,8 116:13 117:15 119:3 127:11 169:10 171:6 173:21 174:1 207:21 208:1 217:1 233:8,9 234:3 240:16,19 241:20 242:4,15 250:2 255:15 260:3,15 266:18,21 267:7 268:1,11,12,13 269:5,7,9,12,15 270:18,20 281:5 283:11,13 286:7,19 303:7 304:2 308:8 309:3,11 310:13 311:12,13 312:3,4,10,14,16 ,20 313:5,6 314:9,16 315:11 316:18,19 317:4,16 318:7 320:6,16 330:4,14,15,20 331:3,7,9,13,19, 21 332:1,9,11,17 333:1,3,6,15,19, 21 334:2 335:21,22 336:2 341:17,18,20,21 342:1 357:13,14
pregnant 2:8 16:20 17:4,6 19:3 20:8 27:3 35:8 38:21 39:9,10,14,17 40:3,14 41:1,15,20 43:19 44:8,13 45:7,14 50:3,10,13,17,21 52:1 55:13,17,21 56:1,3,13 58:8 62:10 78:20 96:22 117:14,17 125:6 126:1 131:9 169:7 172:11,14 173:3 189:20 196:10,12,19 197:5,16 208:7 212:13 235:8 242:3,15 249:4,21 255:18 259:20 261:14 265:21

268:10,15,22 270:22 280:6 286:6 287:17 308:16,17,22 309:7,17 310:14,18 311:16 314:1,17 315:3 318:9,15 319:16,19 320:2,5,9,11 321:8 331:18 332:12 334:4,8,15,20 335:3 336:16 337:20 339:6 342:22 351:3 357:7

pre-licensure 183:6 216:14 236:11 320:1,20

preliminary 124:14 294:17 305:20

pre-marketing 332:13

prematures 195:2

prenatal 39:10 40:8,22 46:3,4,5,6,10 47:3 104:21 126:10 266:15 269:16 315:20

preparation 121:10 124:7 297:8

preparations 227:16

prepare 247:21

prepared 74:14

preparedness 179:18

Pre-pregnancy 270:17

pre-pregnant 233:10 240:16,17,18 267:6

pre-registration 192:19

preschool 322:5,9 324:7

prescient 153:21

presence 44:8,18 45:21 62:16,19 63:11,13 83:6 105:2 106:12 359:10

present 14:6,9,10 39:3 44:17 83:14 103:4 108:14 138:18 139:22 239:9 256:16 301:3

presentation 39:4 46:2 100:6 144:11 215:22 236:3 278:13 321:16 348:11

presentations 51:7 57:18 201:12 253:9 276:21 358:12

presented 32:16 33:20 100:6 173:12 210:13 212:3 221:6 250:6 303:13

presenting 57:14 294:17

presents 88:5

pressed 174:8

pressing 306:15 318:4

presumably 67:13 165:13

presumed 125:13 126:6,11 128:5 309:7

presumption 291:12

preterm 263:5

pre-transplant 91:19

pretty 66:19 67:14,20 69:20 76:17 79:15 80:19 82:1,8 85:22 89:3 90:3 212:17 238:5 327:14 359:2 361:20

pre-vaccination 297:19

prevalence 24:15 25:3,10,22 27:4 64:8,9,14 113:9 141:1 195:15 238:3 259:15 261:3

prevent 79:11 82:3 90:18 116:8 134:4 135:16 137:19 141:19 155:16 196:8 216:6 244:17,22 309:19

prevented 135:3 257:16 328:19

preventing 2:17 93:13 117:21 159:5 303:11 355:1

prevention 11:2 40:3 68:21 119:15 120:11,19 121:11 122:2 136:10 143:7,8 150:4 193:20 194:1 201:13,16,21 202:11 204:16,17,19 206:3 216:17,21 219:22 234:2,18 272:13 297:13

preventive 187:4 350:13

previous 12:2 52:7 57:15 109:2,5,8 131:17 185:8 218:19 272:4 295:10 304:4 325:20

previously 19:21 205:21 303:13 359:1

Prevnar 179:20 184:4

price 275:16,18,21 276:2

primacy 125:8

primaries 102:21 113:18,22

primarily 15:5 260:12

primary 20:14,19 21:2,5,8,9,11,13, 15,17,22 22:2,22 23:5,18 24:1,7 27:8 28:18 33:11 35:17 39:8,11 40:2,3,12 41:3 42:2,5,20 43:1,6,18 44:4,6,11,13,16, 17 45:2 46:11,12,18

50:16 51:19 53:5 55:8,21 56:10 58:17 59:1 60:14 62:10 67:14 68:4,20 70:4 71:9 76:10,14,19 77:5 78:18,19,20 85:15 86:6 92:8 95:20 100:16 101:2 113:5 117:14 119:3 123:1,11,14 124:22 125:16 126:1 127:9,14 128:2,18 137:13 161:12 164:15 171:12 173:21 174:2 198:13 212:10 232:8 249:12 255:19 259:9 260:5 269:13 271:15 282:7 284:5 285:6,18 286:18 287:20 297:4,5,13 302:5,7,14,22 303:2,6,11,12,19 304:2 306:2,12 351:5

primate 106:6,20

prime 135:7 139:11 268:1

prime/boost 139:5 153:8 160:16

primed 139:12

priming 139:15 142:20

principle 135:9

prior 2:19 5:21 20:22 58:21 151:10 173:22 208:1 210:2 266:1 311:13 314:8

priorities 145:21 363:8 364:20

Prioritization 5:4

prioritized 358:18

priority 188:17 189:2 235:8 359:3,17

private 272:16 349:13

probability 209:22

probably 48:21 50:7 54:8 57:18 58:12 59:21 66:9 67:19 81:18 89:5 96:2 101:13 115:8 165:6 196:10 199:2 211:7 221:18 229:21 248:4 261:1,21 264:18 266:7 268:16,18 271:15 273:17 280:15 288:3 301:19 302:2 315:1 316:5 342:13 343:6,9 349:3 351:4 360:6

probe 103:8

problem 14:4 55:13 59:15 90:21 116:21 165:4 171:9 241:8 262:7 330:5

problems 15:4 56:10 62:15 102:3 172:3 213:21

procedures 192:5 276:13

proceed 207:10

proceedings 366:5,8

process 73:14 126:15 166:7 194:17 244:3 246:12 247:6 249:18 252:13,14,15 253:3,15 255:21 283:17 344:9

processes 249:17

produce 159:22 174:4 231:1 254:13

produced 135:9 138:8 141:10 310:4

producing 211:15 221:11

product 177:6 178:18 179:8 181:19 187:9 221:17 222:8 253:18 312:13 314:11 356:22 363:13

production 83:16 165:11

productive 200:11

products 154:15 162:18 181:20 182:19 185:11 221:16 320:8

product's 181:18

professional 246:22 254:21

professionals 204:11 348:21

Professor 118:22 174:7

profile 209:9,12

profound 22:14 52:19

progenitor 227:21

progeny 211:16

prognosis 47:12,13

prognostic 47:15

program 4:4 5:11 11:3,4,5 114:19 117:7 202:21 205:10,12,15 241:4,11 263:19 270:4 272:14 294:6 296:3 301:2,17 302:13 309:16 318:1 323:2 324:1,3 328:9 336:14,21 338:5,7,15 341:9,10 342:8 345:11

programmatic 202:20 328:7

programs 247:2 311:3 322:3 348:16

progressive 21:19 80:3

progressively 41:9

prohibition 309:10

project 57:2

projects 224:16

proliferation 130:6 133:18

prolonged 212:6,8

prominent 97:16 220:11 229:9

promise 201:6
promising 96:20 310:4 317:19
promote 350:1
promoted 325:18
prone 75:6
proof 106:19 229:19
proof-of-concept 210:2 217:2 221:22
proper 215:19
properly 26:15 70:19 71:7 172:5 226:1 293:14
property 140:12
prophylactic 219:12 238:22 239:1
proportion 76:13 78:7 85:15 282:6 283:15 329:14 358:3
proportional 290:15
proportions 347:5
proposal 107:5 208:3
propose 219:16 222:22 228:8
proposed 132:15,18,22 291:15
proposition 291:5
ProQuad 186:6
Pros 350:2
prospective 258:12 259:20
prospects 308:8
protect 93:6 150:18 171:1 208:17 220:4 230:10 275:2 322:16,22 332:8 343:1
protected 59:4 67:16 142:14 150:20 159:9 180:21 181:1 202:9 220:17 268:1 269:21 270:13 271:6 287:16 297:3 299:16,22
protecting 151:11 227:18 275:4 292:4
protection 2:12,13 5:21 8:8,9 86:3,12,17 87:13 92:1 94:14 98:5 129:4 134:17 136:12,14 141:22 143:2,5 144:12 150:14 152:8,9,11,21,22 154:19 155:19 159:6 166:16 170:13,18,19 172:12 179:2 180:11,14,17,20 182:1 189:13 194:10 208:10 209:15 210:14 218:15 220:2 223:4 225:14,18 227:13 228:3,8 230:6 232:10 233:1,4,18,22 267:3,7,11,15 270:18 274:16,19,20 295:13 296:11 297:5 298:11 299:14 300:13,16,17,18 301:11 302:16,19,20 304:4,14 305:4 323:6,8 342:3 355:12 362:12,21,22
protective 21:7 53:7 58:1,11 65:11 117:12 142:11 151:15 154:6 157:1,4,5 158:2 170:12 172:15 209:9 215:13 218:10 228:5 272:22
protein 63:1 95:11 138:21 139:22 141:13,15 215:11,12,15,21 220:11,15 230:6 290:11
protein-based 221:2
proteins 70:20 106:13 112:20 141:15 142:21 161:7 162:19 196:14 211:13 226:19 227:12
prove 99:3
proven 281:6 291:11
provide 10:7 28:10 86:3 152:21 178:19 204:10 244:20 266:17 291:18 308:12 323:8 325:5
provided 117:11 176:9 192:13 315:20 319:17 320:22 324:4
provider 327:20 334:14,17,19,22
providers 328:2 349:13
provides 24:14 172:11 188:12
providing 88:3 323:6 349:13
provocative 161:5 354:18
proximately 311:20
prudently 177:4
psychomotor 197:10
public 8:2 202:22 205:7 207:18 209:3 210:20 233:7 234:21 242:11,13 251:11 295:9 341:11 351:17 354:11 358:20 359:6 361:19 362:20 364:4 366:1,20
public/private 204:2 287:12
publication 114:8 362:2 363:6
publications 248:19
public-funded 349:14
publicly 207:3
publish 62:12 343:10

published 5:14 48:10 59:17 93:19 100:18 101:10 103:17 113:6 114:10 118:3 168:21 171:18 196:22 207:2 219:13 249:9 250:18,19 253:13 254:17,20 259:19 265:10 275:14 295:20 311:6 320:21 327:1 363:12

publishes 254:12

pull 278:12

pulled 114:16 310:10

pulling 243:15

pup 157:12,16 159:22

pups 156:13 159:9

pure 177:4

purely 191:16

purified 141:11 215:11

purity 177:9

purpose 117:8 181:17 360:14

purposefully 238:20

purposes 84:1 123:7 203:13

pursue 317:18 355:3 361:20

pursued 280:17,18

pursuing 319:13

push 168:11

putative 225:18

putting 11:5 12:10 275:18

Q

QS21 138:3 167:17,21,22

QS-21 206:21

qualified 57:18

qualify 235:18 237:2,13

qualitative 81:4

qualitatively 79:8

quality 192:14,16 253:3

quality-adjusted 5:8

quantify 145:14

quantity 174:11 180:16 287:2

quarter 283:20

quartile 293:8

quasi-species 108:13

question 6:19 33:4,15,22 35:18 54:11,22 56:7 57:10,19 58:16 59:6 64:21 65:3,21 66:10 68:12,22 74:11 81:1 86:4 101:22 102:10,12,20 103:7 144:9 145:18 155:6 164:10 165:12 169:13 174:6 199:19 208:11 209:8,10 210:10 213:12 225:9 226:7 229:7 239:3,10 256:19 257:14 259:5 262:3 264:19 267:3 271:7 272:3 277:10 288:17 294:14 303:17 306:19 307:9 318:12 319:11 332:19,20 337:22 338:2,3,8,9,13 339:14,18 342:6 344:6 347:15 348:8 357:5

question-and 321:10

question-and-answer 293:19 306:17

questions 5:18 6:2 11:21,22 12:2 29:2,8,10 49:7,8 51:6,11 54:2 66:11,17 89:19 99:15 149:21 162:14 164:3 175:18 190:2 198:20 204:4,14 219:14 223:17 224:3,4,5,9,18,19 225:1 232:18 246:20 256:13,15 273:20 287:9 292:9 296:7 305:2,13 306:16 315:12 318:5 336:12,13 339:12 341:1 348:13 349:8 356:2 360:12

quick 242:10 357:3

quickly 104:22 113:1 205:16 242:19,22

quietly 321:22

quite 59:10 61:16 63:3 65:13 79:5 85:7 87:22 88:13 92:3 115:6 118:10 122:22 140:9 152:7 157:1,15 175:12 197:3 208:16 224:15 231:5,6,13 235:15 236:18 273:11 279:8,10 280:17 281:4 284:20 290:17 316:12 326:13 329:13 347:5,10 353:16 354:20

quote 98:21 105:19 153:11,15 272:13 273:13 310:10 314:5 343:18

quotes 289:5

R

RA27/3 7:20

rabies 139:13 221:4

race 18:15 32:19 33:3 200:3

racial 17:15 18:18 27:21 32:9,14

Radim 42:18

RAE1 154:12,16

Rafael 34:14 164:5

Rafaela 3:9 214:22

Rafi 97:9
Rafiki 273:10,14
Rafitopes 97:9
raised 239:3 240:10
raising 6:7 73:21 338:9
Raj 148:14
Ralphs 347:20
randomization 126:5
randomized 121:5 123:17 124:6 127:9 178:9 193:22 252:4
range 14:19,20 29:19 68:6 183:13 201:4 205:20 226:11 267:9 300:15 324:8 329:14
ranges 38:16 42:3,6 47:21 227:17 255:13
ranging 201:4
ranking 252:16
ranks 53:15
rapid 342:10
rapidly 341:13
Rapp 152:18,22
rare 195:18
rat 145:7 146:17 149:17
rate 13:21 15:8 21:21 25:15 35:6,7 43:8,13,15 52:13 86:6 100:12,19 104:22 105:13,15,17,22 113:10,18 120:20 126:4 127:16,18 134:12 149:12 170:20 171:2 183:8 184:9 259:2 260:1,20 261:6 284:21 288:8 307:15 342:2
rates 13:22 17:8 18:17 19:17,18 20:3 22:2,18 23:14 24:15 25:19,20 27:4,14,19 52:18 64:8,9 100:11 157:13 184:2 233:18 305:14 307:4 343:13 345:2
rather 36:10 72:17 87:13 122:6 123:3 164:18 193:6 219:9 236:20 254:17 281:12 290:20 352:6
ratings 333:1
ratio 100:15 220:22
rationale 187:8 229:5 294:22
reach 87:1 126:10 197:14 208:2 301:4,8 330:22 331:2 348:5
reached 125:9
reaching 186:18
reaction 133:13,15 240:12 241:6 361:7
reactivate 165:16 185:18 186:7 283:16
reactivated 101:14 283:8
reactivates 63:19
reactivation 63:14,15 69:12 70:6 76:11 77:21 78:8 101:4 102:11 164:7,9,12,17 165:1,10,15,22 166:2,6 168:17 218:4 259:9 283:9 296:22 297:6,15 298:12
reactivations 102:1 282:8
reactivities 105:3
reactivity 104:8 111:15
readily 112:16 166:9 342:16
reading 69:9 77:12 255:22 256:2
read-outs 218:7
ready 221:12 228:14 256:1
ready-to-use 120:3
reagents 103:9
real 46:15,17 48:4,7,12 83:7 92:18 121:4 193:5 243:11 256:1 293:13 345:9 347:7,12 356:12 363:8 364:18
realistic 266:3 267:14,16 285:22 287:6
realities 85:10
reality 87:6 187:12 283:21 285:21
realized 144:15 191:6,14 208:6
realizing 105:12
really 4:9,10 5:18 6:21 7:12,22 10:14,17,20 30:15 32:11 33:5,8,22 36:3,14 58:3,4,22 63:22 64:12,19 65:20 66:5 67:17 68:10,12,17,18 71:9 72:14 75:11,21 77:9,13,20 80:14,16,17 81:5,19 82:15 85:18 87:1,3 89:19,20 90:16 91:10 92:5,6,17 93:7 95:9 101:22 102:21 105:22 109:1,11,20 112:5 113:5 114:5 115:16 117:19 121:18 123:10 129:22 137:14 144:5 146:14 153:21 155:8 156:9 161:6 163:6 165:9 166:10 176:10,17 177:14 185:2 203:12 204:15 205:13 206:11,14 207:13 208:2

209:8,22 213:18,19 219:13 224:4,17,19,21 236:4,7,8 237:8 240:4 247:3,20 253:8 255:11 266:3 267:12 268:14 269:7 270:19 275:1 276:5 281:4 292:11,20 305:19 312:7 315:11 317:22 319:13 320:12 322:7 324:7 327:13 332:4,5 346:5,14 347:12 351:8,11 352:8,21 354:21 358:13,14 359:17 360:17 363:7 364:22

realm 5:18

real-time 48:17,18,22

real-world 282:2

reason 29:19 37:20 39:16 44:21 56:13 68:11 83:2 92:17 101:22 104:18 269:7 320:3,15 335:2 341:2,8

reasonable 73:5 87:22 90:4 126:17 187:17 234:3 236:18 273:16 284:20 288:8 291:12 354:11

reasonably 178:22 179:7 180:4,7 182:2 199:20 230:16 237:16

reasons 86:16 169:11 177:19 201:10 233:7

reassuring 312:7

recall 262:19

recapitulate 149:22

receive 121:1 122:14 127:10 205:8 262:3 266:2 321:22 338:1 350:14

received 1:16 93:20 106:15 120:11,14 134:8,15 140:16 337:12,19

receives 266:13

receiving 137:3

recent 24:13 42:2,5 52:7 84:7 93:1 97:3 108:15 145:1 179:13 180:1 183:20 202:1 225:17 318:22

recently 91:21 92:14 100:20 107:2,12 113:14 114:10 151:3,20 154:8 168:21 179:20 185:4 186:4 207:2 217:13 221:4 331:10

receptor 154:12 317:6

receptor-driven 94:5

receptors 95:7,10

recipient 137:12,21 198:7,12 241:12 313:15 323:10 360:18

recipients 4:18 134:7,15 137:9 140:16 142:13,15,20 143:10 258:13

recognition 66:1 92:16

recognize 50:16,20 55:21

recognized 5:1 7:6 79:19 84:17

recombinant 112:8 132:11 135:8 148:5,12,17,20 152:17,19 154:10 206:19 215:11 220:3 322:11

recombinants 132:9 135:4,5,10

recommend 49:16 204:9 240:15 335:1 351:4 352:12,18 353:10 360:21

recommendation 3:12 197:6 204:20 206:5 243:20 249:4 250:3 282:19 318:8 328:21 331:20 334:15,18 337:3,6 351:5 352:3 353:19 359:5

recommendations 197:2 205:3 239:4 244:6 245:2,5,14,15,20 247:12 248:21 249:2,9,15 250:7,9,12,14,18 251:6,10,13,16,18 252:1 253:10 254:4,19 291:14 318:14,15 320:13 326:3 335:14 337:5 352:14 364:15

recommended 196:19 241:2,19 251:2 255:17,18 275:20 308:16 313:22 322:16 325:22 329:15 330:15 333:16,17,18,20 336:2 338:18,19 339:2,5,8 353:13

recommending 245:16 329:11,15 333:3

recommends 334:20

record 363:13,21 366:7

recording 366:5

recovered 104:9 106:13

recovery 93:21

recruit 238:19

recruited 124:19

recurrence 101:5,6 102:10

recurrent 76:15 93:9

red 25:12 140:21 245:18 299:5,7

300:6,7,14 301:20

Reddehase 151:13

reduce 40:5 142:19 148:20 164:8,13 201:3 208:4 271:16 272:5,6 280:2 286:13 287:18 303:10

reduced 41:20 69:3 134:13 141:1 143:10 220:18 296:3 366:6

reduces 287:2

reducing 121:16 204:13 220:5 279:20 288:5 305:9

reduction 118:16 120:19 125:1 127:20 134:20 141:6 144:13 157:18,22 158:17 159:7 160:20 162:5,7 194:2 267:5 284:18 297:16 299:16 300:1,7,10,15 301:9,13,22 302:13 303:13 304:7 306:4

reductions 153:2 300:22 301:5,16,19

reexposure 69:5

reexpressing 130:9 **refer** 177:16

reference 37:10 42:10 120:8,9 160:11 224:10 248:12 309:14

referenced 161:16 311:8 338:3

referral 115:6,8,15 171:16,22 172:1

referrals 114:21

referred 114:19 115:10 125:6 205:20

refine 148:11

refining 361:11

reflect 33:5 145:17 150:15,22 151:9 153:11

reflected 154:22

reflecting 41:9

reflection 25:11 153:22 155:5

reflective 38:13

reform 328:10

regard 65:9 73:10 81:22 140:20 310:21 313:7 314:3 315:14 316:18 357:15,20

regarding 6:8 8:8,10 84:8 164:6 174:7 185:13,19 319:15

regardless 209:1

regimen 135:21

regimens 139:5 214:16

region 135:7 146:22 147:1 152:7

registration 192:10 193:11

registries 312:3 348:17

registry 262:5,10,22 263:4

regulate 95:13

regulating 95:10

regulation 94:5 357:14

regulations 74:18 176:8 177:1 179:9,22 180:2 246:2 308:21 312:12 320:17

regulator 197:3

regulators 3:2 9:3 198:17 208:12 224:4,5,22 235:15

regulatory 3:4,5 155:12 174:22 175:4,14 176:4,6,7,8,14,20 177:15 178:2 180:5 188:7 189:2,5 190:17 194:14 198:18 199:1,4 201:20 204:8 213:12 235:2 308:13,15 309:10 310:15,19 313:8,20 316:16

reinfect 102:18 112:8

reinfected 103:20 112:16,20 149:10 171:6 288:1

reinfection 24:11 35:18 52:14 53:5 57:16 65:5 70:6 71:22 76:11,16 77:4 78:5,9 102:14 104:11 105:1,5,11,13 106:5,19,21 108:16,19,21 112:13,15 137:17 149:11 161:18 163:2 164:13,15 165:13,14 166:3 170:12,20 171:1 198:14 218:4 259:9 297:7 306:9 343:1

re-infection 101:4

reinfections 33:11 52:8 78:4 100:8 102:1 103:8,16 282:8,11 361:10

reinforce 203:2

reinforced 85:18

reiterating 72:5

rejection 134:20 316:22

relate 303:2

related 15:3,16 16:2 33:2,3 81:1 140:8 145:8 192:17 209:10 241:6 306:20 366:8

relates 8:15 12:16 305:3

relating 317:16

relation 26:18 43:2 191:20

240:14 313:14
relationship 97:11 191:15,16
relationships 145:2 290:16
relative 145:4 150:2 161:17 177:5 263:13 304:3 306:1,11 366:11
relatively 133:20 138:15 143:16 177:3 221:15 232:1 261:6 311:17 362:20
release 83:16 124:13 146:4
relevance 147:6 210:8
relevant 98:7 140:21 147:15 148:7 149:3 159:19 162:21 174:14 176:5 177:18 178:10 196:18 218:7 258:9 263:6
reliable 43:20 45:7 47:3 48:5
reliably 126:13
rely 189:6
remain 77:16 296:21
remained 27:4
remaining 8:16
remains 32:19 160:6 171:5 291:3
remark 123:2
remarkable 93:21
remarkably 92:15
remarks 356:21 361:5
remember 61:8 62:8,13 252:6 254:3 273:20,22 343:10
remind 87:18 124:21 145:10
reminder 123:4
reminiscing 77:1
remove 152:11
removed 148:22
renal 133:17 134:5
render 284:17
rendered 286:12
repeat 281:17
repeated 73:12,17 125:14
repeatedly 213:8
replace 319:14
replaced 111:6
replicate 325:5
replicated 158:11
replicating 133:3
replication 63:9 88:11 146:10,11,17 147:1,2 154:19 158:13 162:6
replicon 139:18 211:9,11
replicons 132:17 139:21
report 5:4,6,14,15 46:16 103:17 282:15,18 294:7
reported 1:11 23:15 36:12 42:17 59:16,19 85:17 119:4 121:22 122:3,6 125:2,10 161:2 263:4 333:9
reporting 1:12 193:15 262:14 268:19 272:1
reports 14:20
represent 202:14 246:16 279:11 285:12 298:16 303:22 304:9 312:1 320:8
representation 1:18 103:3
representative 10:22 28:5
representatives 246:18,22
reproduced 93:18
reproducible 157:16
reproductive 16:10 17:17 18:11 32:4 242:8 302:5 310:18,22 311:4 312:8 313:21 314:2 357:22
reprotox 192:22
Republican 98:1
require 166:10 231:22 265:13 272:15 312:13
required 124:20 179:10 181:6 236:10 267:4
requirement 180:5 209:17 235:2 337:18
requirements 234:16 325:11
requires 182:19 265:20 272:14
research 123:7 145:21 182:18 272:16 309:6,8 329:2
resided 24:17 27:15
resistance 147:21
resistant 147:20
resolved 359:3
respect 11:19 18:15 36:11 56:21 123:15 204:14
respond 296:7
response 65:3,18 92:12,16 95:4 97:6,12 110:22 112:14 118:1,7,9 128:18,22 131:4 138:6,15 142:22 154:18 173:11,14 180:16 181:5 207:6 208:10 209:10 215:20 228:9 230:9,22 231:7,11,15 272:21 323:7 335:9
responses 59:11 69:22 73:21 112:3 133:8 137:4 138:4,17 139:1 142:9,15,16,19 145:14 153:16,17

155:21 161:12 162:20 172:15 182:10 186:16,17,20,22 199:3 211:18,19 220:13

responsibilities 205:22 244:1 279:14

responsibility 272:18

responsible 52:9 247:1

rest 2:6 13:3 336:7

restored 147:1

restricted 291:7 360:9

restriction 101:8 146:22

result 39:22 42:12 54:17 100:17 127:17 134:6 139:16 141:10 142:5 147:14 153:7 169:15 174:13 175:5 177:7 297:13 306:7,12 334:7 341:11

resulted 158:10

resulting 101:1

results 38:2 39:20 40:6,8,10,11,13, 16,17,18,22 41:2 42:7,14,20,21 43:2 45:16,18 46:16 55:15,16,18 60:11,13 62:9 64:19 73:17 78:4 93:15 119:18 120:18 121:6 122:11,16 123:9 124:14 129:13 133:11 135:13 136:3 138:19 139:14 140:9 213:15,16,17 221:5 298:7 299:19 300:21 310:4 345:4 356:9

resume 365:4

resurgence 322:7 324:9

retain 153:19

retained 152:9

retardation 14:17 156:13

retina 84:18

retinitis 14:18 15:7 84:18

retrospect 213:6

retrospective 16:7 48:20 131:6

revaccination 189:14

reveal 52:22

Revello 2:18 36:9 37:9,15 58:10 61:1,7,12,16 97:1 116:20,22 117:3,5,10 128:12,15 174:7,13

reversed 308:20

reverses 97:14

revertent 97:8

review 29:7 97:1 114:13 149:19 171:18,20 176:17 188:17 189:2 244:3 248:1 290:2 311:2 319:18

reviewed 160:9 221:5

reviewing 113:15

RFLP 64:16

rhesus 106:8,9 139:8 145:4,5 149:18 160:8,12,14,21 161:7,11,17

RICHARD 3:9

Rick 140:18 219:2 229:2 261:10

rid 164:14 319:10

Riddell 91:3

right-hand 134:14 138:9,12

rightly 317:6

rise 37:17

risen 289:10

rises 17:22

risk 15:2 19:9 30:22 34:16,17 35:9 40:1 41:15,21 44:19 45:19 50:18 56:4 61:21 75:16 117:16,17 121:16 162:16 173:6 193:2,10 195:12 264:18 272:5,6 279:20 284:5,22 285:5,18 286:14 287:18 288:13 302:6,7 331:14,16 334:3 335:6 342:3 345:14 346:22

risk/benefit 195:21

risk-balanced 66:20

Risk-based 335:14

risk-factor-based 251:17

risking 286:6

risks 6:8 185:15 193:12,13 195:13 212:1 271:1 279:5,13 332:20

RNA 139:21

Robert 11:7

Roberts 3:20 189:21 308:3,6 318:11 319:7 357:5,12 358:6

robust 154:18 155:19

robustness 218:8

Rockville 1:7,10

role 2:13,17 16:5 20:7 45:1,4 69:13 91:11 112:4 117:20,22 121:14 131:10 150:2 151:13 155:18 158:21 160:5 162:5,6 180:12 185:6 209:15 210:19 216:16 227:6 244:19 260:15 268:11 269:13 271:19 272:22 273:1 305:3 306:9 327:12

roles 247:6,7

room 10:12

165:1,6 199:17 234:8 246:6 253:20 262:6 272:13 273:6 277:11,21 364:2

root 170:14

Ross 21:10 85:22 107:12 113:15

Rotarix 183:21 186:12

RotaTeq 183:21 186:12

rotavirus 183:21 275:20 324:4,15 325:1

rough 192:11

roughly 196:5 326:12

round 3:22 211:15 277:5

roundtable 3:7 9:12,21 51:3 190:6,8 276:20 315:17 317:14

route 304:19

routes 162:20

routine 264:22 265:2 267:18 296:8,15 298:7 299:13 325:22 326:7 337:3,6 350:14

routinely 315:20 322:16 326:4 331:19 336:2

Royal 149:8

RSV 341:19

rubella 7:4,5,6,11,16 36:18,20 61:14 196:20 202:11 232:12,13,14,22 266:11 273:22 274:1 280:6,8,11,21 281:1,2,6,9,10,18 288:13,18 291:22 323:11 331:10,13,14 332:5 335:7,11 341:6,13 342:17 345:10,11,12 353:7

rubella-like 352:20

rubella-negative 197:1

rule 177:18 289:6 321:2,4 357:15

rules 246:2 281:7 316:2

run 163:6 233:20 248:6 273:19

Russell 151:4

RV7 152:5

S

safe 4:12 177:3,10 200:18 204:18 226:15

safety 155:8 162:14 177:9 178:3 183:1,3,6,10,16,22 184:12,17 185:3 187:10 212:9 217:9 222:13 235:16 236:2,10,11 242:4 251:9 268:10,15 269:6 270:1 271:1 312:1,21 313:12,14,17 314:12,17 315:5,15,18 316:5,18,20 317:4 333:6 335:4 357:19 358:5

SAGE 252:10,13 253:13

saliva 19:12 33:17 45:21 48:3,13,16,18 79:10 82:5,16 83:13 85:21 107:21 286:5

salivary 154:20 159:21 160:21

Sally 3:8 167:10,13 173:8,16 206:7 210:22 243:3

sample 43:3,9,11 48:18,21 49:20 50:4 83:6

samples 43:1,5,7,8 46:18 48:15 83:12 305:11

sampling 83:5

San 2:18 126:20 221:6

Sanger 64:15

Sanofi 3:9 64:4 136:1,5 214:22 215:8

save 5:7 99:14

saw 11:11 109:7 115:7 173:12 230:18 323:3 325:20 359:10

scale 93:2 181:14 292:5

scandal 10:6

scenario 164:20,21 193:21 269:1 342:21 343:2

scenarios 265:6 295:5 306:10

scene 94:18

schedule 9:16 74:8 125:10 181:15 221:20 244:15,16 247:10,11 253:21 254:7,14,20 255:2,3,8,9,10,11,17 322:13,14,19 323:19 325:14,20 326:6

schedules 244:12 253:19 254:15

scheme 297:10

Schleiss 11:7 143:22 144:3,18 171:3 172:16,19 173:1 220:14 354:14

Schodel 35:20 63:6 68:22 233:6 351:10 354:2

school 325:11

schooling 35:6

schools 330:12 347:18

Schunemann 253:5

SCID/hu 228:13

science 176:9,11,13,17 224:7,11

scientific 8:1 12:8

66:17 77:16 87:11 89:19 90:17,20 187:5,8 194:18 195:4 203:6 209:9 215:3 224:4 316:17

scientifically 89:9

scientists 77:10

scope 205:9

scored 78:6

Scott 106:7 112:7

screen 24:15 45:7 80:7 84:5 115:8,10

screened 311:13

screening 15:11 26:4 28:9 29:21 48:17 50:7 53:18,19 68:8 114:17,18 115:20 246:14 263:19

sea 350:7

seamless 12:6

Sean 221:5 **search** 215:4 **season** 7:10 334:11

seasonal 179:15 333:15 334:10

season's 334:12

seats 10:17 168:10 277:6 278:4

second 9:2 16:2 38:7 39:5 40:6,14,18 41:19 43:11 46:2 49:16 54:8,9 71:8 74:15 123:21 126:3 133:14 169:10 202:9 217:7 246:15 249:4 252:10 253:3 254:9 269:20 280:13 295:17 296:12 305:19 356:16

secondary 45:1 125:20 241:16 249:13 255:19

second-dose 326:12

secondly 65:9 143:2 204:18 244:3 341:16

secretary 75:5 244:21 337:8

secreted 157:9

secretion 44:19

secretions 84:20 174:12

Section 203:19

sector 287:12

secure 199:17,20

security 199:19

seeing 144:12 257:19 289:18 347:16

seek 197:16 270:21

seeking 195:8

seem 66:9 67:14 79:5 91:10 112:13 130:20 131:4 150:9 283:22 285:22

seemed 152:8 166:16

seems 18:9 69:1,11 90:3 91:14 92:17 94:1 161:18 214:4 285:22 360:5

seen 14:22 15:20 16:13 18:1 19:16 20:15 25:9,21 35:1 86:1,5 87:17 88:2 91:8 93:19 109:8 113:14 116:2 137:4,16 191:15 215:18 216:9 228:4 231:8 257:10,12 300:5 309:1 322:14 326:6

segment 207:16

seizures 115:12

seldom 319:22

select 68:6 70:21 97:20

selected 14:21 16:18 68:11 221:22 293:12

selective 265:1,15 281:5

self-replicating 139:20 **sell** 165:21

semen 84:20

send 99:2

sending 99:6 346:17

sense 65:22 66:6 67:16 194:17 234:17 313:16 314:11

sensible 214:4

sensitive 36:19 46:19 47:19 79:10

sensitivity 37:1 41:14,20 42:1 44:10 47:20 48:10,12 82:18 83:9 345:4

sensorineural 12:22 14:15 15:5 21:14 22:1,3,11,14 26:7,10 80:4 160:2

sentence 258:13 280:16 289:2

separate 30:19 37:16 190:8

separately 310:20

separation 136:8

sequelae 4:19 14:4,12,14 15:13 21:8 28:7,16 30:13 113:11 115:10,15 160:2 185:20 216:7,12 282:13 302:8 316:10

sequence 83:22 104:10

sequenced 104:6 107:8

sequencing 64:15,18 85:6 108:8 169:18

sequential 316:1

sera 103:6,9 104:19,21 109:14,21 110:13,21 111:9,15,18,21 112:2 228:9

Sergio 100:18

series 76:22 113:15 151:18 153:4 171:21,22 221:19 323:3 324:3 326:16 328:4,17 329:3,4,6 330:2,12 349:16

serious 7:4 11:12 178:20 188:19

seriously 293:17

sero 209:1

seroconversion 20:3 40:19 44:1 50:20 105:2

seroconversions 55:4

seroconvert 52:12

seroconverted 55:14

seroepidemiology 222:15

seroimmune 20:22

serologic 49:11 70:20 71:11 103:8,21

serological 39:12,18 40:14 42:8 43:6 45:3,6,10 49:21 54:14,16,19 60:7 62:16 72:21 222:10

serologically 54:13

seronegative 38:1 45:2 55:8,9 56:13 57:8 71:11,16 86:12 116:12 133:6 134:7 135:12 137:4 139:1 142:12 160:14 172:14 197:1 198:9 208:17,22 220:5 222:21 258:12 260:1 264:21 265:1 266:16,20 280:14 281:15 284:9 286:3 290:21 332:2 343:4

seronegatives 265:15,20 290:19

seropositive 2:15 38:1 44:15 45:5 51:14,18 57:8,12 66:12 67:3,9 69:3 71:16,19 73:10 85:20 86:11,13 88:12 92:13 93:13 103:19 106:15 109:15 112:8 134:1,9,15,16 136:22 142:20 149:11 162:17 170:11 171:1 208:18,19,22 217:15 222:21 261:13,15 264:21 265:5,8 288:1,4,9 289:17 290:19,21 342:22

seropositives 89:5 135:11 153:14 166:6,10 290:6

seropositivity 17:18,21 18:11,14,20 19:1,6 27:16 36:20 292:17

seroprevalence 16:9,10,14,21 17:3,6,8,12,13,14,16,21,22 18:2,4,6,8,17 20:15 21:21 22:17 23:3,4 27:2,12 28:16,21 31:8,10 34:15 35:6,13,14 36:11,13,16,20 37:17,20 38:3 52:12,15,18 55:6 67:12 92:7 100:12 104:15 164:11 259:6,11 260:1,16,20 261:2,6,19,21 262:2 295:6 297:21 298:2,8,15 299:9 302:18 305:7,21 306:3,6 344:21 346:7,20

seroprevalences 16:16 18:12

seroprevalent 35:8 52:3 303:20

serostatus 41:1 269:22 290:18

serotest 265:19

serotesting 265:14 266:8

serum 43:1,3,4 73:6 104:19,20 120:8

serve 203:5,13,14 246:8 247:7 248:8

served 82:4

serves 120:9

service 1:17

services 1:9 350:14

session 2:2 3:2,10 9:2,4,6,8,9,12,18 11:18 12:12 70:17 86:4 93:17 144:1 163:7,11 174:19 175:19 189:22 210:11,12 225:10 243:15 277:7 306:17 321:11,19 359:22 364:17,21

sessions 8:20 9:22 182:8 189:9

sets 338:7

setting 20:1 58:2 94:12 123:12 201:15 216:5 222:2,6 225:22 238:18,22 275:22

settings 12:15 66:2 80:22 91:8 92:22 93:6 170:3 225:22

settle 74:7 108:4

seven 24:19 103:15 260:5

seventh 9:11

several 52:22 65:17 67:9 81:13 179:13 230:14 261:12 276:9 284:1 301:1 304:21 310:3 336:2

severe 4:18 21:9 22:13 52:19 67:19 80:1,4,9,12 83:1

142:5,6 195:16 267:10 323:9 334:4 335:10

severely 67:15 85:6 263:1 266:5 335:7

severity 44:20 68:3 134:12,17 195:13 306:9

Seward 3:21 243:14 256:12 258:1,7 276:19 277:6,12,16 278:2,9,12,15,18 292:8 308:2 318:13 321:14 340:22 343:19 346:10 349:10 353:3 356:10 361:8 362:12,18

sex 18:20 282:15

sexes 291:16

sexual 18:21 19:4,5,6,7 20:11 24:5,10 35:2,5 73:12 271:19 274:18

sexually 19:8 24:4 102:16 275:4 329:1

sexually-transmitted 328:20

Shanley 152:19

Shannon 21:10 107:12 113:15 114:11,15

share 31:5 163:22 200:12,19 203:20 215:6 279:14,22

shared 151:1 272:18 279:12

sharing 347:4

shed 19:12 69:10 79:16 80:19 305:16 345:18,20

shedding 19:20 69:12 79:7,9 81:3 82:1,5,16 83:13 84:19 160:21 185:15 186:9,10,13 345:14 358:9

Sheila 282:12

shell 363:2

she's 117:1 212:13 266:16,20 286:6 293:22 355:5

shift 363:1

shingles 165:21

shoe 59:9

short 5:9 29:4 133:20 199:11 333:11 362:22

shortage 97:22

shortcoming 156:4

shortcut 289:12

shorten 278:8

shortened 189:3

shorter 302:20

shortly 234:13

shot 321:22

shots 323:14 325:10

shout 168:9

showed 52:16 90:2 91:20,22 92:3 103:18 108:1 113:8 118:22 137:19 151:14 156:21 160:20 166:18,22 170:12 173:20 174:1 207:4 213:15 215:13 220:3,10 230:10,18 295:20 303:20

showing 108:19 111:18,19 112:7 114:4 136:8 145:2 146:3,8,10 156:18 231:5 300:21 325:14 334:13

shown 19:3,11 20:6 32:10 37:7 76:5 82:7 93:5 121:17 122:8 134:7 139:1 146:13 151:6 160:16 181:8 188:11 189:10 211:17 255:14 291:10,21 297:18 298:18,20 300:6 302:10 304:3 329:2

shows 7:22 100:21 108:10 111:21 130:13 133:7 138:19 141:3 183:15 244:10 255:3 261:3 281:13 296:18 298:14 300:7 302:13 324:6 353:20

sibling 286:15 287:5 288:14

siblings 20:13 288:16

sic 261:1 323:9 328:1 348:15

sicker 115:7

sidebar 86:2

sight 170:22

sign 4:7

signal 174:19

signature 126:19

significant 4:15 52:9 101:2 103:22 121:22 122:3 127:21 130:8,10 138:7 174:3 194:2 240:12 247:6 263:21 271:11 289:22 290:17,22 291:4

significantly 16:1 23:13 25:16,19 32:20 261:15 264:10,13

signs 80:6 93:22

silent 289:7

Simanek 290:7

similar 16:15 17:1 20:1 21:12,14 22:2 31:9 43:16 48:10 59:7 84:16 113:9,10 116:3 156:16 161:1 173:20 186:2 200:21 212:2 213:21 232:13,17 262:7

similarities 328:16

similarity 223:22

similarly 18:14 23:8 52:17 71:15

212:15 213:14 225:10,21

simple 221:15 255:7 322:20 344:8

simpler 350:19

simplification 192:13,16

simplistic 270:6,10

simplistically 270:6

simply 37:9 57:14 63:13 69:1 73:16 79:3 133:7 213:20 232:7 281:18 287:1 354:4

simultaneously 282:21 342:8

single 63:1 69:15 117:22 211:15 227:19 328:4 350:20

singular 174:14

sir 351:9

sit 9:18 163:19 190:7,10 277:4 321:22

site 88:16 95:20 133:13 160:18

sites 6:4 24:19 80:4

sitting 347:10

situation 158:1 169:5 229:21 343:14

situations 198:11 237:17

SIV 106:9

six 22:10 118:21 135:22 160:20 232:11 243:6 266:1 269:16 295:13 296:21 323:4

sixth 9:9

size 235:16,18 236:10 272:9 293:16 315:15

sizeable 184:6

sizes 183:3,7 184:2 236:2

skin 133:21

skip 133:10 195:22

slam 353:18

slice 355:7

slide 15:20 16:13 24:20 26:20 29:13 100:9 103:1,13 107:4 108:6 109:10 114:12 130:13 133:7,11 137:9 138:19 139:10 141:17,19 145:1 146:17 149:6 162:4,12 194:19 195:22 206:17 216:15 230:18 243:3 244:10 253:9 276:5 296:18 298:14 303:1 304:4 305:18 335:5 354:20

slides 26:17 81:13 100:5 131:21 132:6 144:12 173:20 174:8 191:7 207:12 213:15 219:4 243:15 253:17 276:8 293:22 299:10 301:3 322:6 334:13 336:6

slight 32:6

slightly 31:17 321:16 331:12

slope 326:15 327:22

slowly 41:9

small 83:8 114:1 115:15 238:12 274:2 311:18

smaller 195:10 325:3

smashed 103:1

smoking 291:1

social 279:17

social/racial 33:5

socializing 284:13

societal 171:5

society 246:22

sociodemographic 20:10 23:8

socioeconomic 16:11 17:9 18:21 32:19,22 33:1

software 298:6

solid 81:7 137:8 142:12,14 196:7 198:4 214:13 288:19

solution 72:10 120:3,6

solutions 329:5,9

solve 359:18

somebody 63:18 89:10 199:21 240:10 242:15 245:10 261:9 348:19

somehow 95:11

someone 31:2,5 36:1 240:22 287:11 306:16 337:10 345:15

sometime 54:12 60:4,5

somewhat 79:17 188:19 274:13

somewhere 26:13 79:15,20 288:2 348:15

son 279:20

sooner 301:12,19

sophisticated 346:19

sorry 31:13 32:7 38:6 61:1,12 62:8 103:13 131:22 175:9,16 190:18 199:3 215:9 240:1 297:3 299:1 304:1

sort 54:4 63:10 67:13 69:9 73:13 75:16,19 76:12 94:4 100:13 103:1 110:11 145:17 171:21 229:16 234:7 252:13 255:21 259:18 262:1 263:8 264:5 265:1 266:10,11 270:5 330:20 349:12 354:15 356:21 360:11

sorts 91:8

SOT 198:1,4
sought 261:7
sounds 190:12 214:1 339:22 360:2
source 82:8 96:5 282:16
sources 27:18 33:18 76:10 106:21 169:1 181:2 205:7 284:19
South 25:9
Southern 158:8
sows 149:10
space 354:11
Spaete 146:8
sparse 28:8
spawned 93:2
speak 116:7 190:13 229:6 239:4 241:16 256:20
speaker 9:17 12:2,3 34:7 69:19 128:10,14 163:22 176:1 218:19 219:1 243:17 278:1,2,6 308:3
speakers 9:16 10:2 11:20 12:5 51:4 57:17 74:16,21 185:8 219:10 280:16 293:20 306:17 319:2
speaking 55:7 293:3 342:3
speaks 230:14 241:18 311:20
special 36:9 188:7 202:6 336:12 357:10
species 145:11,18 146:6,21 147:4 150:13
specific 39:15 95:10 123:3 145:11 177:6 203:3 204:14 223:17 251:9 261:2 308:9 320:3 328:14
specifically 225:11 309:7,18 313:5 315:11 320:7 333:20,21
specificities 52:6
specificity 42:4 46:20 47:21 48:9,11 82:19 104:4 131:12 145:18 146:6 147:4 178:11 201:11
specifics 257:20
specifies 237:5
specimen 49:11,13,16 50:8
specimens 49:14,17
Spector 31:7,14,18 72:4 129:5 153:5 166:13 167:12,19 232:4 292:10 293:5 347:15
spectrum 69:20 79:18 316:9 317:11
speculate 63:7 105:17
speculation 105:20
speeds 283:17
spend 269:6
spent 54:18
spina 15:20 53:17
spite 158:14 311:15
spoke 163:21
spoken 308:7
sponsored 123:18 187:3
sponsors 9:10 10:21 317:18
spontaneous 193:16 340:12 342:1
spontaneously 146:20
spot 85:22 129:19 130:4
spots 48:22 79:5
spread 72:11 83:16 90:2 154:6 191:21 264:11
spreading 129:7 345:14
spreadsheet 294:8
spreadsheet's 294:14
stable 27:5
staff 248:6 336:5
stage 56:19 189:17 194:15 239:17 247:13,16 328:17 331:13
stages 203:5
Stagno 100:18
stakeholders 198:22 309:2
Stan 54:5 91:3,20 166:14 170:12 175:7 200:7 206:13 219:4 232:5,12 239:15,21 325:2 340:22
stance 349:11
stand 6:21 175:22 176:19
standard 48:1 80:14,15,18 82:11 120:8,9 216:18 279:4 280:1 291:2 332:6
standardization 6:6 198:16 216:9 250:5
standardize 62:4 249:17
standardized 129:12 218:7,13
standards 177:8
standing 199:22 332:3
standpoint 68:15 308:13
stands 361:17
Stanford 32:9
Stanley 2:20 7:21 11:7 49:9 56:17 131:16 143:20 167:15 173:12 174:20 199:16 227:2 235:9,22 258:14
Stanley's 102:15

145:22 342:6
Stan's 342:20
start 30:18 51:10 64:17 70:16 71:10 76:1,4 100:4 163:11 175:8 191:7 198:21 200:5 212:18 214:5 225:2 258:9 262:10 277:3 283:13,20 285:3 296:2 301:6,16 308:14 313:21 314:19,20 321:21 324:17 327:9 350:8,10
started 11:11 102:20 112:19 113:5 125:12 126:5,18 143:14 263:10 277:7 301:2
starting 12:2 57:2 280:21 329:5 342:8 344:9 351:20
starts 49:12
state 8:14 86:10 114:22 231:12 300:22 301:4 363:17 366:21
stated 86:9 229:9 289:3
statement 171:8 235:16 289:7,11 290:2
statements 175:3 236:1 243:9
states 4:15 7:11 13:9,17 18:13 23:15 38:9 86:8 114:22 124:8 242:13 245:1,5,17,21 247:4 280:12,18,21 282:5 293:15 294:20 296:9 303:5 322:1,3 323:22 333:19 348:9
static 355:14
statistical 316:3
statistically 103:22
statisticians 127:22
statistics 263:3,4
statue 237:4
status 18:21 26:16 32:19 33:1 54:14 85:1,2 124:11 209:2 312:5,11
statute 337:18
statutory 338:11
stay 74:8 349:6 365:2
staying 281:3
STD 19:2 28:3
steadily 17:22
steady 231:11 300:22 301:4
steady-state 231:16
steering 124:12
stem 140:15 142:20 214:14 227:21,22 228:2
step 91:17 95:7,11 146:19 148:22 265:20 316:15
Stephanie 11:2
steps 9:13 95:21 361:15 364:19
sterilizing 153:2,7 155:18 159:5,10 161:3 166:19 286:12
stimulate 220:7
stimulated 82:16
stimulating 220:12
stimulation 140:6
stimulator 139:4
Stipan 151:3 154:8
stochastic 73:14
stone 198:19
stop 56:14 70:8 74:1,9 75:10 90:15 115:22 116:16 217:4 258:22 327:8,13,14
stopper 98:20
storage 249:13
story 71:18 93:1
straightforward 221:16
strain 6:1 7:20 52:8 64:20 78:6 83:19 84:6,19,20,21 98:19 108:17 133:6 163:1 169:11,15,22 170:8 228:16,17
strains 20:1,5 57:12 64:7,11 69:13 78:1,5 84:9,13,17 168:20 169:6,7,9,20,21 170:7
strain-specific 110:19
Strategic 252:11
strategies 3:19 81:9 94:16 157:20 158:5 162:22 265:13 270:3 271:5 308:5 317:19
strategy 155:21 157:13 173:10,15 196:11 221:14 265:2,16 269:13,22 295:16 309:19 325:12 352:20 360:10 361:17
stratified 293:14
strength 360:21
strengths 150:6 251:21
strep 341:19
stress 77:8 232:22
strict 126:7 246:14
strike 360:1
striking 93:15 137:15 153:7
stringent 246:2
strip 82:7
strong 86:17 92:12 106:19 111:21 138:22 139:2 141:18 142:6 204:20 291:17 292:18 334:14 343:13 349:11
stronger 186:20
strongest 33:9

252:4,16

strongly 290:18 324:16 333:16 352:19

struck 232:9

structural 94:21 211:12

structure 244:2 246:4 296:19 297:9 344:14

structured 293:14

structures 246:5

Stu 170:9

Stuart 20:6 65:1,2 66:3 116:14 135:11 171:3 172:6 242:9 293:22 294:2 343:17 347:9

students 260:22

studied 17:4 62:9 65:13 70:10 83:4 88:12 92:6 96:21 97:18 99:1 160:3 221:2 233:12 334:5

studies 2:11 16:4,15,19 19:2,10,16 22:15 23:10 30:14 35:16 38:8,9 47:14 51:17 65:4 67:1 68:8,21 72:22 75:20 76:1,18 77:2 82:6 84:22 86:4 87:12 89:2 90:14,16 91:21 93:1,3 94:8 96:21 99:9 102:15 106:6 116:11,15 123:12,15 131:6,7,8,10 134:22 145:6 146:7 149:17 150:16,20 151:17 152:16 155:14 159:18 160:15,16 161:4 181:10,19 183:5 184:6,8,13,14 189:8 192:19 202:2 203:7,8,17 205:20 210:3,5,19,21 215:14 222:12 224:11,12 227:4 230:20 232:20 234:14 242:1 249:22 250:1 252:8 259:16 260:12 276:9 287:10,14 308:22 309:3,10 311:4,6 314:4,6,8 317:20 319:19 320:1,2,19,20,21 330:18 346:16 352:5 357:6 358:9 364:10

studying 84:10 116:21 223:3 227:10

stumble 273:5

Subclinical 291:9

subcutaneous 133:12

subgroups 182:11,13

subject 236:5

subjective 188:19

subjects 65:14,17 89:12 183:7 207:8 222:14 231:10 236:4 307:15 311:11 314:14

submission 228:14

submit 192:12 276:17

submitted 189:3 194:21 262:22

submolar 101:19

subpopulation 181:14

subpopulations 27:7 182:6,7,15

subsequent 14:3 47:9 49:14 78:3 101:12 225:10 258:17 267:20 332:9

subsequently 103:10 136:19 226:4 281:10

subset 285:11

substantial 159:22 162:6 174:1 287:4 293:7,15

subtext 57:10

subtle 80:7 160:1 162:20

subunit 92:2 132:11 142:9 152:16 157:8 159:13 201:5 268:18 312:17 322:11

subunits 211:21

succeed 273:4

success 200:15 209:22

successful 110:14 180:20 203:9 219:8 265:12 330:10

successfully 112:11

suffer 323:1

suffice 267:7

sufficient 57:16 183:7 187:1 198:15 204:10,16 206:4 212:21 217:3 358:20 359:4

suggest 49:18 67:18 72:5 292:3 309:12 317:9

suggested 121:7 181:2 295:11 360:7

suggesting 109:7 112:14 113:11 166:8 228:22 363:10

suggestion 90:11

suggestions 364:15

suggests 67:9 85:7 186:19 306:1 339:20

Sullivan 221:5

summaries 187:6

summarize 8:14 24:12 51:17 132:6 189:4 244:7 251:21 270:6 356:22 364:18

summarized 5:14 149:6

summarizes

133:11 363:6
summarizing 154:14
summary 30:4 176:19 256:19 317:15 335:5 345:1
summer 221:6
superinfection 2:15 73:18 168:17
superinfections 100:9
superior 280:18 281:15
supernatant 102:8
supervision 366:6
supplement 271:5
support 6:13,16 45:3 105:21 176:10,20 189:11 204:17 208:13 218:8 224:7 228:7 247:11 262:11 295:7 309:2
supported 80:10
supporting 193:22
supports 54:7
suppose 117:6 194:8
supposed 121:18 144:14 279:3
suppressing 93:7
sure 11:14 30:11 34:9 36:3 58:4 63:21 64:10 68:10 70:11 72:16 74:10,12 93:18 117:11 183:18 190:22 198:6 210:10 235:11,12,19 238:5 240:21 281:21 335:10 340:7 348:22 362:16 363:9 364:22
surely 242:5
Suresh 11:6,17 12:7 58:16 102:21 103:10 113:20 114:11
Suresh's 103:17
surface 219:17
surgical 276:13
surprise 85:8
surprised 200:20
surprisingly 26:8
surrogate 83:5 178:21 179:2,5 180:3 188:22 189:12,16 194:10 214:6 218:8,14
surrogates 82:19
surveillance 78:16 91:1 210:18 262:18 272:1
survey 77:10 329:10 334:13
surveyed 229:16
surveying 97:21
susceptibility 147:22 302:4
susceptible 92:8,9 117:14 296:20
suspect 199:20 290:20
suspected 125:7
sustain 364:5
sustained 335:18 336:3 338:4
swab 82:9
swarm 108:13
Sweden 113:6
Sweet 151:19
Switch 176:1
Sylwester 220:10
symptomatic 14:13,21 21:12 22:7 25:5,7 26:9 30:16 33:18 47:6,14 55:1 56:4 113:10,16,18,21 114:4 115:1 263:2,16 264:1,13 282:13
symptomatics 115:3
symptoms 14:9 39:14,15 50:18 60:12 80:6 216:10
syndrome 7:6,11,15 15:19,20 53:17 195:19 310:1 331:14,15
system 107:6 169:14 211:14 240:11 250:10,11 262:18 268:19 272:1 289:13
systematically 81:14
systemic 133:15 160:17
systems 328:6

T

table 3:22 100:1,2 171:14,16 270:6 330:19 336:22 337:1,2,9,10,15,16 339:18 361:17
tables 250:19 251:20 254:8
tailor 226:15
taking 282:9,18 283:19
talk 11:22 12:17 16:9 38:19 58:22 100:8 101:18 126:8 131:2,22 145:5,9 174:22 184:14 189:22 231:4 239:17 243:18 274:5 292:19 293:21 310:19 313:14 316:16 318:16 321:12 326:20 331:4 343:5,9 353:4
talked 91:13 209:11 236:21 346:14 347:18
talking 12:22 31:18 38:20 57:20 84:15 129:13 144:7 165:2 202:7 258:4 302:1 304:16 316:6 321:18 330:1 337:20 341:21 351:1
talks 9:20 11:21

256:10 309:15

target 3:10 5:2 9:4 53:4 62:5 70:3 75:18 103:5,12 162:18 189:21 197:15 204:9 212:19 217:8 222:19 225:10 235:1,7 243:16 258:5,10,21 264:19 277:3 278:20 283:3 315:2 321:17

targeted 201:22 268:8 280:13 335:6

targeting 150:4 202:5 242:6

targets 95:2 97:21 108:18 148:7 150:7,10,12 160:7

task 144:7 248:18,21 279:1

task-oriented 248:10

Tatiana 3:18 308:2 351:15

Tatiana's 362:17

taught 144:21

tax 337:7

TB 221:3

T-cell 138:16 142:15 211:18 213:16 220:11 229:10,18

T-cells 207:6 209:15 220:16 221:11

Tdap 326:4,11 328:1 333:18

tease 290:15

technical 253:15

technically 203:18

technique 148:13

techniques 64:17 152:1

technology 147:9,18 154:2 273:6

teen 23:12 25:21

teenage 260:15

teenagers 260:15 261:8,11,13,21 298:18

teens 19:2 28:4 326:10 327:12

tegument 138:21 141:13 220:11

teleconference 248:2,3

temperature-sensitive 151:19 152:2

template 311:2

ten 22:10 85:13

tend 75:9 84:14 98:9 169:17,19

tenfold 93:11

ten-year 267:20

teratogenicity 317:7 332:21

term 4:20 310:8,15

terminations 281:5

terminology 77:18

terms 31:11 32:14 33:18 36:4 54:20 58:1 59:10 60:20 61:18 65:4 70:3 72:22 76:18 95:4 108:11 115:4 167:5 188:20 205:1 207:14 209:6 210:14 231:13 235:13 246:8 248:12 270:4 292:12 310:19 311:1 312:7 315:18 317:4 321:4 323:1 325:1,3 340:14 341:11 348:3

test 7:8 41:6,12,13,14,15,17,18 42:1,7 43:11 46:13 50:10,12,21 54:12,13 55:17,20 56:1,2,13 59:13,14,15 132:19 133:21 209:17 311:13 331:20

tested 48:7 55:14 132:13,22 133:6 134:5 135:10,19 137:1,6 141:16 228:10 290:9,10 305:12 331:19

testing 39:9 40:14,18 48:5,16,19 49:21 55:2,10 56:15 60:7,13 81:14 132:8,10,14,17,18 197:10 318:2 331:7

tests 7:13 42:8 45:1,4 46:21 49:22 132:20 135:11 140:14 182:22 197:11

tetanus 196:15

Texas 3:15 260:13,16 261:12 263:8

Thailand 225:17

Thalidomide 308:19

thank 12:8,9,10 29:1,6,10 30:3 38:18 39:1,2 49:1,4,6 50:22 53:9 54:1 73:22 88:3 99:10 111:4 116:16 117:5 124:16 129:20 131:14,19 143:18,20 144:3,4 163:3 173:16 190:1,4,16 199:5,7 200:8,12 206:5,7,9 210:21,22 211:2 214:20,21 215:1,2 218:21,22 219:1,5 223:4,5 243:12,21 256:18 273:17,18 274:5,7 277:8 278:22 292:7 306:13,14 321:6,9,14 336:6 339:10 340:6 346:9 356:9 365:4,8

thankfully 244:15

thanking 10:20

thanks 38:4,17 53:10 99:19 200:7 258:1

292:8 293:1 308:2 318:3 344:7

That'll 278:8

that's 29:1,7,21 30:9,15,20 33:7,8 34:2 35:18 38:11 50:6,22 53:22 63:1 71:13 73:4 74:13 75:4 78:20 79:11 83:2 84:2 87:11,22 91:6 92:14 94:18 96:5 97:1 99:16 105:13,19 106:18 107:1 112:11 122:20 123:16,22 124:1,7 125:2 126:20 127:13 129:11,18 147:15 148:22 149:14 155:6,11 157:15 160:4 161:13 162:2 165:19 167:14,19 171:2,13,17 172:5 175:12 180:7 182:11,18 183:4 184:12,13 188:11 212:6,17 213:10 214:20 215:20 220:20 221:19 223:15 225:8 226:9,22 227:1 230:7 234:6,7,12 237:9 238:22 241:14,21 242:12 243:8 245:17 249:1,10,11 251:12 255:6 256:8 257:8 265:10 266:11,22 270:13 281:12 285:17 287:5 305:12 307:7,21 311:17 312:7 318:17 319:11 322:18 325:8 331:19 337:15 339:10 341:12 342:17 343:16 344:6,13 346:3 348:7 351:13 352:4,8 354:3 355:17 357:21 361:19 364:21 365:6

themselves 64:5,7 74:10,21 284:14 285:3

theoretical 193:19

theoretically 164:16

theory 172:13

therapeutic 178:19 187:4

therapy 81:9 120:13 121:2,11 122:2 148:2 214:16 276:13

thereafter 366:6

therefore 42:9 126:16 239:11 246:1 280:4 284:7 298:16

there'll 247:13

there's 34:6 66:20 67:11,17 75:14 83:21 86:5 89:6 90:11 99:22 100:2 112:1,5 167:18 170:6 182:20 208:8,15 213:22 219:7 222:3 223:10,21 228:21 238:18 239:10 241:3 242:13 245:16 246:14 248:22 250:2 265:12 266:9,10 267:1,12 269:13,21 270:1 271:11 289:18 292:1,18 306:21,22 307:3,13 309:2,9 314:2 316:11 318:14,20 323:1,10 328:6 329:13 332:14 333:14 335:21 336:1,22 337:22 338:2,3 339:18 340:21 341:2 349:8 350:13 362:13

they'll 254:17 345:17,20 359:9 363:1

they're 30:12 33:10 57:13,19 98:6 115:6 141:11 170:5,8 176:1 177:3,4 200:20 247:6 248:10,11 270:22 284:10,13 288:9 309:13 320:16 325:7 337:21 345:13 347:22 348:1 352:17 361:12

they've 19:19 35:1 106:8,10

third 9:3 40:10 54:15,22 124:4 136:18 138:10 157:11 266:10 286:21 296:13

thirties 268:6

thirty 13:16

thoughts 257:5

thousand 13:16 87:22 183:12 259:22 290:9

thousands 13:6 196:19

three-dose 135:21 221:19 328:17 329:3

three-week 228:18

threshold 144:13 159:8 231:15

throat 133:16

throughout 7:22 96:18 248:8

throw 77:12

thus 181:4 191:22 299:16 302:5 312:6

tight 9:16 10:5

Tim 107:1 108:6,12

timelines 189:2

timer 98:13 99:22 100:2 258:7

Tim's 108:6

tired 365:1

titer 63:19 109:20 110:4

titers 63:15 109:7 111:19 139:16 157:15

158:15,16 342:22
title 117:7 321:12,15
TIV 318:17
Tiziana 2:9 38:19 49:6,10 50:22 51:4 54:18 58:16 60:16 61:22 63:12 122:17 124:16 126:8
TLR4 138:3
today 4:10 6:18 8:20 77:17 124:14 150:1 198:18 200:9 201:10,12 206:15 216:2 251:3 285:15 294:16 333:13 355:5
toddler 272:11 286:9
toddlers 19:19 134:3 135:21 233:14,22 234:18 280:13 281:14,20 282:21 283:18 284:16 285:9,16 287:2,14 288:11 296:5 342:9 345:19
Toledo 135:6,7
Toledo-Towne 185:9
tolerance 316:22 317:12
tolerated 135:20 221:9
Tom 76:22 82:13 85:5
tomorrow 6:18 9:6 170:17 210:12 356:22 362:15 365:1,5
tonight 277:8
tool 162:9
tools 205:19
top 137:9 140:4 248:18 255:14 293:8
topes 97:10
topic 39:8 46:2 47:17 192:3
topics 8:12 39:3
total 92:15 285:12 304:10
touched 113:2
tough 257:8 349:17,18
toward 144:9 151:11
towards 179:19 188:22
Towne 65:4,7,12 66:3 96:7 103:3 132:8 133:6,12 135:6 139:7,8,16
Towne-Toledo 132:9 153:13
toxicity 311:4 313:21 314:6
toxicology 192:21
toxoid 322:11
toys 19:22
track 188:17,20 363:18
traditional 61:14 64:15 177:17 178:7,16 179:3,6 180:13
traditionally 332:13 333:14
tragedy 308:19
transcriber 74:12
transcribing 1:16
transcript 1:15 74:13 153:12 363:20
transcription 366:7
transcriptionist 363:18
transfer 91:2 129:8 137:20,21 156:3 157:2,3
transferred 170:4 305:3
transfers 172:12
transiently 97:6
transitions 12:5
translate 304:5
translates 281:21
translating 303:7
transmission 3:18 19:13 34:16,18 35:2 44:20 54:6,9 55:1 58:1,8 60:17,18 61:22 66:1,18 72:22 76:20 78:3,14,18 79:2 80:9 81:2 82:3,15 85:19 86:5,7 87:15 88:14,21 89:4,6,11,16,18 92:21 93:14 98:5 99:5 105:17 106:1 108:21 120:20 121:16 126:4,15 127:16,18 143:9 149:12 170:15 174:15 185:16 209:16 213:21 218:17 220:1 227:5 233:14 234:18 286:17 293:21 298:3 343:12 345:7 347:1 352:7 353:14 356:15 358:9 360:15
transmit 35:5 50:18 66:13 72:2 93:9 130:7,22 243:4 286:14,19 287:16 305:17
transmitted 19:8 24:4 53:1 59:1 102:16 108:3 118:20 329:2
transmitter 52:11 118:9 129:16 130:3,15,20
transmitters 58:18
transmitting 20:7 41:16,21 56:20 59:4 67:10 117:16 229:15 287:18 296:5
transparency 249:19
transplacental 76:19 79:2 82:3,15 87:15 89:6,15,18 93:14 99:5 219:22
transplant 4:18 9:8 81:7,8 83:10

92:2,3,10 94:7 102:18 133:17 134:6 137:7,8 140:17 142:13,14 143:10 150:3 196:4,5,6,7 197:21 198:10 212:16 214:19 229:21 237:14 238:4,6,7,17 243:17 258:12 292:1

transplantation 134:8 214:8

transplantations 257:13

transplants 93:6 214:14,19 288:19,20

treat 336:12

treated 119:12,19,20 120:21 125:19

treatment 125:12 126:5 127:10 128:6 174:10 216:17 227:7

treatments 128:3 178:20

tremendous 104:13 108:10 344:4

tremendously 161:16

trend 16:16

trends 262:17

trial 6:3 9:7,9 68:15 71:10,14 81:21 87:14 96:17 132:9 134:2 140:14 144:10 161:2 166:1 180:20 187:13 201:15 203:11 204:6 225:17,20,21 226:1 238:8 275:14 306:22 307:3,8,12,13,14 ,18 311:19 315:2 316:8 318:2

trials 2:19 6:13,17 12:16 68:20 75:3 131:18 132:12 142:8 143:6,9 178:9 181:5 193:4,5 194:9 196:12 203:8,17 212:19 214:17 218:15 221:8 222:18 225:2,13 226:4 242:2 252:4 272:4,11 281:13 295:8 306:20 308:18 310:3 311:10,19 315:21 316:19 323:17,20 332:14

triangles 139:2

tricky 62:1 337:19

tried 171:21 173:1 340:10 342:7 345:1 354:22

trigger 215:15

trimester 54:8,10,15 55:1,18,19 62:11 126:3 157:11 196:10 227:5 269:20

trimesters 260:4

trivalent 333:21

trivial 15:16

trophoblast 227:20

trouble 293:10

troubling 354:15

true 28:11 37:17 60:4,6 117:13 171:3,8 197:21 241:14,21 287:1 289:7,11 291:7 319:12 366:7

truncated 157:9 207:1

try 30:19 39:18 72:14 78:12 109:19 110:16 112:7 144:19 147:6 152:1 156:2 158:4 190:19 249:16 259:14 262:16 282:22 330:8

trying 70:8 75:1 78:15 88:19 148:11 262:2 286:1 296:7 307:17

TS 151:21

tube 310:2

Tuesday 1:5

tuned 349:6

turn 148:1 174:20 363:15

turner 256:1

turns 351:18,19 361:3

tweaked 151:9

twelve 269:19

twenties 263:13

twenty 13:16 14:16

twentyfold 93:11

Twenty-two 43:14

twice 25:14 120:15

two-day 215:7

two-dose 328:1

two-thirds 124:19 286:18

type 73:3,20 111:22 113:13 125:4 180:16 238:20 338:11

types 95:18 107:19,20 214:13,19 216:10 221:16 252:4,6,8

type-specific 103:9 110:21 111:15 112:2

typewriting 366:6

typical 187:15 213:3

typically 86:9 157:20 183:5,9 184:12 284:5 324:20

U

U.S 2:6 3:4 7:20 10:21 13:2 16:13 17:2 18:2 53:19 76:17 81:16 124:4 176:4 184:22 188:4 194:8 297:20 302:11 303:9 304:16 313:3 318:7 325:11 335:19 345:17

U.S.-licensed

312:11
UAB 21:4,10 23:16
Uh-huh 73:8 237:19 275:10 339:11
UK 280:13 281:2,7 330:10
UL73 107:9,16
UL97 147:10,17 148:5
ULb 135:7
Ulie 104:13 111:4
Ulie's 116:1
Ulrich 147:8 168:3,4,14,15
ultimate 216:5
ultrasound 46:6,13 80:10 120:17
unaware 173:7
unbiased 15:13
uncertain 27:3 143:2 354:19
uncertainties 296:14,17 344:18
uncertainty 8:7 185:19
unclear 15:7
uncontrolled 89:1
uncovered 225:17
underestimate 271:13
underestimated 16:6 22:19 28:13
undergo 119:8 172:2 211:14
underlying 17:16 23:2 25:11 38:14 176:9,11,12,17
underscore 151:12
understand 55:19 56:3 57:22 66:11 68:13 75:2 87:10 89:9 90:13 91:12,16 97:12 106:2 152:2 169:11 218:16 227:5 241:7 249:18 295:2 305:8 306:10
understanding 6:11 66:7 77:11 88:20 89:16 176:12 218:3 240:22 241:1 271:8 296:15 306:8 348:1 356:12 361:13
understands 74:12
understated 220:10
understood 88:18 95:20 307:17 319:2 339:13 354:2
underway 179:11
underwent 119:17 127:12 250:16
undetectable 285:4
undetected 15:12
unequivocally 308:8
uneven 122:19
unfair 292:6
unfortunately 10:6 28:18 135:10 148:9 174:13 194:4 226:11 289:11
UNIDENTIFIED 219:3 223:12,14 225:5 277:19 278:7,10,14,16 318:22 347:14
unified 362:7
unilateral 22:13
uninfected 19:21 103:21 109:18 263:20 264:2
Union 224:18
unique 202:5,6,14 241:10
United 3:17 4:15 7:11 13:9,17 18:13 23:15 38:9 124:8 242:13 245:1,17,21 247:3 280:12,17,18,21 282:4 293:15 294:20 296:9 303:5 322:1,3 323:22 333:19
units 120:7,12
universal 18:4 22:6 223:2 237:12 270:9 295:16 352:3
universally 89:4
University 2:6,9,13,15 3:16 12:18 29:11 49:9 172:8 261:4 278:19
unknown 75:10 143:4 195:13
unknowns 75:8,10
unless 84:2 131:7 182:20 188:11 280:6 331:2 350:10 353:20 359:2
unlike 18:3 358:19
unlucky 286:21
unmet 188:18 195:14
unmodified 76:21
unnecessarily 270:12
unnoticed 28:14
unpublished 61:20
unrealistic 283:2
unrelated 109:1 110:7,8,15
unreliable 39:17 44:3,22
unspoken 234:8
unsuccessful 156:3
untreated 125:19
unvaccinated 205:14 335:3
update 8:11 319:6,8
updated 254:15
upon 42:14 70:21 71:13 79:17 245:8
upper 100:20 138:9 300:7
upstream 226:20
uptake 283:3 326:11,15,17,19 327:22 334:17 355:22

up-to-date 24:14

urge 268:22

urine 19:12 44:18 45:21 48:2,7,15 49:17 79:10 82:5,9,16 83:13 104:6 106:13 107:8,11,20,21 133:16

urine/saliva 48:4

US2 112:10

USA 283:6

usage 247:3 250:9 351:18

useful 7:3 57:7 73:20 78:17 92:3 156:12 181:4,7 182:8,14 189:13,17 210:4 211:5 214:7 271:4 316:19 346:20 347:12 363:15

usual 256:5

usually 16:6 28:14 178:12 269:16 271:3 280:7 335:6,15

utero 78:14 156:14 196:9 286:20 287:5,19 338:5,12 340:11

uteroplacental 90:8 92:5

utility 225:13

V

vaccinate 232:1 265:19 266:12 318:9 327:10 329:18,21 341:3

vaccinated 96:11 134:21 136:9 140:19,22 141:5 152:10 191:17,20 196:20 198:9 222:8 267:6 270:11 276:1 296:10 297:2,3 334:21

vaccinating 274:14 300:8 301:6,7,17 304:19 326:21 327:12,21 330:12 341:13

vaccination 75:18 88:7 91:19 97:20 134:2,22 159:15 161:14 164:14 171:7 172:19 185:20 196:9 197:8,13,17 198:7,8 202:13 208:6 235:5 258:10 259:8 267:17 268:11 280:14 281:14,15,19 291:13,19 294:18 295:1,12,17 296:1,3,8,16 298:8,15,16,17,20 299:1,3,6,7,13 300:4,5,10,13 301:2,16,21 302:4,10,13 303:9 304:8,13,19,21 305:8,22 311:14,17,20 318:15 323:21 324:16 325:17 327:16,18 328:11 329:7 330:6,21 332:3 333:10 334:1 341:5,10,16 345:5 350:2

vaccinations 267:20 295:5 325:19

vaccine 2:19,20 3:11 4:4,13 5:2,3,6,11,18 7:1,18 8:4,15,18 9:5 11:3 26:18 49:10,18 53:4,7 57:7 58:6 63:2,3 65:4,12,19,22 66:3,5 67:2 70:7,22 71:1,10 73:20 75:3 77:7 81:21 84:2 86:18,19 87:8,12 90:18 91:21 92:2 95:1 96:3,7,12 102:15 106:8,9,15 112:18 116:7,11 129:14 131:17 132:2,20 134:5 135:2 136:1 137:11 138:11,16 139:18,20 140:12,13 142:8 143:14,17 145:14 148:7,19 149:16,22 150:16,17 152:8,14,16 154:3,5,10 155:4,7,11,14 156:19 158:5,15 160:3,15 161:4 162:2 165:12,13,21 166:1 172:11,13 173:3 176:22 177:14,16,19,21 178:7 180:10 181:12 182:2,4,5,7,10,12,18 183:1,6,10 184:12,17 185:1,3,17 186:2,10,19 187:16 188:5,16 189:15,17 192:1,10,15 193:8 194:12 196:16,20 200:11,19,21 201:2,17 202:1,3,8,13,17 203:9,10 204:19 205:6,9,11,12 206:15,18 207:4,15,17 209:11,17,19 210:1 211:6 212:10 215:4,6,9,10 216:6,19 217:3,6,16 219:12,16,19 220:6,17 221:9,12 223:3 226:13,15 229:5 230:15 232:13,15,18 233:13 234:11,15,17,22 235:4,6 236:5 237:2,4,11,12 238:17 239:1,8,10 240:16,17 241:2,4,6,8,11,13,19 242:1,4,20 243:16 244:5,13 247:1,3,12,17 248:12,14 249:13

250:15,17
251:1,3,8,11
253:12
255:3,4,5,8
257:18 262:3,20
264:15,20
265:5,12,18
266:2,9,12,14,19
,20 267:4,12
268:8,14,17,19
269:5,8,11,12,15
,18 270:4
271:10,12,13,16,
17
272:2,10,11,14
273:15
274:15,21 275:1
276:10,17
278:21 279:5,6
280:4,8 281:8,11
282:17 283:4,12
285:3 286:8
287:2 288:16
294:9,11
295:8,9,13,20
296:10 298:10
299:12,20,21
301:9
302:16,19,20
304:4,13,22
305:6 307:10,18
308:9 309:15
310:12 313:4,6
316:8,18 318:17
320:4,9
322:2,9,19,20
323:10,18,22
324:3,6,10,22
325:9,13 326:2
328:9,18,21
329:7 330:17
331:10
332:15,16
333:1,22
334:11,12,17,20
335:1,3,7,14,15
336:13,22
337:1,4,9,12,14,
19
338:1,17,18,19
339:1,4,18
341:6,19,20,22
342:8,21 343:3
346:16 347:20
349:14
350:6,8,10
351:12,20,22
352:2,12 353:2,7
354:21 356:17
357:6
358:10,15,18,19
359:9,11,12,13,2
0 360:2,13,18,22

vaccinees 133:19
134:10,13
135:19 137:5

vaccine-induced
62:17

vaccine-preventable
244:22 322:17

vaccines 1:4 3:21
4:6,8 5:5,9,12
8:22 12:16 71:5
84:10 132:7
143:11 144:9
145:13 148:15
150:2,4
151:10,18
152:20 153:6,13
155:20
156:20,21
157:1,8
159:12,13
162:8,17 167:6
176:5 177:1,10
179:15,17
183:12,15,17,21
184:7 185:6,9
186:4,5,12,15,21
187:4,14,15
188:3,14,16
189:5 190:18
191:9 192:12
193:19 196:17
197:3 205:10
211:22 213:3
218:11 219:16
221:2,9 223:21
226:11 228:10
229:3 231:22
233:10,11
236:1,22
237:9,10
244:8,11,17
245:4,9,12,13
246:17 247:19
249:11 250:3
252:12
258:14,15
265:13 267:19
268:21
275:13,16,20
291:16 294:7
310:22
312:6,11,15,18,1
9 313:17 315:10
318:6 320:2,10
321:13
322:10,12,16,21,
22
323:3,8,13,15,17
,20 324:2,13,20
325:1,13,14,15,2
0,22
326:4,6,10,18
328:3,4,12
330:1,14 331:8
332:11
333:3,6,15,20
335:5,17,19,22
336:1 341:18
347:17 348:10
352:15 353:17
355:16 357:17
358:16,19
365:11

vaccines-related
185:10

vaccinia 109:12
110:1 139:9
148:17,18,20
152:17

vaccinia-infected
109:18

vaccino 193:14

vaccinology 193:7

validated 70:19
71:7 197:11

validation 6:6
198:16

valuable 81:5
269:2

value 10:15 42:11
46:22 47:1,6,11
86:13 205:1
340:15

valued 340:14

values 42:10 44:1
122:1,6 347:13

variable 14:19
36:15 160:17
247:19

variables 128:1

variant 338:20

variation 64:20
65:14 108:17
163:1 170:8

varicella 325:15
326:13 328:1
331:10,16,20
332:6 338:17,18

varicella-zoster
186:5

varies 16:10
103:12
259:11,12

344:13

variety 148:16 153:5 157:18,19 160:15 183:17 294:10 351:1

various 3:13 9:10 12:15 142:22 145:20 150:6 171:2 177:1 182:6 216:10 243:20 244:6 246:2 247:7,13,19 249:5 250:3 252:5 255:14,18 270:3,5 303:4

Varivax 186:6

vary 17:8 42:9 150:12 170:6,14,20 205:5 296:10 299:20 345:2

varying 16:16

vascular 4:22 89:22

vast 14:9 312:15

Vaxfectin 219:20 220:19

Vaxfection 221:8

VCF 336:14

vector 112:9 138:20 142:17

vectors 106:17 132:12,14 133:4 138:18 139:5 142:10,21

Venezuelan 139:18

venues 330:9

verify 47:15

123:13 179:10

versa 198:4,12

version 168:22 169:2,3 181:16

versus 19:17 33:17 57:8,14 60:18 64:8 68:4 78:8 105:3 109:5 111:21,22 113:17,22 114:19 115:10 118:9 123:18 124:6 130:3 150:3 159:15,16 165:10 170:3 193:4 195:12,16 196:6 198:7 209:13 256:22 316:22 329:4 333:8

vertical 126:15

Veterinary 149:8

VFC 338:15 339:8

via 78:21

viable 343:7 359:14

Vical 3:9 140:13 188:15 219:2,15

vice 198:3,12

video 253:1

vie 57:7

view 66:20 69:8 117:13 175:4 191:4 210:14 226:12 234:20

views 215:6

vigilance 193:15

viral 2:12 44:7 46:15 63:3 70:20 82:5 83:19 85:7

88:14 95:2,8 97:15,16 100:14 107:15 108:17 112:18 131:2 132:12 144:13 148:18,19,20 153:2 154:17,18 155:20 156:15 157:12,17 158:3,13 159:8 160:17 162:6,18 186:9,10,13 215:12 220:19 286:22 324:20 325:14,15 331:8

viremia 35:21 36:4 79:1,3 80:21 81:8,18,20 137:10,15 140:21 141:1,4 142:19 159:7 222:11

Virginia 172:6

virion 146:4

virologic 71:12 106:2 119:14

virological 39:12 44:2,22 45:1,4,11 75:20 76:1 119:2 127:11 214:5

virologist 86:14

virology 9:1 171:20 174:10 289:5,20

virulence 84:8 153:17,20

virulent 84:13 148:10 154:20 180:18 228:17

virus 7:7,17 8:6 19:12,13

30:10,12 41:16,21 44:3,18 46:14,17,20 48:8,16,18 52:8 59:1,5,11 63:9,11,13 65:19 73:4 77:11,22 79:7,11,17 80:4,18 82:4,12,20 83:3,14,15,22 84:3 85:9 87:7 88:5,9,10 89:11 91:16,17 93:7 94:19,22 97:11 99:1 102:8,14 104:6,9 106:13,17 107:7,8 108:10,11 109:1,5,7 110:7,8,15,16,17 111:13 112:11 130:18,21,22 132:8 133:3,6,9,15 134:4 135:3,6 139:16 141:20 142:9,13,16 147:10,15,22 148:5,9,17 153:19 154:21 155:4 158:10 159:21 162:13 165:16 167:6 170:2,4 174:12 185:5 186:2 191:21 201:5 211:12 227:5 232:21 283:8,21 284:2,7,14 286:13,14 287:3,16,18 288:15 292:22 305:16 322:10 324:22

345:14,18
virus-containing 186:5
viruses 64:4,6 66:14 101:13 102:2,6 106:22 107:10 108:2,3,9,13 110:11 111:8,14,17,20 112:19,21 152:17 153:18 170:6 228:17 325:5 347:5
virus-like 133:2
visible 335:9
vision 13:7 273:6
visit 39:10 40:9,22 194:14 266:15 269:16 350:15
visits 326:22 327:1,3
vital 273:3
vitro 102:7
vivo 91:18 148:1 154:19 169:2 228:19
voice 275:12
volume 79:6
volumes 83:8
voluntary 262:14
volunteers 133:7 138:22 139:1,12
Vons 347:20
voted 245:8
voting 246:6
VR1814 228:17
VRBPAC 153:12
vulnerable 271:6
VZV 165:20 186:6

W

Wagner 147:8
wait 127:3 128:6 272:19
waiting 87:13
waiver 182:20
wake 308:19
walk 199:12 299:19 356:8
walking 347:19
wanes 295:14 302:9
Wang 282:6
warning 225:5
wasn't 38:15 113:12 180:21 308:15 324:11 339:14 348:2 353:15 354:5,6 361:10
watch 349:6
watching 355:18
water 74:15,20,21 298:13
ways 72:18 96:10,19,20 200:15,16 233:3 364:12
web 256:3
webcast 349:7 364:1
website 192:10 250:20 252:2,22 253:1,6,13 255:22 256:2 294:1,4 330:19
we'd 204:14 335:12 344:12
week 41:18 42:3,5 43:5,12,19 45:8 46:10 133:14 248:4 274:1
weeks 41:12 46:7,8 48:3 49:15,16 50:4,5,11 79:11 125:13,14,15 126:2,6,11,15 269:16,19 331:17 343:5 345:13
weight 257:2 263:5
welcome 4:4
we'll 8:11,20,21 9:2,4,7,12 29:4 34:22 62:18 74:4,7 99:17 163:11 175:17,18 189:6 199:7 200:5 207:8 210:22 214:22 239:19 256:14,15,16 258:2 277:1,3 278:5 293:20 315:15 321:10 351:3 356:20 362:7,14 365:4
well-baby 24:17
well-controlled 178:9
well-defined 205:17
well-designed 276:5
well-done 276:8
Weller's 76:22 82:13
well-known 75:5 193:8 340:18
well-received 113:7
we're 4:9 10:7 11:8 29:20 33:20,21 37:13 62:17,22 72:8 73:9 84:15 116:18 148:11 175:7 176:18 190:5 200:3,10 202:7 210:13 211:4 212:5 219:9 221:13 223:6 224:6,8 225:7 240:8 251:12 256:3,9 269:10 273:19 277:1,2 286:8 292:13 309:19 319:9,13 326:14 327:10 328:16 330:1,4,6,7,13 335:19 337:20 341:21 347:16 348:11,22 349:1 362:4 363:22
Western 13:9 16:15 17:2 148:3
we've 19:16 28:18 30:10 35:16 57:6 72:6 75:20 77:17,18 79:1,14 82:11 83:17 85:13,16 90:22 91:13 92:22 93:19 111:1,2,6 147:16 148:8 150:1 157:18 174:18 182:21 191:15 206:11 209:11 226:18

227:20 229:1 233:9 234:15 236:1 244:8 249:16 251:2 255:5 259:10 261:17 276:21 285:15 296:16 308:20 309:1 316:6 319:9 321:18 322:3 326:14 344:15 352:13,14 354:7 356:6 363:14,15

whammy 177:22

whatever 6:5 83:22 164:19 249:6 312:21

whenever 128:17

whereas 26:8 120:13 121:11 122:10 142:5 281:2 285:14 293:13

whereby 291:15

where's 223:7 229:19 289:14 348:2

Whereupon 365:9

whether 15:7 21:13 22:21 23:12 24:10 35:17 36:21 37:22 54:16 58:5 63:7,16 64:12,18 66:20 70:4 75:17 79:8,17 81:4 87:14 89:7 90:9 91:6 93:3,17 95:5 101:22 116:7,12 118:6 119:7,9 122:14 123:13 144:9 151:9 155:9 159:4 164:7 169:14 171:12 191:18,19 197:10 225:21 230:21,22 233:13,21 240:17 281:19 289:18 302:4 314:10 336:3 338:4,12 339:19 345:5 346:21 349:4

whichever 47:20

white 23:13 24:21,22 25:16,17 32:20 199:11

whole 38:3 85:5 169:18 184:13 201:4 243:7 255:21 293:15 294:9 322:10 349:8 350:13 357:1,19

whom 182:7 279:21 366:3

who's 36:1 173:6 243:18 258:2 284:11,12 286:2,3 288:4,14 294:13 308:3 363:18

whose 21:17 261:11 334:22

wide 14:19

widely 129:10 187:11

wider 264:11

widespread 18:7 80:8

wild 191:21

wilderness 143:15

wild-type 84:3,4 154:14 161:10

WILLIAM 2:15

win 253:7

window 343:6

winning 207:20

wiped 87:9

wise 258:20 268:16,18 273:10,11

wish 192:6 199:10 240:13,22 257:21 272:4

Wolfram 146:13,18

woman 31:8 40:1,3 41:1 49:12 50:10,21 54:14 55:13 78:20 109:17 117:14,17 123:11 127:4 173:3,6 217:14 242:14 269:8 280:7 286:2 332:2 336:16 339:6,7 342:22 343:4

woman's 268:3

women 2:8,15 3:14 16:10,20 17:4,6 18:10 19:3 20:9,17,18,19,21 23:16,18,22 25:18,20 27:3,11,14,15 31:17 32:4 34:16 35:8 37:18 38:22 39:9,10,14,17 40:14 41:15,21 43:19 44:9,13,15 45:3,5,7,14 46:19 50:3,13 52:1,6,20 55:17,21 56:1,3,13,20 58:8 59:1 62:10 66:12 67:10 71:11,16,19 73:11,15 88:12 92:8 93:9,10 96:22 103:18,19 104:2,8,16,17 108:20 111:8 116:11 118:19 119:6,8,12,17 120:11,14,15,21 121:1,20 124:22 125:6,7 126:1 127:8,10,12 130:6,8,17,18,22 131:9 142:12 143:7,8 169:7 171:5 172:14 189:20 192:22 196:10,13,19 197:1,5,15 201:22 204:21 205:13 207:20,22 208:7,18,19,22 209:1 216:22 220:5 222:20 242:2,6 249:4,21 255:18 258:5,11 259:7,8 264:20,22 265:1 267:5,6 268:8,10,15,22 270:4 271:10 275:4 280:14 281:5,15 283:8,15 284:4,6,19 285:18 286:18 288:1 302:5 308:16,17,22

309:7,17 310:13,14,18 311:10,16 314:1 315:3 318:9,15 319:16,19 320:2,5,10,11 321:8 329:8 330:20 331:1,18 332:13 334:4,8,15 335:3 337:20 341:7 346:22 351:3 355:12 357:7,8,9,18 358:1

women's 17:19

wonder 32:12 62:15 279:9

wonderful 79:9

wondering 30:5 63:16 64:4 164:19 233:21 257:5

work 12:20 20:6 28:20 58:8 61:18 75:4 81:6 85:5 86:10 88:16 97:1 99:18 100:20 104:13 107:1,2 144:5 145:15 146:13,19 147:12 154:8 159:1 160:5,11 165:20 167:6,7 182:13 213:10 227:3 247:7,13,15,16,20 248:2,3,4,8,10,13,15,17,18 249:6 252:22 254:21 283:5 294:17 295:11 298:4 304:17 330:7 342:15 344:15 350:10

worked 4:20 29:21 65:8 111:17 121:19 172:3 213:11 334:5

workers 19:11,15

workhorse 96:16

working 65:9 129:18,22 168:7 200:16 324:14

works 82:9 91:20 92:10 233:13 281:12

workshop 1:4 4:8,9 144:5 187:2 297:8 365:11

world 2:6 4:16 7:22 13:3,12 81:12 82:7 194:5 197:14 252:11 259:18 275:7 347:8,13 359:19

world's 97:19

worldwide 7:9 13:5 87:21 91:4

worried 144:14

worry 322:21 363:3

worse 30:17

worst 229:12

worth 98:22 180:9 256:2 308:11 361:1

worthwhile 129:6

wrap 98:15

write 61:4 216:15 343:17 363:6 364:9

written 166:21 198:19 250:1 272:20,21 279:8 290:1 347:11

wrong 72:8 241:1 275:21 292:7

Wu 152:19

X

Xavier 64:3

xenograft 228:13

Y

Yamamoto 85:17 282:9

year's 254:20

yellow 326:7

Yep 278:9

yet 6:20,21 33:22 34:12 67:18 77:20 84:21 86:15,16 92:6 98:4 132:11,22 141:16 143:2 158:21 169:11 190:2 199:4 274:16 330:13 347:22 358:18

you'll 10:8 170:19 285:5 322:6 362:22

young 15:9 18:16,22 19:6,11,19 20:11 23:11,12,16,19,20 24:3,8 27:19,20 32:5 33:9 35:2,9 52:1 216:7 222:5,20 232:1 260:13,17 261:4 263:1 264:3,16 301:21 304:19 305:1,8,15,16 327:11 346:7

younger 35:5 264:13 338:17

youngest 264:14 283:10

yourself 29:8

you've 54:18 58:7 64:5 77:19 87:17 99:3 113:14 116:2 201:11 213:16 214:13 223:17 229:17 322:14 326:6 343:6 363:16

Yow 260:14 263:10 272:20 273:22

Z

Zdenek 103:11

Zealand 18:16

zero 49:13 135:22 284:22 285:5 297:22 307:3

zone 42:17

Zostavax 184:4 186:6

zoster 338:17,20