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CMV 101, in partnership with Midwestern University and
Phoenix Children's Hospital
Presenter: Kathleen Muldoon, PhD

- [Christy] It is my pleasure to welcome Dr. Kathleen Muldoon. She's gonna be presenting today, CMV 101: What is Congenital Cytomegalovirus? And at this time, I'll hand the mic over to you, Dr. Muldoon.

- Thank you very much for that introduction. I very much appreciate being here to speak with everyone today to talk about cytomegalovirus, especially in its congenital manifestations. So this course is really an overview, CMV 101, just some basics to improve your knowledge and awareness of this virus, but especially how it impacts maternal and children's health, because it is something that is very much on the minds of audiologists and healthcare providers who work with children who are deaf and hard-of-hearing. So I very much appreciate you being here to learn about this with us. Let me see if my slides advance, they do. So these are my disclosures. And I think that's all I say about that. And here are our learning outcomes for today.

So I believe that you are able to download the quiz for CMV credit, and I have provided some clues to which slides have the answers to those questions. So if you have those and you can read along to the end of these learning outcomes, which are after this course, participants will be able to define congenital cytomegalovirus, or cCMV is the acronym that we'll use in the presentation and populations most at risk for seroconversion. After this course, participants will be able to describe the primary modes of transmission of congenital cytomegalovirus. And after this course, participants will be able to identify the problems with and importance of early detection and treatment of newborns born infected with cCMV. So I am the first in a seven-part series to talk about congenital CMV with you.

So I hope that if you haven't already signed up for the whole series, that you consider it, because again, this is an overview, and I will be touching briefly on aspects of congenital CMV that will be explored more fully with other presenters in this series. And it's really important that we're kicking this off in this way because June is actually CMV

Awareness Month. Here I have our proclamation from the state of Arizona where I currently live, but this is also recognized on a national basis. And again, I am the one here speaking to you on behalf of our local collaboration, Stop CMV, or in Spanish, Alto CMV AZ, where we have websites. If you Google us at stopcmvaz.org or altocmvaz.org, you can find more resources.

And I am the one here speaking to you today first, but we really are a collaboration of a group of people who are very interested in raising knowledge and awareness about congenital CMV, locally and nationally and internationally, and to anybody who will listen. And we are a collaboration of healthcare providers. So at the top of the slide, you see the Phoenix Children's logo. Phoenix Children's is one of the co-sponsors of this webinar with AudiologyOnline and Dr. Page. And we'll be presenting separately on the physiology of congenital cytomegalovirus infection. And Dr. Deborah Flynn is an audiologist who will be co-presenting on treatment and management of hearing outcomes in children who are born infected with cCMV.

We also work in collaboration with folks at our local early hearing detection and intervention services, and the people who administer the newborn hearing screen, as I'm sure many speakers or participants on the call do as well. Our local chapter of Hands and Voices, which is a nonprofit dedicated to helping and supporting parents who have children who are born with hearing difference, deafness or hearing, hard-of-hearing children. And parents who joined in the collaboration and are typically in most places, the main voices that are raising awareness and advocacy for greater congenital cytomegalovirus knowledge amongst healthcare providers. So I myself am a professor at Midwestern University where I do a lot of research on the social and general knowledge aspects of CMV.

And I'm also a CMV parent. So I'm happy to answer questions about any of those perspectives and hats that I wear if you have them and if they come up along the

presentation. So we're gonna start with some basics. What is CMV? CMV stands for cytomegalovirus. And it's a common virus that is typically harmless to anybody who is not immunocompromised. So we use the shorthand word healthy, so otherwise not with any underlying health conditions. And this is true for kids and adults. And if you contract CMV, it typically has no symptoms. You don't know that you're sick. You might feel a rundown or tired, but nothing that you would probably go to the doctor for. But it can cause cold-like symptoms, so sore throat, fever, fatigue, swollen glands, just kind of a non-descript malaise is what most people describe it as.

Most adults have been infected with CMV by the time they are 40 years old. It's very, very, very common in children ages one to three years old, and we'll talk a little about why that is in a few slides. And this is especially if they attend daycare. And this is just because, you know, it's a virus that's around, it's around all of us. It has some aspects of its biology that make it susceptible to something that we can pick up. But very, very common. It's a herpesvirus, and I wanted to just explain what that means, right, because sometimes we hear that term and have a different connotation. But all that herpesvirus means it's Latin, it means a virus that is hidden, it hides in your body.

And so once you are infected, herpesviruses of any sort, which include chickenpox, mono, Epstein-Barr, and CMV, once you're infected with these viruses, and particular CMV stays in your body in an inactive or latent state for the rest of your life. So once you have it, you have it for life. You develop antibodies, but it can also reactivate. And when that happens, it's in a lytic state. So therefore, it is reproducing in the areas in which it is hiding in your body, which typically tend to be your kidneys where urine is produced, your salivary glands where saliva is produced, in women is often hiding in the uterus and also the organs of hearing in the inner ear, so in the organ of Corti, in the spiral ganglia, these are all places where it hides, but when it becomes active or goes in inside lytic stage, it will reactivate and partially replicate in those organs.

And this can happen periodically throughout your life. And so that's the kind of definition of what herpesviruses does. But it's also very important to understand that as something that CMV does, because when you're initially infected, it may or may not cause you to feel sick, but this ability for it to kind of hang out in your body and then go into a replicative phase again means that it is going to be present in those organ systems or in the bodily fluids produced by the organs that where CMV is hiding out, intermittently throughout your life. And when this happens, you won't feel sick, but the virus will be present in those bodily fluids. And so that's important for understanding how it spreads through a community, especially as it relates to maternal and children's health.

So when you have it, you usually don't get sick, and then when it reactivates, which technically you're in an infected period or an infectious state, it's typically what's called hidden or asymptomatic. And we're all a little more familiar what that means right now. So you can have an infection or you can be infectious and have the ability to spread it to other people with no signs or symptoms. So that's why it's sometimes called the stealth virus when people write about it in the literature. And maybe you've heard about it that way. So how common is CMV amongst women? We've just talked about the fact that it, most people have it by the time they're 40. And in fact, of those people, most people are infected when they're young children.

But we're concerned about women, right? Because women are the part of our population which who become pregnant and therefore can pass it on to developing babies or embryos and fetuses. So how common is CMV amongst women is an important question. CMV's seroprevalence or how common it is in a population, it varies by age, ethnicity, and other factors that are associated with low socioeconomic status or SES. So this is something that is, we know to be true for many health conditions, right? And it relates not to something that's biological, right, but to those social determinants of health, things that are barriers to access to health education,

barriers to access to prenatal health, regular doctor's appointments, all of the things that we are now more part of our consciousness as healthcare providers and healthcare educators.

So it's not equally present in all populations across the world, but especially in the US. There is a disproportionately high risk of primary or first time maternal CMV acquisition and therefore congenital CMV infection in socially-disadvantaged communities, right? Because socially-disadvantaged communities tend to exist along axes of these, the spectrum of socioeconomic status. So let's look at what that looks like with some data. A term that you may have become familiar with over the last few years is force of infection, which is a term that relates to how the risk per unit time for susceptible individuals to acquire a disease. So for someone to go from being negative for a disease to being positive. So in the general seronegative population, about 2% of people seroconvert per year, right, or two per out of a hundred, will go from being negative to being positive for CMV in a year.

But we just said, it doesn't really exist along these equal axes, right? Where everyone is equally at risk of seroconverting. So I think it's important to take some time to look at that. So this is a graph, I realize it's a little bit fuzzy, so I apologize for that. But it's plotting seroprevalence or positivity along the y-axis against age, right, because we know the longer you're alive, the more opportunities you have to acquire CMV. So we're gonna break this down just a little bit. So if the general seronegative population seroconverts at about 2% per year, if we highlight the lower line in blue and just pick out the white population, non-Hispanic white population, it's actually lower risk for seroconversion than the general population, it's 1.4% per year.

So let's compare that with the other lines on the chart, which is that in non-Hispanic Black populations, and in Mexican American or Latino populations, the risk of seroconverting is actually three times higher than the general seronegative population.

So about 6% in non-Hispanic Black populations and about just over 5% in Mexican American populations. So there's a huge discrepancy in the risk along ethnic lines that likely relates to the kinds of jobs that people have, the access to prenatal care that puts them at risk for acquiring CMV in these different populations. And this is especially true, right? If you look at what's happening around ages 20 to 29, if you fall along the black two-headed arrow there, that there is a huge discrepancy in seroconversion around that age where you can see the gap from about 40% of non-Hispanic whites at 20 to 29 years of age have seroconverted, whereas 70% in the non-Hispanic Black and Mexican American populations have already seroconverted by that age.

So this is an important thing to keep in mind when you are seeing patients, when you're evaluating children for deafness or hard-of-hearing with no known cause. It's an important thing to take these risk factors into mind. It's also important to look at the slope of the curve in these areas highlighted now by the yellow box. And that is that, in the ages of prime childbearing years, which are between, you know, they're teen to late 20 years for most of us, there's a difference in the rate at which people are acquiring CMV. So if you look at the blue line or the non-Hispanic white population, it's kind of flat, right? So there is no increase in rate in that population after people get into adolescence.

But that is not true for the non-Hispanic Black and Mexican American population, where there's a higher rate of acquisition as people are becoming sexually active, as they're beginning to have families. And so there is a risk, a corresponding risk, of people acquiring CMV during these years as they're also potentially starting their families. So this makes this an important point of conversation for clinicians and healthcare providers to be having with underrepresented minorities who are in their care. And then if you add onto this data, infection rates for seronegative women who work in childcare are actually between 10 and 20% per year. So even greater than what we're seeing along these ethnic lines. And that is because access and opportunities for

infection increase when you work or in common community with young children and toddlers who we said children ages one to three are often infected and acquire a CMV infection during this time period, so that really increases the rate.

So in addition to this conversations with underrepresented minorities, we wanna also be taking occupation into account when we're having these conversations about CMV knowledge and awareness with our patients and our clients. So why is this a problem? Like, you know, so I've looked at this, these data about who seroconverts, you know, well, how are people acquiring CMV? How is CMV transmitted? It is spread by direct close personal contact with essentially every bodily fluid, but not every bodily fluid equally. So in order of decreasing presence, when you're shedding saliva, urine, mucus, tears, blood and other bodily fluids, are the fluids that carry CMV. So if you come into direct personal contact with these bodily fluids, if that person happens to be shedding CMV at any moment, then you are in at risk for acquiring CMV or seroconverting yourself.

So examples are kissing on the mouth or face, that would be an example of a direct close personal contact. Kissing on the mouth is obvious because, you know, you're directly exchanging saliva in that moment, but also on the face, because if you kiss somebody in the face, especially a child, and if you think about what children's faces look like, especially, you know, if they're upset when it's socially, not only socially accepted, but socially encouraged to love on your kids or on people that you're babysitting, you know, you often are kissing faces that have tears, that have mucus on them, that have saliva on them, from children that are, you know, teething and/or mouthing different toys as they explore their environments.

And so that can often, even though we don't think about it very often, like consciously provide direct personal contact with those bodily fluids. CMV can also spread by indirect contact with the virus on hands and common surfaces so it can survive on a

surface outside of the host long enough to provide an opportunity for transmission. So some examples are that CMV will persist on hands, so direct hand-to-hand contact, for example, in the handshake or wiping a child's face, a child's nose, wiping a child while doing a diaper change, because urine is a common source of infection for caregivers. It can persist on these services and plastics. So toys for at least 15 minutes. And on food, which is also a source or a substrate or a fomite for at least five minutes.

So that's long enough to be transferred through indirect contact to a mucosal surface. So if you pick up a toy, you put it away, you didn't wash your hands in between, or you didn't wash the toys, and then you wipe your eyes or your nose or your mouth, that is an opportunity for infection as well. So why is this important, right? Well, let's again revisit this information that the children are often infected and when they are initially infected, they're often shedding the virus for a period of months to years in those bodily fluids where CMV hangs out. So here are two graphs from a 2011 paper. The first is showing the percentage of individuals that are shedding CMV in which CMV is detectable in their bodily fluids.

And in this study, I believe it was saliva and urine in which it was measured versus age. And these are kids that are otherwise healthy, so not with no known underlying conditions at daycare centers. And so you can see about 80% of kids by the time they're two or three have evidence of CMV present in their bodily fluids, which means that anybody who comes in contact with those fluids has the opportunity to seroconvert or become CMV positive themselves. If you look at this, you know, and that makes sense, because kids are together, they're in community, they're experiencing close, close, directional personal contact with each other. In that setting they're, you know, interacting with each other, mouthing with each other, just together, right?

But they're also exploring their environments with their own toys, which are often not cleaned in between those encounters. So those are opportunities for those children to become infected and then have shedding for, you know, in their bodily fluids. The second slide is, or second graph on the slide is healthy children not in daycare centers. And even though those children don't have the same opportunities for exposure to infection, that around one years of age, you can see about 40 to 50% of children are also shedding. So where it's higher for children that have opportunities to interact in environments outside of the home, even for children who are not in daycare centers, they are often shedding because, you know, we all still go to the grocery store, to the libraries, those children are probably not isolating at home, but still have those opportunities for infection.

So when does CMV become a concern, right? Because I said also, you know, you catch it, you catch it for life, once you have it, you're probably not gonna get sick if you're otherwise healthy, and then you just have it for the rest of your life and you may or may not know if you're shedding it. So you could ask the question like, who cares about this then, right? But CMV does become a concern in populations that are immunocompromised, in which case CMV can cause damage. And the population that we are concerned with today, and for its implications for the deaf and hard-of-hearing community is when a baby catches CMV before birth or becomes infected before they're born.

And this is a condition that's called congenital CMV, or cCMV. Congenital, meaning present from the time of birth. And it's very common for the contact with the saliva or urine of a young child to cause a CMV infection in pregnant women. So when the pregnant woman comes in contact with the saliva or urine of a young child and becomes pregnant, or becomes infected herself, is a common way in which the developing baby or the embryo or the fetus can become infected as well. Remember, CMV can survive on objects long enough to be transmitted between people by

touching surfaces. So let's just play out what that actually looks like in real life, and how this virus can spread from person to person.

So here is a situation in which the mom is colored black in this cartoon that we're gonna walk through because she is seronegative, she does not have CMV, she's never had CMV in her life. But here's little Tommy coming home from the daycare center infected, right? And how did he get infected there? Well, he was playing with a toy or sharing food with somebody or, you know, doing something that, you know, giving kisses on the face to one of his friends, right? And ingesting those bodily fluids that another child in that same age group, ages one to three, is also shedding the virus any one time. So little Tommy is infected in this scenario. So that's why he's pink, okay?

Tommy is still in diapers and so need someone to help change him on the changing table with a diaper change. And so in this case, for example, it may or may not be the pregnant mom who's changing little Tommy. It may be the partner, her partner, or another person in the household, someone that she has close, intimate contact with as well. Whoever is changing the diaper, if they're not wearing gloves, if they're not washing hands after they change that diaper, then they are coming into contact with the infected urine of little Tommy, and then that person can become infected as well. So now, not only do interactions with Tommy present a risk to the mother, in this situation the pregnant mom, but also now the partner has it, and any intimate contact or close direct personal contact between the partner and the pregnant woman in this situation can be an opportunity for infection.

Pacifiers are a surface, a plastic surface on which CMV can live for 15 minutes. So it used to be commonplace if a pacifier fell out somebody's mouth, you know, it was socially acceptable to pick that up, put it in your own mouth to clean it before putting it back into Tommy's mouth. And right there again is another opportunity for a CMV infection. Even handling the handle of it though, right? Even if you don't put that, the

binky part, the part in your mouth, then you still have the opportunity for infection. Rattles, toys, anything plastic, 15 minutes CMV can live on there. And every time you touch it, you're washing it, every time you touch it you're washing your hands, if not, and then you touch your own face, or eat your own food or do anything, then you are also providing the opportunity for indirect contact and transmission for CMV.

Food, a lot of times when we're trying to get people to eat new foods, when they're between one and three years old, when they're trying solids, sometimes it's a bite for Tommy, it's a bite for mommy. If you're pregnant and you have a one to three-year-old, or if you're a caregiver, or if you work in childcare, you know, if there's extra crackers on the plate and you haven't had an opportunity to sit down and eat all day, then maybe you pop those into your own mouth, right? But if Tommy has handled them in any way or if they've been on the plate, and they've acquired CMV from that indirect transfer of CMV, then that's another opportunity for infection.

Utensils are a surface on which CMV can live for 15 minutes. So it provides an opportunity if you're sharing utensils, even if you're not sharing the food stuff itself, is an opportunity for infection. And toothbrushes and other common household items that are sometimes shared within families, you know, go directly into your mouth. So saliva onto the object directly into your mouth can also be another route of transmission. And so through all of these pathways, you can see just through every day, often in the home, opportunities for CMV transmission are common, and they're not scary, they're not something, they're a lot of times socially encouraged, right, kisses on the face, cuddles, all of these things while you're pregnant are just things to be aware of because if you are not and you don't know how to take the precautions to avoid contact with those bodily fluids or are not advised to do so while you're pregnant, then that is how we get infection in the maternal population.

So I keep talking about all the ways that you can get CMV, but it's actually really, really easy to get rid of CMV on all these surfaces. It is not a virus that hangs out, that hangs on, and fights against the mechanisms that we know work, universal precautions for avoiding getting sick through viruses. So CMV is preventable by following universal precautions, especially during pregnancy, which are the same things that you do to keep yourself healthy from any germs affecting your pregnancy. So washing hands after changing diapers, preparing food, sharing food, washing hands doing all those things, cleaning surfaces often, especially toys, kissing on the top of the head instead of on the face or direct mouth to mouth kissing while you're pregnant to avoid those bodily fluids.

And also using your own cups, utensils, toothbrushes, et cetera while you're pregnant. All of these things are proven effective ways to rid those surfaces of the virus and have resulted in zero transmission when they are implemented. And this is true for just plain water. If you have no access to soap, water and soap, antibacterial soap, it doesn't take much. It's not a very strong virus if you know how to get rid of it. So taking all those precautions reduces to eliminates your risk of contracting CMV while you're pregnant. So what is congenital CMV? So we said that it is, when the infection is present from birth. And so let's walk through what that can look like as well.

So we are concerned with not just all women who contract it, because most women who contract it, if they contract it before they are pregnant, if you know or are thinking about become pregnant, even though it will hang out in their system then they will not be at risk for passing it on to their child in general. However, if the maternal population catches it around the time of conception or during their pregnancy, that is considered a first time or a primary infection, or it is also known that you can have a secondary reinfection. And I'm happy to answer questions about that. I'm gonna walk through a little bit of that in this slide. So that's what we consider the maternal population.

The timeline in which it can affect a pregnancy is anywhere from conception through birth. And so we're just gonna walk through what that looks like. So if a woman contracts it who is at around the time of conception early in the pregnancy, then it can cross the placenta. We know the placenta is the organ of community between a mom and the developing baby, and it's not a perfect barrier, right? It's a place for transfusion or transmission back and forth of nutrients and waste products. And so the virus is strong enough, small enough, that it sometimes can pass through the placenta, the placenta doesn't catch it. And so if that happens, the placenta will often catch it if it is formed and fully-functioning.

And so it creates kind of a bottleneck. So, you know, hopefully not all the virus gets through and hopefully it does its job in trapping that virus. But if it doesn't, then the virus can establish a placental population and replicate within the placenta. And so that is an opportunity for the developing baby to become infected. If it does pass through the placenta, it's still, all of that doesn't necessarily make it all the way through into the blood. That is another bottleneck where there is a filter, where some of the virus can be caught in that time, so we call that infection of plasma as a bottleneck. So even if the placenta becomes infected, it doesn't mean the baby will become infected, it means that it has to pass through this other filter.

But if it does pass through that filter and infects the blood, then it will be in the blood plasma and set up a population there from which it is also continuing to replicate. So if it's in the blood plasma, then it will start, if it does make it through that filter, then the virus will replicate within the blood system. And we know that the blood is the nourishment for the developing organ systems in the baby. And from there it can pass to those organs of, particularly of saliva production, so the parotid gland, the other salivary glands where saliva is produced, and it will also transmit to the developing kidneys where urine is produced. And if that happens as well, then there are separate populations of the virus that are set up in these organ systems.

And as it's replicating within these systems, it will be perpetuating itself in the blood, in the saliva, in the urine, for example, of the baby as it's developing. So it is possible that throughout the pregnancy, that CMV will continue to pass through these bottlenecks, and you'll have reinfection from the placenta, reinfection from the, let's just say reinfection from the environment, reinfection from the placenta, there can be reinfection from the blood to the saliva and the urine. This is an interesting aspect of biology that I'm happy to answer questions about, but it's kind of beyond what I wanted to get to for what you should know. But it's just, is kind of a continuing process, and that continuation process is why there is some variation in what the outcomes are for CMV when babies are born, which we'll talk about in just a moment.

You can also have reinfection between the saliva and the blood throughout the pregnancy and also after birth. So all this virus developing in the developing organ systems in partnership with the developing organ systems, it means that babies that are born with CMV infection, so they're already infected as they're born, it means that CMVs have been a part of those, that development of those organ systems and that puts those babies at risk for neurodevelopmental complications, which we're gonna talk about for the rest of the time together. It is also true that breast milk is a bodily fluid and baby can become infected or reinfected through breast milk. But at that point the baby is born and the organ systems are developed, and in particular we're considering like, you know, the brain and the inner ear that the organs that are associated with hearing.

So if this is the root of infection or if there's infection from the environment, like a child comes home from daycare and infects within the home or in the grocery store or anywhere else where you can become affected, if it's after birth, the baby is done the critical periods of development, and these children who are born, who are infected after birth, even if it's immediately after birth, are not generally at risk for

neurodevelopmental complications. So they do not have any of the risks that we are gonna talk about for the rest of the time. So what are the ways for testing CMV? I see in the question and answer, there is a question from Lori that says, is there a titer for women prior to pregnancy to determine if they are seropositive or seronegative?

Yes, there is. It is not standard in the US. It is only standard if you are getting assistance with achieving pregnancy, then it is the standard part of just the health of the parents as they're becoming pregnant, but it is not a standard test and it is one that you can ask for. And in fact, if you donate blood through the Red Cross, they automatically check your CMV status. So you can just ask to know if you're somebody who donates blood or maybe that's a reason to donate blood, especially this month, to know your CMV status. Because if you are CMV negative, then you are eligible to give your blood to micro preemies in the NICU, for example, so that you don't pass your CMV infection onto to children that in that case are immunocompromised and would be at risk for some complications of having a CMV infection when they're that compromised.

But the general ways that you can ask for CMV testing is yes, to know your CMV antibody testing. So you can do that through your blood type, you can do that through urine testing, that can happen before or after conception at any time, whether you're pregnant or not. When you are pregnant, you can determine your CMV status by, through various forms of virus isolation or PCR tests. So a standard one is fetal in the amniotic fluid. Amniotic fluid is made up of a lot of fetal urine. So if CMV is in the kidneys and if it's reproducing within the urine as the baby is developing, then it will be picked up, typically by an amniocentesis. When the baby is born, in the newborn period, there are many highly sensitive tests to know what the CMV status of the newborn is.

Saliva is the gold standard and is generally checked with a urine test. But this must be done in the first weeks of life, the first three weeks of life. And that's a really, really important point, a very, very important point. And that's because that is the only way to kind of determine that it's a congenital infection that might have some effects on fetal, on development, rather than in an environmental infection, which will have no implications for neurodevelopmental complications. So you wanna make sure you're getting it in that time. And this is why, and we'll talk about in a few moments, the newborn screen is a really great way for kids that refer from the newborn screen to do that CMV test as a check to see where that hearing difference is coming from.

After three weeks of life, it is still possible to check if there was an infection at birth. So within that three-week period, if you live in a state where the dried blood spots for the metabolic disorders are kept, Arizona's not one of those states unfortunately, but there is lower sensitivity because blood is not typically a place that has high levels of virus as a bodily fluid. It's much more common to be present in urine and saliva. So key point, it is possible to test for CMV. It is something that's being done in many states now. It's an easy and cheap test to ask for with any baby that is born, but it must be done within the first three weeks of life, otherwise you don't know for sure if it was a congenital or an environmental infection.

And congenital infections are the ones that have the risk for neurodevelopmental outcomes. So CMV is the most common virus that can harm a developing baby during pregnancy. And hopefully that shocks you a little bit because maybe that's why you're here, right? Because it's one that not many people know about or talk about in either healthcare professional training or in prenatal visits. So it's something that I'm hoping that you take this information and share it in within your communities as well, because congenital CMV is really common. One out of three pregnant women infected with CMV will have a child born with CMV, because those filters don't always work, the

placenta filter and the blood plasma filter. And so we know CMV is very common in the environment.

We know there are lots of opportunities for our pregnant women, especially one who interacts with young children to come into contact with the bodily fluids of CMV, so it's something that we all need to be talking about and sharing information about, so that we can protect ourselves from that congenital infection. This translates to one out of 200 babies every year are born infected with congenital CMV. That's a lot of kids. That totals, if you look at the US birth rate nationally, to 30 to 40,000 babies in the United States that are born infected with CMV every year. And since I live in Arizona, I always like to make it relevant to my state, but that's 400 to 600 babies in Arizona infected every year.

And I will also put kind of an asterisk on this because we don't universally screen for congenital CMV. These numbers are likely underestimates, right? These are what we know from some studies, where we did kind of point estimates of screening. So it's likely many more kids than that in reality. So congenital CMV is serious, okay? Unlike when you catch CMV when you're a healthy adult and it's just maybe a common cold or nothing, or when you intermittently shed throughout your life and nobody knows, when kids acquire CMV in utero, when it's a congenital case, it's very serious. One in five babies infected with congenital CMV will have lifelong disabilities, even if they're born with no signs of infection at birth.

So they can have no visible clinical suspicion, no tests for it, the kids go home, but those kids are still at risk for developing neurodevelopmental outcomes. So if we take these numbers and extrapolate them to the United States, that's again, as an underestimate, we know at a minimum, there's 6,000 to 8,000 babies in the US and 120 babies in Arizona per year that will have CMV-related, serious and lifelong health conditions. So these are the kids that we're concerned about and we're here to learn

about, so let's take some time to think about what that means. So congenital CMV is serious, let's put it into context, right? So again, I'm trying to kinda wow you about why haven't I learned about this before.

So here are your two graphs, side-to-side. On the y-axis, you have a number of congenital conditions that you have likely heard of before or maybe not. So at the top is congenital CMV disease, so those are kids that are born infected and have long-term implications from it, the infection, fetal alcohol syndrome, Down syndrome, spina bifida or anencephaly or neural tube defects as they're known more broadly, congenital types of HIV/AIDS, invasive hemo influenza B, for which there is a test that's widely administered during pregnancy, and CRS stands for congenital rubella syndrome. Rubella being the R in the MMR vaccine. So again, a vaccine was developed to stop the congenital effects of this virus on pregnancies.

So the y-axis is the same for both of these graphs. The x-axis for the graph on the screen on your left is the number of children who are born, who will have long-term sequelae or disabilities from the condition on the y-axis. And the graph on your right is the number of childhood deaths or the deaths that result from the conditions that are on the y-axis. So let's start with the number of children with long-term disability from the conditions. So if you look, even though you probably have known for quite some time, right, either through your own life experience or education, about things like Down syndrome or fetal alcohol syndrome or spina bifida, CMV outnumbers all of them, right, in terms of number of kids that are disabled every year by this virus.

So congenital CMV causes, you know, six to 8,000 kids per year to be disabled. And that's more than fetal alcohol syndrome, more than Down syndrome, spina bifida, HIV/AIDS, and any of the other conditions combined in actuality, and we still don't know about it, we're not talking about it enough. Most of the kids who are born with congenital CMV are disabled rather than have pass away from it, but it is still a leading

cause of childhood deaths. And this is typically because of those, the outcomes that we'll see, some of them which are acute, typically liver problems, epilepsy, for example, that are a result of the brain damage caused by congenital CMV. So the normal childhood deaths is about four, between four and 500 kids per year, which is more than spina bifida or anencephaly, which is the next to highest graph and more than the other conditions as well.

So we should be talking about this, this should be shocking to you if you haven't heard about it before, and something that is worth talking about as well. And if that doesn't kind of get you thinking about, you know, this is definitely having an impact on our children's health and our family's health here in the US, then we can also look at the numbers. And this was now 23 years ago, but it was also the last estimate specifically for congenital CMV, but the direct annual economic costs of caring for children who are born with congenital CMV is in excess of \$4 billion per year. And this is estimated through, you know, the Medicaid programs and public insurance programs that go to, you know, supplementing costs for in-home care, community-based services, implantation, hearing aids, et cetera, and all the things that are sometimes covered by different programs.

So that's a lot, that's a lot, especially for a condition that is preventable if you know how to say precautions during a pregnancy to prevent yourself from being affected by this condition. So it's serious. Babies born with congenital CMV may have lifelong disabilities. Not every baby, but a significant number enough that we should be paying attention, right, as we just looked at on that last slide. So I'm gonna show you a chart that is a spectrum. And the spectrum exists from babies that are born. I'm gonna start with the right hand side of the screen with no symptoms of being sick. And this is how 90% of babies infected with congenital CMV are born. So they do not present with any signs that would tip off a test.

They are asymptomatic and that's 90% of those babies. But of those 90%, 10 to 15% will develop long-term disability. It just won't be present at birth. And if it's not present at birth, there's probably no suspicion to have a CMV test in that newborn, that critical newborn period of the first three weeks. And so if a child goes on to develop a disability and the number one disability that it develops is deafness or hearing loss, there will be no known etiology and no way to go back and test. And so it's really, really important to kind of keep this in mind as we move forward through the rest of the talk. So that's what the asymptomatic kids are. So even though 90% of babies are born infected with CMV are asymptomatic, 10 to 15% will develop long-term disability.

And at the other end of the spectrum, on the left hand side of the screen, are the babies that are born with symptoms of being sick and 10% of those babies, they'll be the other 10% of the babies born infected. So they are not always tested and caught on clinical suspicion, but a lot of the time, 'cause they're born infected, they have a classic presentation we'll talk about in a moment. And of those, a greater percentage, 75% will develop long-term disability. So let's look at the spectrum, okay? So you are seeing a chart in various shades of blue, which range from babies with severe outcomes, which tend to be the kids that are symptomatic at birth through moderate to mild.

And the kids with the mildest long-term outcomes tend to be those that are born with no symptoms of being sick at birth. So we'll start with that again, we'll start with the asymptomatic kids who tend to have mild outcomes. And there are a significant number who have no apparent developmental differences or disabilities. But again, I would put an asterisk on this and say we just haven't studied it enough because we don't have universal testing to know which of the kids that present later in life with autism or hearing loss or learning disabilities actually may have been born with an infection. So we just don't have the data to really evaluate that although that data is emerging.

What you'll notice is, you know, then as we move towards the left hand side of the screen, you know, that there are kids that have no other sequelae except deafness or hearing loss or communication differences, developmental delays, cognitive delays, vision differences, hearing differences, feeding/sleeping issues, into the more moderate to severe end of the spectrum, which are multiple disabilities such as cerebral palsy's very common, adding in comorbidities such as seizures, feeding issues, failure to thrive, and then a small number of kids either are lost to miscarriage, stillbirth, or die within the first months of life, typically because of seizures or just the complications of being infected. So one thing I wanted to point out on this slide also is that, look how many of these categories include hearing differences, right, and differences in hearing thresholds.

And that's because CMV, as we'll talk about, is actually the leading non-genetic cause of hearing loss and is the reason why AudiologyOnline partnered with us to bring this to you today. It's a really important thing for this population to be hearing and talking about. So cCMV is a leading cause of deafness even in babies born without symptoms. So you saw that hearing differences was highlighted in many aspects of that chart that you have on your handout. And hearing differences or deafness is present in many different ways. So it can be present at birth, and even if it is, it's generally considered to, you know, be falling into the asymptomatic category of kids as they're kind of evaluated at birth.

But it can also change, those thresholds can change later in childhood. So hearing loss associated with congenital CMV is considered progressive and fluctuating. It can also kind of come in and out of different threshold levels. Babies with congenital CMV may have hearing differences in one ear, so they may be unilaterally deaf or hard of hearing, and may later develop hearing differences in the other ear. So it can become bilateral, sometimes it's asymmetric, sometimes it's fluctuating, but it typically progresses in that

manner. So I know there's another webinar in the series, there's two actually that specifically focus on the management of hearing loss. One from an otolaryngologist perspective and the other from the audiologist perspective. So I really encourage you to sign up for those in the series to learn more about how to manage that and how what it looks like, you know, as it's progressing.

So children born with cCMV, with or without a demonstrated hearing difference benefit from services and monitoring by healthcare team because again, babies are born asymptomatic and you don't know which are the ones who are going present with hearing loss later in life and how will it progress. So monitoring by audiologists at regular intervals is really important. So, you know, why don't people know about it or why is this still an ongoing public health crisis that we're talking about here? And I wanted to, again, you know, I'm a professor by trade and so I like charts with data. So we did a study where we looked at awareness of conditions and compared it with incidents. So I'm just, there's a lot of animations on this slide that you have as a handout.

And I'm just gonna walk you through some of this data in a little more detail. So the blue bars here represents a percentage of women, and these are your college-educated women who are surveyed, who have heard of a condition, who could pick it out of a list, right? And so what you'll see is, if you ask women, have you heard of this when they have a list? And 9% of women will say, yeah, I've heard about congenital CMV, and they'll check the box. And that's in contrast to, for example, 85% of women who have heard of Down syndrome, so, you know, most women. Or, in fact, more than 90% of women who have heard of congenital HIV or AIDS.

And in fact it's a fairly standard test to be tested for HIV during a pregnancy. It's important to compare that with incidents or the actual occurrence of the number of children who are disabled by the condition each year. So that's what these orange dots

on your chart represent. So what I'll point out is the top dot here is a number of children disabled by CMV. And we took the lower end of the range, which is 6,000. And if you look to all the other dots in comparison to congenital toxoplasmosis or rubella, fetal alcohol syndrome, spina bifida, a lot of the same conditions that we talked about just a moment ago, then you can see that, the number of children disabled by CMV is actually more than all of these other conditions combined, and it is equal to the number of children born and disabled by Down syndrome.

So again, just pointing out, this is a virus that is equally as prominent and causing as much disability as other conditions, and yet we don't know about it, right? And in contrast, the number of children disabled by congenital HIV is actually very small, right, because your risk for passing HIV on is actually constrained to some very specific populations and behaviors. So the chart that you have in front of you is pairing that data so that we can look at what this can actually mean. So I'm gonna take this just kind of condition by condition. And if we look at Down syndrome, right, then what you'll notice there is the orange dot and the blue bar line up.

And so the way that we can phrase that there is no gap between awareness and occurrence, right? So you can consider that maybe even a public health success story, right? That you should be about as aware as something occurs in the environment, right? That seems to make sense. If we compare that congenital HIV/AIDS, the women, you can also frame it as that they're hyper-aware of congenital HIV compared to its occurrence, right? If only less than 200 kids are born with it, but, you know, more than 90% of people know about it, you know, they're over aware of it, even if they're not a person who's generally at risk for passing HIV onto their children. And that's good.

Maybe that's also a public health success story, right? Maybe that's why there are so few kids that are born with it, right, in part. But let's compare that to CMV. Look at all that white space, right between the orange dot and the blue bar. We call that the CMV

awareness gap. And that is why CMV continues to be an ongoing problem for people who are impacted by it. And we call that the public health crisis, right? What we wanna do is bring that orange dot and the blue bar together and hopefully, you know, bring the blue bar way up in the orange dot way down so that we get rid of that white space. And you are a part of this, and so I really appreciate you guys being here.

And to walk through that again, if you like, at any time, there's this recording that'll be available to you. And there's also a video on YouTube, in the National CMV YouTube channel where we walk through the CMV awareness gap. And not only does it occur in women of, you know, just in the general educated public, but when I did a study looking at the same thing and healthcare professionals, in particular OTs and PTs, you know, how well are you aware of these conditions compared to, again, commonly known other conditions on the y-axis like cerebral palsy, breast cancer, pink eye, things that we see commonly, like how well do you know about CMV? 52% of healthcare providers, PTs and OTs, were able to self-report familiarity with CMV.

So they said, yeah, I know what that is, I can pick it out. But when we dive deeper, only 18% could identify modes of transmission for congenital CMV and what put them at risk. And that's a problem, right? Because that means that they don't know the ways to protect themselves or their loved ones from becoming infected. So it's really important you guys are here, part of the solution to improving public health knowledge of CMV. And here is a timeline that I put together that's just look at all the different times and interventions for where you can treat CMV during a pregnancy or where you can educate people to avoid infection in the first place. And this can happen at any time throughout the timeline of a pregnancy.

There can be education. As you guys have now, you can ask for screening and know your own titer levels and your own CMV status, but that can happen any time throughout a pregnancy. There are times that you can ask for, if you know that there's

an infection during pregnancy for treatment. I'm happy to answer questions about that. But what I want us to be aware of is the screening and that having screening data is a great way to identify children with hearing loss and get them onto some of the treatments that will be spoken of in different aspects of this series and get children into early detection and intervention. Currently, none of these interventions are routine in the US although if you follow along with National CMV, we're working on it on an advocacy level.

As for vaccination, vaccination's been on top of everybody's mind the last few years, and has been since 1999, for CMV, ranked as a top priority for research and industry because of those public health conditions. So we are happy to announce that there is actually a CMV vaccine that is in trial right now. And trials are recruiting in different areas. I've listed the Arizona areas. But you can go to the Moderna website, which is cmvictory.com, to look to see if a trial is right for you and or someone in your family or someone that you know to assess the efficacy of preventing CMV from affecting a pregnancy. For more information, from a family perspective, especially as a child who has undergone management through cochlear implantation for deafness at birth, Megan Nix, who's a personal friend, and advocate for CMV awareness, has written a book that just came out, which is called Remedies for Sorrow.

I highly recommend it. It features my family as well, as one of the chapters of my son Gideon. To learn more about her entry into awareness and her journey with a child with deafness. So, you know, I wanna end you with the most important point and hopefully have a couple of minutes for questions, I'm happy to hang out a little bit afterwards, is that congenital CMV is preventable, it can survive on objects long enough to be transmitted between people by touching surfaces. But if you take these actions while pregnant, you'll protect your baby from all germs. And again, those are washing hands often, giving hugs and kisses on the forehead or top of head instead of the face during pregnancy, making sure you clean and disinfect surfaces such as objects such as toys

often, eat only your own food and drink, use only your own utensils and plate and cutlery, and only your own toothbrush.

And if you do these things, you can prevent congenital CMV from infecting someone you love or yourself, or even people that you don't love. Just tell everybody that you know, by practicing healthy pregnancy tips to avoid all germs. So I'm happy to take questions now or at any time afterwards. This is my contact information and reach out to me anytime. I'm always happy to talk about CMV. And I just wanna take a moment to thank all the partners and including AudiologyOnline for hosting this webinar series. So thank you very much.

- [Christy] Thank you so much, Dr. Muldoon. We are gonna go ahead and open the floor for any questions or comments that you have for Dr. Muldoon. Please feel free to type them in. And if you happen to think of anything after the fact, you're welcome to reach out to her as she's provided her contact information graciously. We just really wanna thank you so much for coming on and sharing with us, and shining the spotlight on this topic. It's really important. And I can tell you in the past hour, I was just telling myself I did not know that. That's unbelievable. That's crazy. This is just so common, but just not enough knowledge out there. So I really appreciate everyone on the team putting this series together. And then I know that you, Dr. Muldoon, is one of the guest editors on this series, so thank you so much for all of your hard work putting the series together for AudiologyOnline, and all the members who are gonna benefit from this content in the future.

- I really appreciate it. And I really hope that people do tune in for the audiology-specific hearing loss management aspects, because I think that's a really also underlooked portion of the complications of CMV. I'm seeing a question coming in. Do I have time for me to answer it real quick?

- [Christy] Yeah, absolutely, Dr. Muldoon.

- Okay, so Ruth is writing, is hearing loss the most common effect of cCMV or is SGA more common as a risk factor? It's actually, it's hearing loss, that is the most common aspect of long-term disability, and that's because of the way that CMV infects the organs of hearing. So the spiral ganglia and the organ of Corti is an area where CMV hangs out and reactivates during the life of the person who is infected congenitally. And in that time, it basically kills the hearing cells. And so Dr. Page, in his webinar in the series, will be talking more about the pathophysiology of that. But that is the risk factor that's associated with hearing loss and why hearing loss associated with CMV is progressive, why it can be fluctuating, why it's kind of tricky to manage from that medical standpoint.

I see also, Wendy has a question. Hi, Wendy. Are audiologists at greater risk for catching CMV if they work with kids with CMV? Audiologists, I would frame it differently, audiologists or any healthcare professional that interacts with children period, are at higher risk for contracting CMV, in fact, 10 to 20% higher risk, but not children who are born with CMV. They're not any greater risk than the general population. They don't shed at a higher rate. If you practice universal precautions with all children, then you are protecting yourself from contracting CMV if you're somebody who works with the pediatric population. It has actually been written by the American Academy of Pediatrics or Pediatricians that children who are born infected with CMV are at no greater risk than other children, and so therefore should not be excluded from school or healthcare settings or any other setting as risk to a pregnant woman, because any child, as we looked at in the earlier graph, especially between the ages of one and three, is you can just assume that they're shedding CMV at any time and take those universal precautions.

So to not work with a child with CMV, which I'm just reading a little bit into your question, as a healthcare provider, if you know they're born with CMV, is actually considered a form of discrimination because they are no greater risks than any other child, especially if you keep working with children. So the greatest way to protect yourself is just to practice those universal precautions with all children that you come into contact while you're pregnant, which is the only time that it can affect the developing pregnancy. It is totally an urban myth. I see your extra comment there, Wendy, so thank you. Lee, is there a typical or textbook configuration of hearing loss on the audio ground that we see for adults who have cCMV?

So this is a question actually, I will refer you to the presentation in our series that is presented by Dr. Flynn, and Dr. Steuerwald, and Dr. Nickerson, who will be talking about the audiological management of CMV. And I would say the tricky part of CMV from my knowledge is that it is not consistent and it fluctuates. A child that is born with congenital CMV, if they have deafness, even if it's late onset, typically happens by the end of the teenage years. So an adulthood late onset congenital CMV, while I don't think it's impossible, would be rare, tends to happen sometime before they're an adult if that's the cause. But for more information, or you can email me and I will put you in contact with the people who would have a more in-depth answer to that question, I would tune into the presentation by Dr. Flynn et al, or the presentation by Dr. Page and Dr. Bhuskute, which is I think coming up shortly. And those are the questions I see, Christy.

- [Christy] Yes, I think that's it, Dr. Muldoon. We'll go ahead and wrap up the classroom here. If you wanted to leave any closing comments and then we'll go ahead and close out.

- I wanted to close with a sincere appreciation and gratitude for your presence today. I think this is a topic that every audiologist and every healthcare professional who

interacts with people who are deaf and have hearing differences needs to be aware of, and not only for understanding their patient population, but for helping to spread awareness within the healthcare professional community. So thank you very much as someone invested in this topic. I really appreciate your attention and your time.