Core Working Group Meeting #2 Notes **9/1/22**

Attendees:

- Megan Honor Pesch
- Paul Romitti
- Sheila Dollard
- Sondra Rosendahl
- Tammy O'Hollearn
- Tatiana Lanzieri
- Ashrita Rau
- Chas Debolt
- Gail Demmler Harrison
- Ginger Mullin
- Jane Fornoff
- David Kimberlin
- Karen Fowler
- Kate Woodworth
- Kelly Raines
- Kirsten Coverstone
- Kristen Nichols Heitman
- Mark Schleiss
- Max Sidesinger
- Scott Grosse
- Angela Shoup
- Stephanie McVicar
- Jessica Leung

Introduction:

Stephanie McVicar:

- Reminder: Surveillance case definition should not influence clinical diagnosis. Should not influence diagnosis/treatment and is all about case ascertainment to achieve more continual and uniform reporting.
- Case classification of congenital cases will occur after clinical diagnosis and is for public health department purposes such as describing case trends, connecting families to services & resources, and flagging cases for follow-up
- Different levels of case definition based on level of certainty.
- 3 Typical categories: Confirmed, probable, suspect:
    - Suspect: cases where clinical features were compatible with the disease or condition but either further investigation is required or investigation of the case did not provide support evidence for the disease or condition
    - Probable: Cases where alternative etiologies were investigated and excluded, and/or substantial supportive information for disease or condition was found.
    - Confirmed: Cases with highest level of certainty.

Discussion:

Based on laboratory criteria, what would you consider a confirmed positive CMV case?

David Kimberlin: Looking at Karen Fowler and folks from UAB, I believe ours would be similar—a saliva PCR would be the typical approach and if that comes back positive, a confirmatory urine PCR would be standard, perhaps a confirmatory 2nd saliva PCR but urine would be preferred. As illustrated on the spreadsheet, we would also require virologic confirmation for confirmed CMV infection.

Scott Grosse: I'm curious how many people would consider a positive DBS as confirmed rather probable?

- *Max Sidesinger*: In UT we consider those confirmed cases
- *Mark Schleiss:* I think it all depends on context; I think for the ValEar study it would be appropriate—it was part of enrollment criteria. To David's comment about saliva testing followed by urine PCR, it depends on babies undergoing work up in symptomatic category vs babies in universal screening programs who are asymptomatic. It's been challenging to get babies (particularly asymptomatic) back by day 21—family and primary care physician can be unmotivated.

Karen Fowler: I think a urine culture that's positive would be indicative of a confirmed CMV infection. We don't do that very often but there are still places that do. If we want to have a more inclusive surveillance definition, we could include that; if we're not careful we will end up with few confirmed and a bunch of probable. Urine's perfect for confirmation but there's time with such high viral load in saliva repeatedly, and when you throw in calcifications, are we going to say two tests for everything or one test? Because you could repeat a DBS? It's a little tricky.

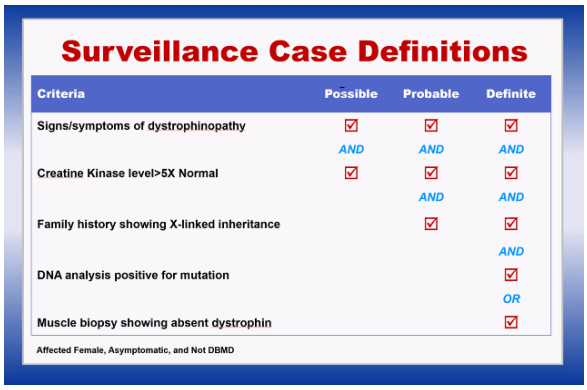
Stephanie McVicar: It's tricky, this is a hard task to come up with this—I think that's why there hasn't been more robust public health surveillance, there are so many moving parts.

Gail Demmler Harrison: Also, do we want to consider in utero fetal demise/stillborn infants as part of this reporting process- if so, we may want to include fetal tissue or POCs positive for CMV? If so, do we accept histopathology, PCR, both in this clinical situation? cCMV is an important cause of stillborn/fetal demise.

Stephanie McVicar: That's a good point, to be inclusive for public health surveillance it is important to count in fetal demise and still births to get the full scope of the issue of cCMV. I would say that should be considered in here.

Megan Pesch: In MI, our asymptomatic cases are often over 3 weeks of age and I check the urine, then we send off for the DBS. If the DBS is positive, then it's positive.

Paul Romitti: I don't have as much experience with CMV as other conditions, but going back to the question about fetal demise, I think the difficulty is you'd like to get a diagnosis but doing the stillbirth surveillance, half the parents don't have autopsies and how are you getting fetal tissue access on a consistent basis? That's the idea but it's difficult to access. Back to the case definition, the muscular dystrophy one we created, I guess I'm thinking if we did a case definition it'd be in this format where it's this and this or this or this in a table…



I'd think about case definitions as hierarchy of evidence, and it would range something like this. It brings in signs and symptoms, clinical laboratory test, family history, DNA. Some of that isn't relevant for CMV. Testing is going to evolve for CMV and will include other methods such as more consistent blood spots.

Kristen Nichols Heitman: Once we get to clinical signs and symptoms, that's something we can look at—that's a question I had, are there some symptoms where you want more than one to meet the case definition? It will be a hierarchy, and in combination w/ some of these less sensitive or specific lab tests clinical criteria may be important for determining those as well.

Chas DeBolt: I just want to say for those of you who haven't worked on position statement templates, there are tables for case ascertainment and case definition that do what the previous speaker's slide suggests - with criteria that are sufficient by themselves for reporting or necessary, so it's a system of S for sufficient, N for necessary, and anyone else from CSTE on here? Not sure about O…but tables offer a combination of criteria for reporting and there could be a separate table as a combination to meet confirmed, probable, or suspect criteria.

Tatiana Lanzieri: DBS testing…if there is clinical suspicion of CMV in a child with diagnosed hearing loss and if several other causes are ruled out and DBS testing is done; the testing is diagnostic because it was the residual sample from birth and there is a high predictive positive value of test. In contrast, if DBS is used for screening, we don't have experience of just testing DBS and in fact, states that will begin universal screening, or will pilot DBS testing, will require another specimen, typically urine, for confirmation. So, I think the science is evolving perhaps to not have all the evidence to say we don't know about contamination for example. Perhaps a child that has signs and symptoms and positive DBS for surveillance purposes would be a confirmed CMV case but with babies identified through screening sensitivity will be lower. I'm just trying to get back on the question of false positive DBS: if we have that, would we need confirmation from other specimens?

Sheila Dollard: I know Ontario has been having false positive blood spots; I've been talking to their lab director to troubleshoot. The MN study did not; in the beginning we had uncommon false positive blood spots but once we started re-testing them, they went away 100% and we tested 24,000. If you test twice (the second one is a different punch), the few false positives went away. In the beginning we were testing once and reporting but the project manager in the beginning was saying in newborn screening all tests are repeated when there's an abnormal with every newborn screening test, they repeat it. In the MN study with US bloodspots, they're highly specific. I agree they have a sensitivity issue, but they are also specific. Because they're still new for a screening specimen, studies are including urine to confirm, which is great. But I'll predict eventually a twice blood spot positive will be confirmatory for cCMV.

David Kimberlin: What if for simplicity's sake if we say that a confirmatory is either two virologic samples or one virologic sample plus histopathology? Would that capture what we're talking about?

Mark Schleiss: I agree that histopathologic confirmation outside of scenario Gail suggested would be rare; I would agree that it will be unusual to have histopathologic confirmation in a living newborn with cCMV.

David Kimberlin: I agree, it would just be the fetus' where that would be a possibility, but it would be potentially be a simple approach—if you get a positive virologic test, you'd repeat with a virologic test. The downside is you'd potentially get 2 salivas; I'm not specifying a different site so I'm not sure if it covers all the permutations.

Mark Schleiss: While we're on the topic of saliva, do you want to draw distinctions between babies that have been breastfed? That might be a point of practical significance.

Stephanie McVicar: So, you're thinking there's a caveat that maybe one positive PCR saliva might be suggestive if babies didn't ingest breastmilk?

Mark Schleiss: Yes, and you'd want to include donor milk as well.

Karen Fowler: I think we need to go back. There's a lot of talk with saliva's false positives-we didn't see that in the CHIMES study in the first few days of life. It was a very low rate. I think before we say we've seen this…we've seen false positives but there's ways we can work around that. We may need to look at what's been published at 2 or 3 weeks-I know there's issues and we may have to say guidance. We want to keep it simple, I would imagine if you start surveillance and have people participating we will see different permutations. We need to figure out if we're going to use 2 tests or different tests or the same tests. I'm not ready to fully commit today, I want to keep the conversation broad before narrowing things out.

Mark Schleiss: I'm not sure I agree with my own comment—it's certainly complicated.

Karen Fowler: Suresh and Pablo aren't here and I'm sure they'll have additional comments as well.

Kristen Nichols Heitman: Maybe we can bring the spreadsheet back and instead of talking about classifications right now we can make sure we're including all possible tests and specimens that may be used for diagnosing cCMV? Under lab criteria we were trying to make sure we have a cumulative list. It sounds like we're not ready to define suspect, probable, and confirmed, but making sure the list is complete will be most important and then we can move to clinical criteria and decide which symptoms to include and based on how that goes we can talk about if there are combinations of lab tests that aren't as sensitive with other clinical criteria that may add up to a case. **Looking at this list, is there anything we're missing right now?**

- *Gail Demmler Harrison:* Add tissue (histopathology or tissue with PCR or tissue and culture). Or if a baby has a biopsy, tissue viral detection.
- *David Kimberlin:* I would add blood culture for PCR; dried blood spot is a type of blood but it's a very specific collection method. People could theoretically send a whole blood PCR to the lab - blood or plasma PCR.

Megan Pesch: Is there a specific age limit we're talking about? I know we're talking about infants, but sometimes we have 4-year-olds come in; I just wanted to throw that out there?

Kristen Nichols Heitman: We had talked about the timeframe with days of life, I guess we should discuss if we're only looking for cases in newborns or what happens if there is a 4-year-old and it's discovered later…would you try to go back to the dried blood spot or would you do serology testing? Is that something that we're trying to capture with this surveillance?

Stephanie McVicar: I would think yes just because we know that early diagnoses of cCMV can be missed.

Max Sidesinger: I don't think Dr. Park is on this call, but he'll test dried blood spots for kids as long as they're available - and if those cases do not come back positive, we consider that a confirmed case (at the very least probable). I do think it is worth it to look at kids who are missed at birth and might have the dried blood spot tested at 5 or 6 years.

Kristen Nichols Heitman: That's still 21 days of life to me because it's a DBS sample, is there ever a case with a lab test on older children like 4-year-old we would want to include?

Megan Pesch: In Michigan, they keep the DBS forever, but in other states they don't have a DBS for long – we just did IgG for a kid like that and called him presumptive. I had a girl come in 4 years old with unilateral hearing loss, but because DBS isn't super sensitive and takes a long time to order, in older kids if the IgG is negative we don't proceed to the DBS with older kids. If the IgG is positive but DBS is negative, we end up in a probable situation where we don't know.

Paul Romitti: I think you have to ask what the purpose of the surveillance system is –to identify CMV in the neonatal period? What do you plan to do with the data when you have it? When you have a case of a 4-year-old, you're not comprehensively surveying all 4 years old, you could solve that question clinically for the family but I don't see it as part of the surveillance system because it won't be done systematically and DBS are not available systematically if you're trying to develop a system used nationally.

Stephanie McVicar: Nationally, the length of DBS retention is all over the place—it would be difficult to have that data captured. Right now, it won't be done systematically using DBS.

Kristen Nichols Heitman: We have to answer the mission of this and the goals for surveillance b/c we do write that out in the position statement.

Mark Schleiss: It is important to have context. It's not as though you're going to have a newborn with all clinical symptoms and order a DBS PCR when disease is the motivating factor. In the statement, we want to add comment that there may be situations where retrospective diagnosis in states with newborn DBS can be valuable, but I don't think that's going to be a part of routine testing. For screening, it's different—Minnesota will be focusing on dried blood spot PCR when universal screening is rolled out in 2023.

Stephanie McVicar: Have we captured all the possibilities under lab criteria?

- *Gail Demmler Harrison:* Add histopathology to tissue (besides PCR or culture)
- *Chas DeBolt*: I heard a mention of serology, but I don't see it on the list unless I'm missing it. I think an IgG in an older child was mentioned.

- *Gail Demmler Harrison*: A positive CMV IgG antibody wouldn't be diagnosis of CMV but some people might consider a positive IgM antibody…do you want to consider that as anything positive?
- *Stephanie McVicar*: Alone it can't be.
- *Chas Debolt*: For the present, we should just be getting serologic testing (IgG and IgM) on the list and defining them later. If IgM isn't really used it could be specific for IgG antibody. The clinical practice vs standardized case definition…sometimes getting the tests that you want are difficult but if you're starting with standardizing the case definition you just do that and not worry about the viability of the specimens but would define a confirmed, probable, or suspect case. You've got to start somewhere on trying to understand the burden of disease rather than harmonize with clinical practice providing the specimens.

Stephanie McVicar: **Should we switch to clinical criteria?** (see clinical spreadsheet). This could be a discussion on what would be appropriate to include as a clinical sign or symptom. What are some of the clinical signs and symptoms to consider in the case definition in terms of whether we're going to define symptomatic vs. asymptomatic?

Gail Demmler Harrison: Are we going to agree that any cCMV infection is going to be part of this reporting process not just tip of iceberg symptomatic CMV?

Stephanie McVicar: We'd like to capture as much as we can. We were meeting in preparation for this yesterday…

Kristen Nichols Heitman: That's something we were discussing, whether we want to have different categories/conditions within this position statement: symptomatic, asymptomatic, asymptomatic w/ Hearing loss cCMV. We kept going back to what we're trying to do with the surveillance and data, so whether that's looking at asymptomatic cases w/ hearing loss…this is not going to be what should have been looked at but rather what's reported. It's not going to be inclusive of all testing. With this data, what's the public health action? If we have this data, we could use it to say this is how many symptomatic and asymptomatic cases we have. That could be used to make arguments for screening programs and have advocacy for different services. Should we have the different condition categories be asymptomatic, symptomatic, or asymptomatic w/ hearing loss?

David Kimberlin: Many participated in the effort that Bill Rawlinson from Australia organized; this is really hard. It would be better to have asymptomatic and the spectrum of symptomatic if we're going to do a national sweep but the challenge for me is how to define degree of symptomatic. With the Rawlinson approach it was "more than a couple" of symptoms and we didn't really get into, except for examples, what that might be. A transient one-time low platelet might not be impaired. Generally speaking, for recommendations, treatment is not recommended unless moderate or severely impaired. The Europeans were more precise than us, but it's still a very difficult thing to do.

Kristen Nichols Heitman: That's why we have the list of symptoms, so we can decide which we want to include in the case definition. We don't necessarily need to have a spectrum; it can be symptomatic vs asymptomatic and that will just be used to look at differences between these 2 groups. Hopefully we'll have a case report form where we can list the symptoms and have checkboxes to indicate which symptoms were included for the cases so we can describe the clinical picture of these cases more.

David Kimberlin: Not all babies that look asymptomatic are going to have bloodwork…they won't have things like platelet work done.

Kristen Nichols Heitman: That is a limitation of surveillance; we are limited to say this is what was reported in the surveillance data. That's why having multiple symptoms for the case definition is important so we are capturing everything that might be found in a case.

Megan Pesch: I know it's semantics, but I really think we are doing a disservice by perpetuating symptomatic vs asymptomatic nomenclature; technically they're signs and it's misleading to the general public and primary care physicians clinically. Some of my most impaired patients were asymptomatic at birth; I wanted to throw that out there b/c I don't have easy solutions but I really hate those terms.

Kristen Nichols Heitman: Is there a benefit to having the categories? Should we only be looking at laboratory evidence?

Karen Fowler: The only problem with not using any definition of symptoms or asymptomatic is they're going to be kids who we're going to say are probable b/c they have petechiae, CNS, microcephalic, calcifications and no one tested them in the first 21 days of life…that happens and we've heard that through CMV parents because the kids don't get tested in 21 days. We want to count them as probable or we might decide they're confirmed, I do think that some kind of…the Rawlinson paper did say moderately to severe symptomatic. I like the term asymptomatic with isolated sensorineural hearing loss. The Europeans call a child with sensorineural hearing loss symptomatic. We want to be clear in our definition for when we're compared across the world.

Tatiana Lanzieri: If we are conducting surveillance we want to be able to compare estimates from different states, states that are doing some type of screening even if just in NICU or just reporting cases based on ICD codes, they may have different counts and we just need to make sure that we can relate what categories are being compared across states and surveillance data can help provide data for estimating disease burden even if its biased and not based on true population prevalence.

Stephanie McVicar: Closing reminders: Doodle poll for the next Large WG - complete that and update entry in Google sheet with your information. The CDC and UT leads will meet next week and we will send the notes out along w/ another Doodle poll for the next core WG meeting that will take place in the beginning of October. In the meantime, we will put together some examples and ideas to get your input. This spurred a lot of thought and it's only an hour, but if you have ideas please send them my way and I will compile more food for thought for the group.

The Chat:

From Gail Demmler Harrison MD to Everyone 03:14 PM: Yes I consider NB DBS positive as confirmed cCMV. Also, do we want to consider in utero fetal demise/stillborn infants as part of this reporting process- if so we may want to include fetal tissue or POCs positive for CMV? If so, do we accept histopathology, PCR, both in this clinical situation? cCMV is an important cause of stillborn/fetal demise.
From Kirsten Coverstone to Everyone 03:18 PM: If an infant has DBS or Saliva screen positive, has physical symptoms but didn't get urine until 30 days..... confirmed or probable? In my mind, confirmed.
From Scott Grosse to Everyone 03:19 PM: The Ontario universal screening program refers infants with

positive DBS PCR for confirmatory testing in urine specimens. They report not all screen-positive cases are confirmed as cCMV cases.
From Kristen Nichols Heitman (CDC) to Everyone 03:19 PM: The goal is to include all possible laboratory tests and specimens, even if the tests/specimens are rare.
From Kate Woodworth (CDC), she/her to Everyone 03:19 PM: I agree Kristen, it allows for picking up stillbirths, even if to Paul's point it isn't often done.
From Kirsten Coverstone to Everyone 03:20 PM: Yes - Paul...I think the table/hierarchy would be a good idea.
From Scott Grosse to Everyone 03:20 PM: Positive DBS result in a symptomatic infant might be regarded as confirmed.
From Karen Fowler to Everyone 03:20 PM: I like Paul's example.
From Angela Shoup to Everyone 03:20 PM: I agree. I appreciate the model.
From Kristen Nichols Heitman (CDC) to Everyone 03:24 PM: The Excel spreadsheet showing the list is meant to make sure we include ALL criteria that should be discussed to make the decisions around the classification (confirmed, probable, suspect). When looking at the list, is there anything missing that should be included (regardless of if it's confirmatory)? We will do this process for clinical criteria as well.
From Sondra Rosendahl - MN Dept of Health Newborn Screening to Everyone 03:28 PM: Agree with what Sheila said about retesting the spots. That said, for the purposes of newborn screening, we will ALWAYS want confirmatory labs regardless of how specific our screening is in detecting the condition.
From Scott Grosse to Everyone 03:28 PM: I have to leave now for another meeting. I look forward to seeing the notes from today's call.
From Max Sidesinger to Everyone 03:28 PM: Thank you Scott.
From Karen Fowler to Everyone 03:30 PM: Let's see the FP rates for saliva before we rule out saliva.
From Jessica Leung (CDC) to Everyone 03:33 PM: Histopathological evidence of CMV?
From Kate Woodworth (CDC), she/her to Everyone 03:35 PM: and would tissue include placenta?
From Gail Demmler Harrison MD to Everyone 03:36 PM: add CMV positive histopathology by immunoperoxidase staining as well to tissue. Kate-- Good questions re: placenta- in fetal infection, placenta is always infected, but if placenta is infected, fetus not always infected, so we would probably need to include fetal tissue in addition to placenta. thoughts?
From Karen Fowler to Everyone 03:37 PM: I don't believe Alabama keeps DBS very long and not sure about other southern states.
From Gail Demmler Harrison MD to Everyone 03:37 PM: Texas keeps DBS one year.
From Kristen Nichols Heitman (CDC) to Everyone 03:38 PM: I think Georgia only keeps them for 4 months :(.
From Sondra Rosendahl - MN Dept of Health Newborn Screening to Everyone 03:40 PM: MN keeps the spots indefinitely. We are considering defining a timeline, however. https://www.newsteps.org/data-resources/state-profiles?state=mn&tab=03 - has state profiles and shows retention practices under "Policies"
From Mark Schleiss to Everyone 03:49 PM: Toward an effort to be in sync with some of the European guidelines I think there should be reflection on whether an infant with isolated SNHL is truly “asymptomatic”.

From Karen Fowler to Everyone 03:49 PM: Rawlinson et al 2017 Lancet Infect Dis - defines moderate to severely symptomatic (multiple manifestations & CNS), mildly symptomatic (one or two isolated manifestations), asymptomatic with isolated SNHL, and asymptomatic.
From Kirsten Coverstone to Everyone 03:50 PM: Yes - it should include 'asymptomatic' as well.
From Gail Demmler Harrison MD to Everyone 03:51 PM: So if we include asymptomatic CMV cases in the reporting process, we are left with only CMV positive laboratory criteria as the inclusion criteria for reporting, after which we categorize the congenital CMV case as symptomatic or asymptomatic, etc.
From Angela Shoup to Everyone 03:51 PM: I agree with Mark. I have always had concerns with calling children with SNHL only "asymptomatic".
From Mark Schleiss to Everyone 03:51 PM: To some extent it's semantics but It's a point of chronic confusion not only among primary care doctors and ID clinicians but for parents - how can a baby with SNHL be called "asymptomatic"?
From Kirsten Coverstone to Everyone 03:53 PM: same Angela and Mark.... SNHL really is a symptom of cCMV...whether that is with other symptoms or not.
From Gail Demmler Harrison MD to Everyone 03:54 PM: Yes, the realization that babies w/ asymptomatic cCMV may have hearing loss at birth, evolved as routine NBHS evolved to be routine. So we should evolve our definition. Yes, agreed, primary neurophenotype with only CNS involvement can appear "asymptomatic" at birth, and their neurologic symptoms become apparent later as they grow.
From Mark Schleiss to Everyone 03:55 PM: Agree with David's comment. I've struggled and had significant push-back from providers, third party payers, parents, clinical practice committees, administrators, and local thought leaders in getting complete laboratory assessments on healthy babies with asymptomatic cCMV in our Mn study
From Kate Woodworth (CDC), she/her to Everyone 03:56 PM: Yes, clinical manifestations could be used to differentiate between confirmed/probable, without being separate definitions of asymptomatic/symptomatic?

Comments Stephanie received after the meeting:

From Karen Fowler:

Another laboratory parameter

CMV PCR test of amniotic fluid obtained by amniocentesis – a positive indicates cCMV infection in the fetus.

From Megan Pesch:

I wanted to circle back about my comment about Symptomatic vs Asymptomatic. I wonder if it would be possible to say "with signs at birth" vs without instead. It would be more precise and a step in the right direction in terms of getting away from the messy

symptomatic vs. asymptomatic. Or you could even say “with signs at birth”
then define it somewhere below e.g. laboratory, physical exam, eye exam and/or cranial imaging abnormalities. Or even if you use Moderate to Severely symptomatic per the Rawlinson 2017 paper, in the table where you define the criteria for “Symptomatic” refer to them as “signs”. As you probably know, although I didn’t until I went to medical school, signs are objective findings whereas symptoms are the person’s subjective experience. So low blood pressure is a sign, but dizziness is a symptom.
Not only is symptomatic an inaccurate term, but it also implies suffering, that these kids are experiencing negative physical effects from their cCMV, which isn’t necessarily true.