Case-Finding and Validation of Congenital Cytomegalovirus (cCMV) Related Hospital Admissions in Michigan Infants under One Year of Age

A report prepared by the

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MBDR MICHIGAN BIRTH DEFECTS REGISTRY

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Background Information:

Cytomegalovirus (CMV) is a herpesvirus. It is a common infection that is usually harmless. Once CMV is in a person's body, it stays there for life. Among every 100 adults in the United States, 50–80 are infected with CMV by the time they are 40 years old.[1] The virus is generally passed from infected people to others through direct contact with body fluids, such as urine, saliva, blood, breast milk, and semen.[2]

Pregnant women who are infected can transmit CMV to their fetuses, referred to as a congenital CMV (cCMV) infection. This can cause serious disease in babies who are infected before birth. About 1 in 150 children are born with cCMV infection.[1] Most (90 percent) infants who are infected with cCMV appear healthy at birth. Children with cCMV infection are more likely to have permanent disabilities if they had symptoms of CMV infection at birth.[3] Congenital CMV is the most frequently identified viral cause of mental retardation and the leading nongenetic cause of neurosensory hearing loss.[4,5]

In the United States, the estimated birth prevalence of cCMV infection is 0.7 percent (or 70 per 10,000 live births) and approximately 12.7 percent are symptomatic at birth. The cCMV mortality rate within the United States is 0.5 percent (or 50 per 10,000 livebirths).[6] Congenital CMV is a reportable condition to the Michigan Birth Defects Registry (MBDR). In addition, Michigan has other sources of data on CMV cases. From 2004 to 2011, a total of 101 infants under one year of age were reported to the MBDR with a diagnosis of cCMV infection. In searching Michigan resident hospital discharge files and linking with birth and death files, 74 additional children were identified.[7] From 2004 to 2011, the prevalence of cCMV in Michigan was about 0.9 confirmed cases per 10,000 live births and the mortality rate was 0.1 confirmed cases per 10,000 live births.

There is no drug licensed to treat cCMV infection. There are limited data on the use of antiviral medications in infants with symptomatic cCMV infection with central nervous system involvement.[1]
To avoid exposure to children's bodily fluids that might contain CMV:

- Wash your hands often especially after
  - ◊ Changing diapers
  - ◊ Wiping a young child's nose or drool
  - ◊ Handling children's toys
- Do not share food, drinks, or eating utensils used by young children
- Do not share a toothbrush with a young child
- Avoid contact with saliva when kissing a child
- Do not put a child's pacifier in your mouth[2]

Purpose:

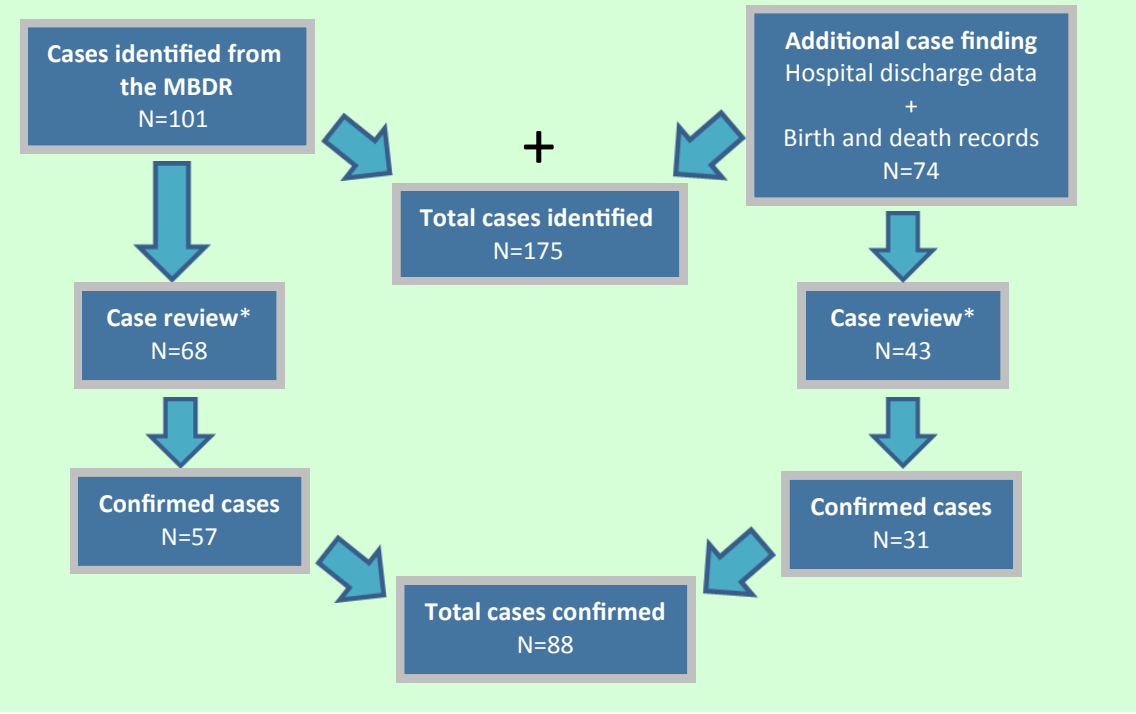
The purpose of this study was to assess the accuracy of cCMV data in Michigan through a comprehensive health record review at hospitals where infants were treated for cCMV. Results were used to assess the validity of cases reported to the MBDR, and ascertained from the Michigan Inpatient Database (MIDB) and to assess the completeness of reporting of cCMV related deaths using MBDR data, hospital discharge data, birth files and death records. This study aims to provide a better understanding of effective approaches to CMV surveillance and the public health impact. Findings were used to characterize the prevalence of cCMV in the Michigan population, while identifying the typical course of treatment and the clinical pathways of infants treated for this condition.

Methods:

Data from the MBDR, hospital discharge data, and death records were utilized to identify hospital admissions for Michigan resident infants born from 2004 through 2011 who were less than 1 year of age when treated for cCMV. Approximately 101 infants under one year of age were reported to the MBDR with a diagnosis of cCMV infection. Michigan resident hospital discharge data was linked to birth and death records as an additional avenue to identify children for review. Seventy-four (74) additional children were identified from these sources. A comprehensive, retrospective review of health records was performed at the facilities where these infants were treated in order to validate the diagnosis of cCMV, document the typical course of treatment and verify congenital versus perinatally acquired infection. Hospital admissions data related to the diagnosis and treatment of cCMV, including related complications and comorbidities were compiled. Those diagnosed with HIV and/or Heart Transplant patients were excluded from this study. Data variables were extracted directly into a table of cases and a field map was developed for reference. Results were analyzed using Statistical Analysis Software (SAS) version 9.2 [SAS Institute, Cary, NC] to assess the validity of cCMV cases and describe the socio-demographic and clinical characteristics of Michigan infants treated for cCMV.

Results:

Figure 1: Congenital CMV Case Validation Process and Outcome: cCMV Case Review 2004-2011



**Reviewed cases are less than the identified number as facilities did not submit health records for all cases identified.*

Validation of cCMV Cases Reported to the MBDR

Of 101 cases reported to the MBDR, 68 medical records were reviewed, of which 57 (83.8 percent) were found to be true positives (Table 1). Four cases (5.9 percent) were false positives or did not have cCMV and seven cases (10.3 percent) had insufficient documentation to confirm cCMV diagnosis. The positive predictive value (PPV) for cCMV cases reported to the MBDR was 84 percent [57/ (57+11) = 0.84 = 84 percent]. Thus, among Michigan infants under one year of age reported to the MBDR with a cCMV diagnosis, about 84 percent were confirmed to actually have cCMV.

Validation of cCMV Cases from the MIDB

Of 74 cCMV cases identified from the MIDB, 43 were investigated by a comprehensive health record review, of which 31 (72.1 percent) were confirmed to be true positives (Table 1). Four cases (9.3 percent) were false positives or did not have cCMV and eight cases (18.6 percent) did not have enough documentation to confirm cCMV diagnosis. The positive predictive value (PPV) for cCMV cases from the MIDB was 72 percent [31/ (31+12) = 0.72 = 72 percent]. Thus, among Michigan infants identified from the MIBD to be diagnosed with cCMV under one year of age, 72 percent actually had the disease.

Validation of Total cCMV Cases in Michigan

A total of 175 infants from 2004 to 2011 were identified as having a cCMV diagnosis in Michigan. A comprehensive health record review of 111 cases determined 88 cases (79.3 percent) as true positives (Table 1) and eight cases (7.2 percent) as false positives or not having cCMV. Fifteen cases (13.5 percent) were found to have not enough documentation to confirm cCMV diagnosis. For all combined cCMV cases, the positive predictive value (PPV) was 79 percent [88/ (88+23) = 0.79 = 79 percent]. Thus, among Michigan infants under one year of age identified with a diagnosis of cCMV from all sources, 79 percent actually had the disease. Reporting to the MBDR (PPV=84 percent) had a higher predictive value than presence in the MIDB (PPV=72 percent). However, there was no overlap between cases; both were important for case-finding.

Table 1: Validity of cCMV Cases in Michigan: cCMV Case Review, 2004-2011

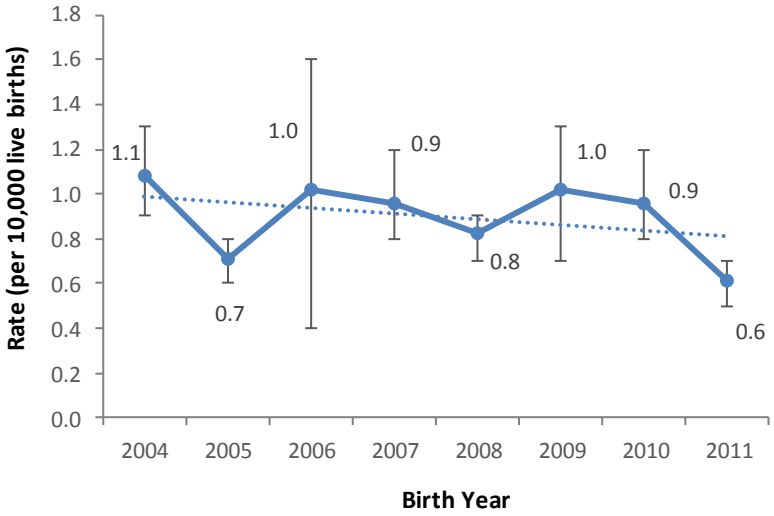
Source and case (cCMV)	Health Record Review			Positive Predictive Value (PPV)*
	Case (cCMV)	Non Case (No cCMV)	Total	
MBDR	57 (TP)	11 (FP)	68	84%
MIDB	31 (TP)	12 (FP)	43	72%
All sources	88 (TP)	23 (FP)	111	79%

**The probability that a reported positive is a true case.*
Cases with insufficient information to either confirm or exclude cCMV infection were included in the denominator.

Congenital CMV Prevalence Rate Trend, 2004-2011

Analysis of data for cCMV confirmed cases from 2004 to 2011 indicated that although prevalence rates varied throughout the years, there was a slight decreasing trend in cCMV prevalence overall (Figure 1). In 2004, the prevalence of cCMV was about 1.1 confirmed cases per 10,000 live births and about 0.6 confirmed cases per 10,000 live births in 2011 (Figure 2). However, this decrease did not reach statistical significance (p=0.5550).

Figure 2: Prevalence Rate Trends of Confirmed cCMV Cases in Michigan Reported by One Year of Age: cCMV Case Review, 2004-2011



Delivery Type

Analysis of cCMV confirmed cases indicated that more than 50 percent of infants (52.9 percent) were born by vaginal delivery, 37.7 percent through cesarean section (c-section) and 9.4 percent had an unknown delivery type. The association between the type of delivery and case status from medical record review was assessed. A statistically significant relationship between the two variables was observed (p-value <.0001). Analysis showed that infants born by vaginal delivery were less likely to have a negative status (4.1 percent) compared to infants born through c-section (8.6 percent; Table 2).

Table 2: Delivery Type and Case Status for all Reviewed Cases: cCMV Case Review, 2004-2011

Delivery Type	Case Status			
	Positive (Case)	Negative (Non Case)	Unknown	Total
Vaginal	45 (91.8%)	<5 (4.1%)	<5 (4.1%)	49 (100%)
C-section	32 (91.4%)	<5 (8.6%)	0 (0.0%)	35 (100%)
Unknown	8 (53.3%)	<5 (1.0%)	6 (40.0%)	15 (100%
Total	85	6	8	99

Demographic Characteristics

We found that of the 88 positive cases, over half (52.3 percent) were males and almost half (47.7 percent) were females (Table 3). However, no difference was observed in the prevalence of cCMV between males and females from 2004 to 2011 (Table 3).

Confirmed cCMV cases were also analyzed by the region of cCMV diagnosis. These regions approximate the pediatric specialty care service areas in Michigan (see Appendix). Although, more than a third of cases (34.1 percent) were reported in Region 1, Region 6 had the highest prevalence with 2.5 confirmed cases per 10,000 live births (Table3).

Table 3: Confirmed Cases by Sex of the Infant and Region of Diagnosis: cCMV Case Review, 2004-2011

Demographic Variable	cCMV Confirmed Cases		
	Number	Percent	Rate[1,2]
Sex of Infant			
Male	46	52.3	0.9
Female	42	47.7	0.9
Region of Diagnosis			
Region 1	30	34.1	1.1
Region 2	9	10.2	0.9
Region 3	9	13.6	1.2
Region 4	12	17.5	1.3
Region 5	*	*	*
Region 6	12	13.6	2.5
Region 7	*	*	*
Region 8	*	*	*
Region 9	*	*	*
Region 10	*	*	*
Michigan	88	100	0.9

**Data suppressed when fewer than 6 infants were confirmed with a diagnosis of cCMV.*

[1]Prevalence rates are based on births to mothers living in Michigan at the time of delivery. Data are current through July 2014.

[2]Prevalence rates are expressed as cases per 10,000 live births.

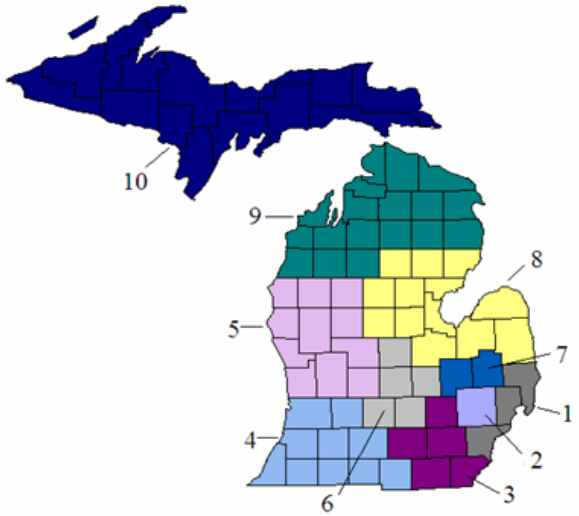


Figure 3: Geographic Regions Approximating Pediatric Specialty Care Service Areas

Confirmed cCMV cases reported to the MBDR were analyzed by selected maternal demographic variables. Of confirmed cases, 25.5 percent were born to mothers aged 20-24 years, 63.6 percent were born to White mothers and 45.4 percent of infants were born preterm at less than 37 weeks (Table 4). Prevalence rates of cCMV were highest among infants born to mothers less than 20 years of age (1.4 confirmed cases per 10,000 live births) and infants born to Black mothers (1.0 confirmed cases per 10,000 live births; Table 4).

The prevalence of cCMV was 8 times higher among infants born preterm (2.4 cases per 10,000 live births) compared to infants born full term (0.3 confirmed cases per 10,000 live births; Table 4).

Table 4: MBDR Confirmed Cases by Maternal Demographic Characteristics: cCMV Case Review, 2004-2011

Demographic Variable	Number	Percent	Rate[1,2]
Maternal Age			
<20	13	23.6	1.4
20-24	14	25.5	0.6
25-29	10	18.2	0.4
30-24	12	21.8	0.5
35+	6	10.9	0.5
Maternal Race			
Whites	35	63.6	0.5
Blacks	18	32.7	1.0
Other[1]	*	*	*
Gestational Age			
<37 weeks	25	45.4	2.4
37+ weeks	30	55.5	0.3

**Data suppressed when fewer than 6 infants were confirmed with a diagnosis of cCMV.*

[1]Encompasses women who do not define themselves as black or white and includes Native American, Asian/Pacific Islander, etc.

Physical, Clinical and Laboratory Presentation

Data indicated that about a third of the infants (34.3 percent) were small for gestational age at birth. Over 5 percent of the infants (6.8 percent) were born extremely premature at 22-26 weeks, one presenting with overwhelming sepsis and another with growth restriction. Another infant with a confirmed diagnosis of cCMV was born premature at 27 weeks.

Over two-thirds of the infants (70.5 percent) presented with hematologic symptoms, including petechiae or purpura, hemolytic anemia, direct bilirubin of less than 3 mb/dl, platelet count of less than 75,000/mm, elevated alanine aminotransferase levels, and jaundice at birth (Table 5). Approximately half the infants (53.4 percent) had neurologic deficits, including intracranial calcifications, the majority (62.8 percent) of which were detected by ultrasound, microcephaly, seizures, neurologic abnormality and chorioretinitis, with nearly a fifth (19.3 percent) having hearing impairment (Table 5). About 20 percent of the infants had hepatosplenomegaly and 13 percent had pneumonia and (Table 5). Results also revealed that about 14 percent of the infants had individual cases of other congenital complications, including, but not limited to hemangioma of skin and subcutaneous tissue, benign neoplasm of spinal meninges and retrolental fibroplasia (Table 5). More detailed information about how these infants presented clinically can be found in Table 5.

Table 5: Clinical Presentation of Confirmed Cases: cCMV Case Review, 2004-2011

Clinical Presentation	Number	Percent
Hematologic Symptoms[1]	62	70.5
Petechiae or purpura	21	23.9
Hemolytic anemia	27	30.7
Direct bilirubin >3 mb/dl	41	46.6
Platelet count <75,000/mm	40	45.5
Elevated alanine aminotransferase (ALT) levels (> 100 IU)	16	18.8
Jaundice at birth	34	38.6
Neurologic Deficits[1,2]	47	53.4
Intracranial calcifications	24	27.3
Microcephaly	14	15.9
Seizures	8	9.1
Neurologic abnormality	10	11.4
Chorioretinitis	2	2.3
Hearing impairment	17	19.3
Hepatosplenomegaly[3]	17	19.3
Hepatomegaly	19	21.6
Splenomegaly	18	20.5
Pneumonia	10	13.0
Other congenital infections	12	13.6

[1]*Encompasses infants with any of the sequelae. Symptom totals will not equal individual totals because symptoms totals includes individuals that have any of the listed complications.*
[2]*Functional abnormality of a body area due to a decrease in the function of the brain, spinal cord, muscles, or nerves.*
[3]*Encompases infants that have both hepatomegaly and splenomegaly.*

Congenital CMV Mortality and Fatality Rates

Findings indicated that five cases confirmed for cCMV resulted in death; three of these infants presented with other complications, including acute catastrophic Necrotizing Enterocolotis (NEC) with perforation, heart problems, massive infection, perforated bowel, and organ failure. From 2004 to 2011, the mortality rate of cCMV was 0.1 confirmed cases per 10,000 live births, whereas the fatality rate was 56.8 deaths per 1,000 confirmed cases.

Tests and Treatment

Initial Apgar scores showed that more than a third (35.5 percent) of infants confirmed to have cCMV had a low Apgar score (Apgar scores from 1 to 6). However, results improved by a second testing; only 4.8 percent had a low Apgar score.

About 4 percent of the infants were treated with Cytogam®, Cytomegalovirus Immune Globulin (CMV IG) administered in utero. CMV IG is an immunoglobulin G (IgG) containing a standardized amount of antibody

to CMV. About a third (32.8%) of the infants who were confirmed positive cases were on antiviral treatment or other medications with 41.9 percent receiving Ganciclovir. Other medications for treatment included Acyclovir, Gentamycin, Vancomycin, Tobramycin, Valganciclovir and Cefataxine.

CMV virus was cultured from urine in 82.1 percent of the infants, from saliva in 3.9 percent of the infants and from another medium in 9.0 percent of the infants in the first 3 weeks of life. Shell vial culture/DEAFF test which is a rapid culture technique used to detect viral antigens was conducted from urine in 9.0 percent of the infants and from saliva in 20.0 percent of the infants in the first 3 weeks of life. For infants with a confirmed diagnosis of cCMV, 1.4 percent had urine samples stored, 4.1 percent had serum samples stored and 25.7 percent had virus samples stored.

Discussion:

Reproductive-age women of middle and higher socioeconomic status are at higher risk for primary CMV, as approximately half are seronegative (not previously infected) for CMV antibodies and are therefore susceptible to infection during pregnancy.[8] By analyzing our data by maternal age, we found that of the infants reported to the MBDR with a confirmed diagnosis for cCMV, those born to mothers less than 20 years were the most affected, with a prevalence rate of 1.4 confirmed cases per 10,000 livebirths.

Previous studies have found that of CMV-infected children who are asymptomatic at birth, 8-15 percent will develop hearing loss and psychomotor delay later in life.[9] Of 88 cCMV confirmed cases in Michigan from 2004 to 2011, 19.3 percent had hearing impairment.

Infants may acquire CMV infection by contact with infected blood and genital secretions during delivery and via breast milk after delivery.[10] However, peri-conceptional primary CMV (CMV acquired around the time of conception) carries a small increment in risk of 4–12 percent.[11, 12, 13] Some authors have suggested that the risk of neonatal infection is as high as 50% when vaginal delivery occurs through an infected birth canal.[14] Analysis of our data showed that infants born through c-section were more likely to have a negative CMV status compared to infants born by vaginal delivery.

Studies have shown that though there is no specific therapy for the affected newborn, neonatal treatment with Ganciclovir showed prevention of hearing loss progression.[15, 16] Nearly half the infants with a confirmed cCMV diagnosis who were on antiviral medication were treated with Ganciclovir.

Congenital CMV manifestations include growth restriction, microcephaly, intracranial calcifications, chorioretinitis, hepatosplenomegaly, and disseminated intravascular coagulation.[14] Clinical manifestations were similar among confirmed cases in Michigan from 2004 to 2011.

Study Limitations:

To test the validity of cCMV reported cases, only cases reported to the MBDR and cases retrieved from the MIBD were investigated. As a result, sensitivity could not be calculated due to our inability to review non-cases.

Public Health Implications:

Congenital CMV has serious consequences for those affected, including lasting disabilities or even death. Pregnant women can lower their risk of exposure to CMV by hand washing and so reduce the risk of cCMV infection of their fetus. Public health programs can promote knowledge and awareness to lower the occurrence of cCMV; for example, the EHDI Program developed a 5-year strategic plan to address CMV in

Michigan from 2015 to 2020 (See Monitor Volume 7, Issue 2: Prenatal Infection and Birth Defects: Cytomegalovirus located at: http://www.michigan.gov/documents/mdhhs/MiMonitor_Fall_2015_505728_7.pdf).

An investigation of a selection of cCMV cases presented in the MBDR and other sources by a comprehensive health record review confirmed that nearly 80 percent of the cases were true positives. Case ascertainment from hospital discharge files linked with birth files and death records provided useful sources for identifying additional cases. Health record review provided useful information about the clinical presentation of children with cCMV. We found a statistically significant difference between the type of delivery and case status. Boys and girls were equally affected. Nearly a fifth of the infants had hearing impairment. Potential future direction includes intersecting with other systems such as the Early Hearing Detection and Intervention (EHDI) system for the proportion of children with hearing loss.

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Appendix

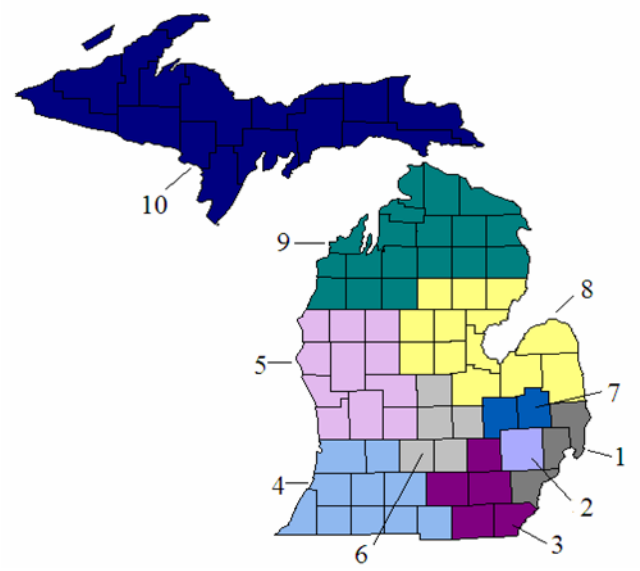

Figure 3: Geographic regions approximate pediatric specialty care service areas.

Region 1	**Region 5**	**Region 8**	**Region 10**
Macomb	Ionia	Arenac	Alger
St. Clair	Kent	Bay	Baraga
Wayne	Lake	Clare	Chippewa
	Mason	Gladwin	Delta
Region 2	Mecosta	Huron	Dickinson
Oakland	Montcalm	Iosco	Gogebic
	Muskegon	Isabella	Houghton
Region 3	Newaygo	Midland	Iron
Jackson	Oceana	Ogemaw	Keweenaw
Lenawee	Osceola	Roscommon	Luce
Livingston	Ottawa	Saginaw	Mackinac
Monroe		Sanilac	Marquette
Washtenaw	**Region 6**	Tuscola	Menominee
	Clinton		Ontonagon
Region 4	Eaton	**Region 9**	Schoolcraft
Allegan	Gratiot	Alcona	
Barry	Ingham	Alpena	
Berrien	Shiawassee	Antrim	
Branch		Benzie	
Calhoun	**Region 7**	Cheboygan	
Cass	Genesee	Charlevoix	
Hillsdale	Lapeer	Crawford	
Kalamazoo		Emmet	
St. Joseph		Grand Traverse	
Van Buren		Kalkaska	
		Leelanau	

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