Perinatal Hepatitis C Virus in Michigan

Viral Hepatitis Surveillance and Prevention Unit 2015
Michigan Department of Health and Human Services

Background

In the U.S., there is an estimated 23,000-46,000 children living with chronic Hepatitis C Virus[1] (HCV). Childhood HCV is the leading case of liver transplants in adults in the U.S. and those cases face a 26-fold increased risk of liver-related deaths later in life. Economically, in the past decade pediatric HCV has been estimated to have cost between $199 and $336 million[2]. For HCV-positive women, the potential of passing HCV to their child can cause stress and anxiety throughout pregnancy[3]. If the child is HCV positive, ethical questions arise regarding the need to reveal the child's HCV status to daycares, schools or other actors involved in the child's care. Perinatal HCV - transmitted from mother to child - is a rare occurrence without any known means for prevention. Therefore, these cases are often missed, overlooked and/or underreported.

Abbreviations	
AASLD	American Association for the Study of Liver Diseases
AB	Antibody
CDC	Center for Disease Control and Prevention
HCV	Hepatitis C Virus
MDHHS	Michigan Department of Health and Human Services
MDSS	Michigan Disease Surveillance System
PEG-IFN	Pegylated Interferon
RNA	Ribonucleic Acid
SVR	Sustained Virologic Response

Mother-to-Child Transmission

The vast majority of children with HCV are infected via perinatal transmission, which is the transmission of HCV from mother to child. This is also called vertical transmission. In the case of HCV, perinatal transmission is believed to occur in utero or during childbirth. Since the prevalence of HCV is low amongst women of childbearing age in the U.S. (estimated at around 1.2%[3]), routine HCV testing is not recommended during prenatal screening. However, HCV testing of pregnant women is recommended if the mother reports known risk factors[6].

Table 1. Risk factors for vertical transmission of HCV.[1345]

Transmission Risk Factors	Increased Risk to Infant
HIV Co-Infection	10-20% of children born to co-infected HCV/HIV mothers are infected with HCV
Viral Load	The higher the viral load of the mother during pregnancy, the higher the risk of vertical transmission
Membrane Rupture	Prolonged or premature rupture of membranes increases risk of HCV transmission to child
Maternal Blood	Fetal exposure to maternal infected blood consequent to vaginal or perineal lacerations may increase risk of vertical transmission

Perinatal transmission is estimated to occur in 5%-15% of children born to HCV-positive women. To date, the exact mechanisms that cause perinatal transmission of HCV are poorly understood. HCV is not transmitted through breastfeeding and HCV mothers are encouraged to breastfeed, unless there is mastitis or bleeding[4]. Certain factors, such as the co-infection of HIV in the mother, can significantly increase the risk of HCV transmission to the child (see Table 1). Cesarean sections and alternative

modes of delivery have *not* shown to reduce the risk of HCV transmission. Receiving certain treatment for HCV during pregnancy is contraindicated and may cause birth defects or miscarriage. If possible, women should avoid becoming pregnant for six months after the completion of interferon-based HCV treatment. The effects of direct-acting antivirals on pregnancy have yet to be adequately studied. However, preliminary findings point towards more favorable outcomes than interferon treatments.

Therefore, there are no distinct ways to prevent transmission from mother to child. However, if HCV is transmitted from mother to child, approximately 15-40% of children will clear the virus without treatment. The majority of cases will clear the virus before the age of two; however several studies reported childhood HCV cases that cleared the virus up to the age of seven[2].

Testing for HCV in Infants/Children

In order to confirm HCV status in infants and children, the American Association for the Study of Liver Diseases (AASLD) recommends different testing procedures for infants born to HCV+ women depending on the age of the child (see Table 2). The AASLD guidelines recommend testing infants after 18 months of age using an anti-HCV antibody test. If this test is done prior to 18 months of age there is a high risk of false positives as the infants may be carrying maternal HCV antibodies. At the earliest, a HCV RNA test can be conducted 8 weeks after birth. However, confirmatory HCV RNA testing should be repeated after 12 months of age.

Table 2. AASLD Guidelines for HCV Testing in Children

Age at Testing	Testing Procedure
After 18 months	Anti-HCV Antibody
	OR
After 8 weeks	HCV RNA and repeat after 12 months

Treating HCV in Infants/Children

HCV positive children generally have little to no symptoms and disease progression is minimal for the first 20 years of life. In terms of treatment, the AASLD guidelines are constantly changing and continually being updated. The effectiveness of treatments depends on the HCV genotype. As mentioned, many children will clear the virus without treatment. Therefore, some studies recommend waiting to treat until the child is beyond the age where spontaneous clearance is likely. Currently, the FDA-approved treatment for children ages 3 to 17 years is a combination of pegylated interferon (PEG-IFN) with ribavirin. With this treatment, the overall sustained virologic response (SVR) rate in children is comparable to SVR rates seen in adults[7]. However, with the development of direct-acting antiviral agents for adults, clinical trials in children are currently underway and some suggest deferring treatment until interferon-free regimens are available for children[8].

HCV in Infants & Children in Michigan

Aim

The purpose of this report is to inform on current demographics, testing and classification practices in regards to infants and children with suspected HCV in the State of Michigan. The aim is to raise awareness and improve practices for infants and children with potential HCV in Michigan.

Methodology

Data was collected from the Michigan Disease Surveillance System (MDSS), which is the web-based communicable disease reporting system for the State of Michigan. MDSS aids the secure follow-up and analysis of communicable disease surveillance information between local health departments, MDHHS

and federal agencies, such as the Centers for Disease Control and Prevention (CDC). Cases are submitted electronically or manually by testing facilities, medical providers or local health departments. If cases are redundantly reported they are deduplicated based on an algorithm of name and date of birth.

This report includes data from a MDSS disease-specific search. All reported cases[a] of chronic HCV (including probable, unknown and non-cases) born between January 1, 2005 and July 14, 2015 were exported for analysis. The search thereby captured all cases of infants and children under the age of 10.5 years old that were reported for HCV testing in MDSS as of July 14th 2015.

Background

In the past decade, the number of new chronic HCV cases has remained relatively stable. However, there has been a steady increase in the proportion of new cases among the population between 18 to 25 years of age in the State of Michigan[9] (see Figure 1*)*. A 2013 report by the MDHHS attributed a portion of the rise in HCV amongst young adults to intravenous drug use amongst 18 to 25 year olds across the State of Michigan[10].

Figure 1. Chronic Hepatitis C Cases between 18 and 25 Years of Age, Michigan, 2004-2013[8]

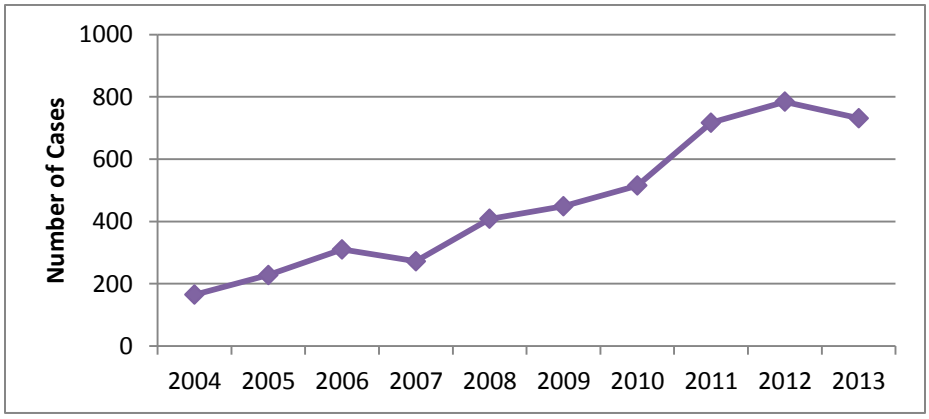
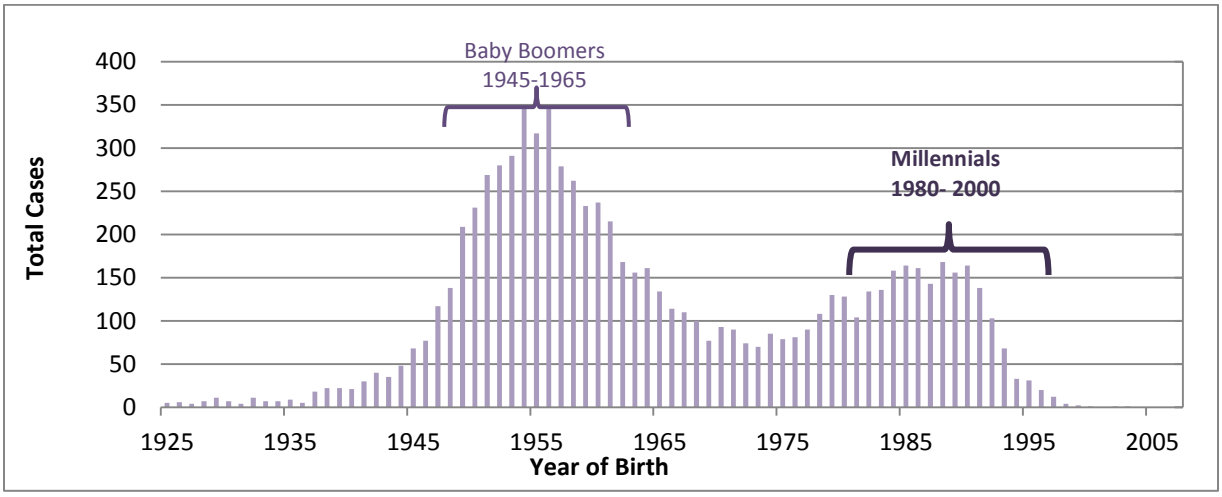


Figure 2 shows the total number of HCV cases reported to MDHHS by year of birth. According to U.S. statistics, '"Baby Boomers," those born between 1945 and 1965, are five times more likely to be infected by HCV than other adults. In Michigan, the "Baby Boomer" cohort is greater than any other birth cohort with HCV. However, there is also the emerging peak of HCV cases amongst "Millennials", those born between 1980 and 2000. Women in the "Millennial" birth cohort are currently in peak childbearing ages, which the CDC defines as women between 15 and 44 years of age. Given the rising prevalence of HCV in women of childbearing age, it stands to reason that there may be a subsequent increase in perinatal HCV transmission in the near future. Therefore, these cases and their newborns should be closely monitored.

[a] A "case" is any confirmed, probable, suspect, not a case, or unknown HCV investigation that was submitted to MDSSS. A "case" does *not* entail HCV confirmation, but rather that laboratory results have been reported to MDSS.

Figure 2. Number of Hepatitis C, Past or Present Cases Reported to MDHHS by Year of Birth, 2014[11]



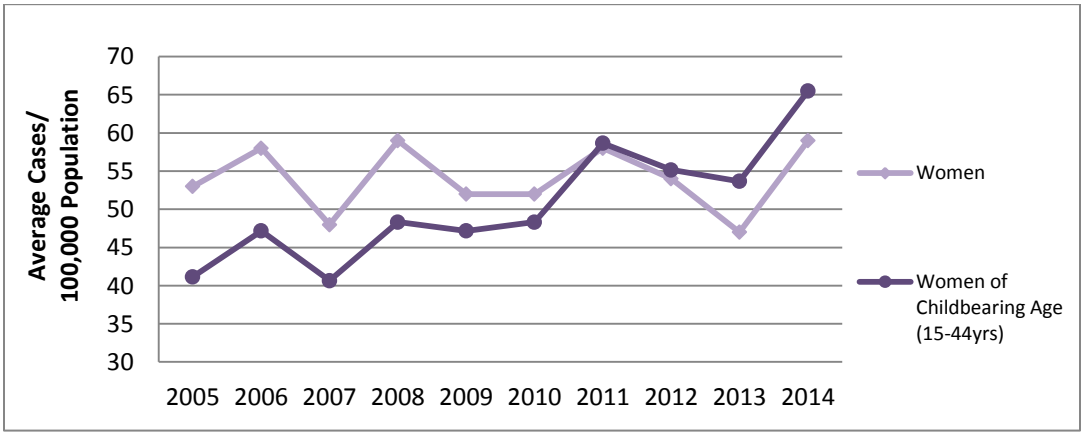
Findings

The following section provides results and information on women, infants and children with suspected HCV in Michigan based on cases reported to MDSS.

Women:

Between January 2005 and December 2014, there were approximately 7919 total, confirmed and probable, cases of chronic HCV reported for women of childbearing age in Michigan. The HCV rate per 100,000 population was higher in women of childbearing age compared to the rate for all women (see Figure 3). While this data shows that all female HCV have had a 11% increased rate per 100,000, over the past decade women of childbearing age have had a 61% increased rate per 100,000 population.

Figure 3. Average number of Hepatitis C Cases per 100,000 Population, Women of Childbearing Age compared to Total Women, 2005-2014



Infants and Children:

Demographics. Between January 2005 and July 2015, 319 infants and children under the age of 10.5 years old had reported testing for HCV. Of those tested, 52% were males, 46% were females, and 2% were unknown. Of these cases, 150 were identified as Caucasian, 22 were African American, 4 cases

were American Indian/Alaska Native, 2 cases were identified as Asian and 141 cases did not provide any information on race (see Figure 4). Wayne County (excluding Detroit) had 16% of the reported cases, followed by Oakland County (10.7%), Genesee County (10.3%), Detroit City (6.3%), Macomb County (6.0%), and Washtenaw County (3.8%). The remaining cases were spread throughout Michigan.

Case Status. Of the 319 infant and child HCV cases, 158 were classified as confirmed/probable HCV cases, 153 were classified as non-cases and 8 cases were unknown (see Figure 5). Cases were classified in MDSS based on lab results from various HCV tests. Testing will be discussed in a later section.

Figure 4. Racial Distribution of Infants and children reported for HCV Testing, 2005-2015

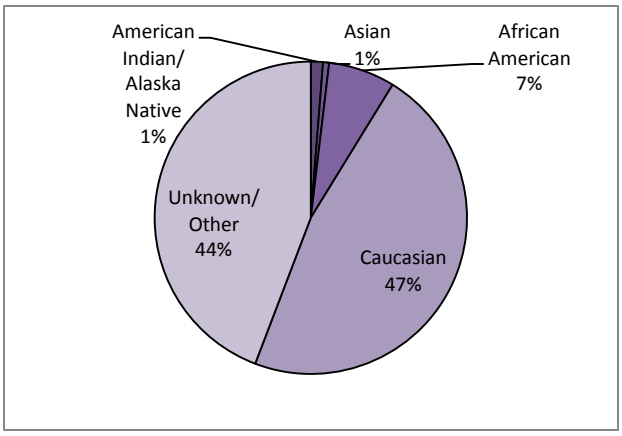


Figure 5. Case Status Classification for HCV in Infants and Children, 2005-2015

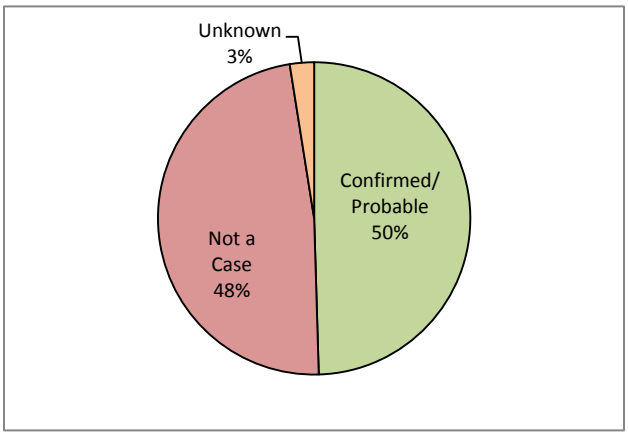
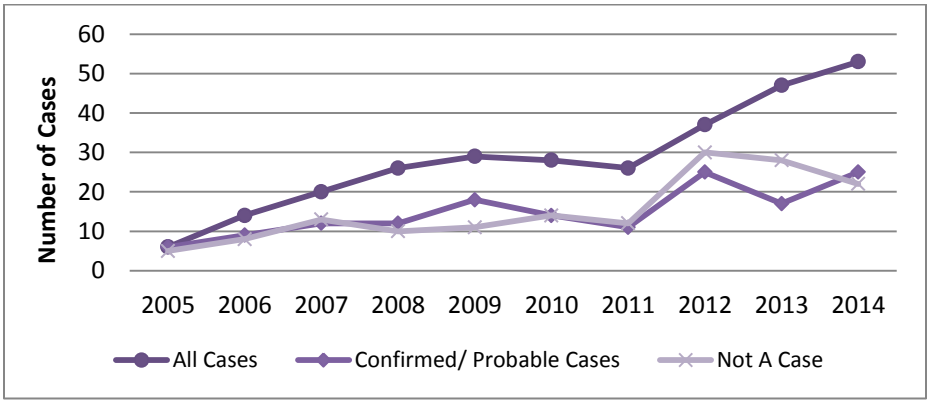


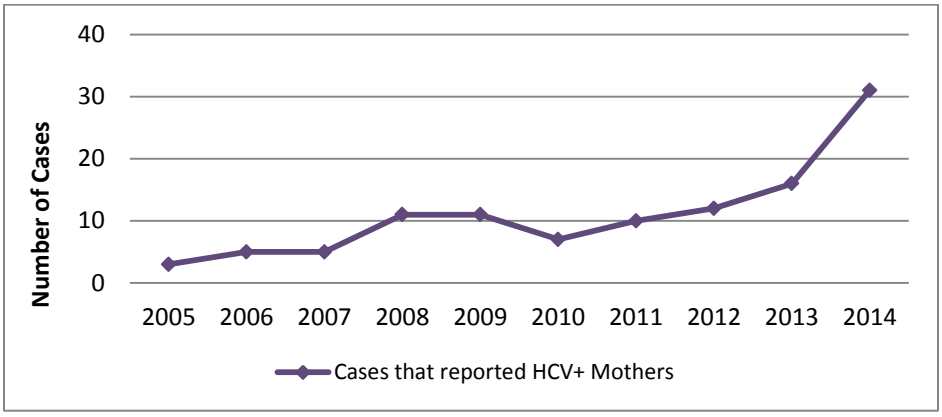
Figure 6 depicts the upward trend of reported infant and child HCV cases between 2005 and 2014. However, it is important to note that this may be due to greater awareness and testing of infants born to HCV-positive mothers. Approximately 38%, or 122 cases, reported that the reason for testing was because the mother had confirmed or suspected HCV. The remaining 62% did not report any specific reason for testing. The more testing being done, the more cases will be confirmed. Therefore, it is difficult to pinpoint the mechanism of this rise, while it may be due to an actual increase in infant and child HCV cases, it could also be attributed to increased screening of mothers and perinatal testing. It is important to note that Figure 6 only captures those *reported* for testing. The State of Michigan does not require reporting negative lab results and therefore these figures may only capture a portion of the total testing ongoing in Michigan. However, it is required to report positive/reactive HCV lab results, which has shown a slow but steady upward trend over the last decade, as depicted in Figure 6.

Figure 6. All Reported Cases of Infants and Children Tested for HCV, 2005-2014



Alongside these trends in case reporting, there has been a sharp increase in the number of cases that reported the HCV status of mothers. Figure 7 shows the number of infant and child cases between 2005 and 2014 reported to MDSS that the reason for testing was due to a HCV-positive mother. Once again, reporting the mother's HCV status is not required. However, this trend may indicate greater awareness and understanding of perinatal HCV amongst practitioners in Michigan.

Figure 7. Number of Infant/Child HCV Cases that Reported HCV+ Mothers



Testing Infants & Children. Positive results for anti-HCV AB and HCV RNA are reviewed by providers and entered into MDSS as either *confirmed/probable* cases or *non-cases,* based on current case definitions[b]. The MDSS data on infants and children was analyzed to assess whether the AASLD testing recommendations are being followed by Michigan providers and to assess how testing practices affect classification of disease in MDSS.

Figure 8 shows the distribution of lab tests used to classify *confirmed/probable* cases and *non-cases* in MDSS. Of the total reported cases, 80% used the anti-HCV AB as the first laboratory test. The remaining were tested with the HCV RNA test and 2 cases were unknown. Beginning with an anti-HCV AB test is standard procedure for diagnosing adults. However, for diagnosing infants and children testing must be done at the appropriate age. For all reported cases, the average age at the time of the first lab test was 11 months of age, which is less than the minimum age recommended for using the anti-HCV AB test but appropriate for the use of the HCV RNA test.

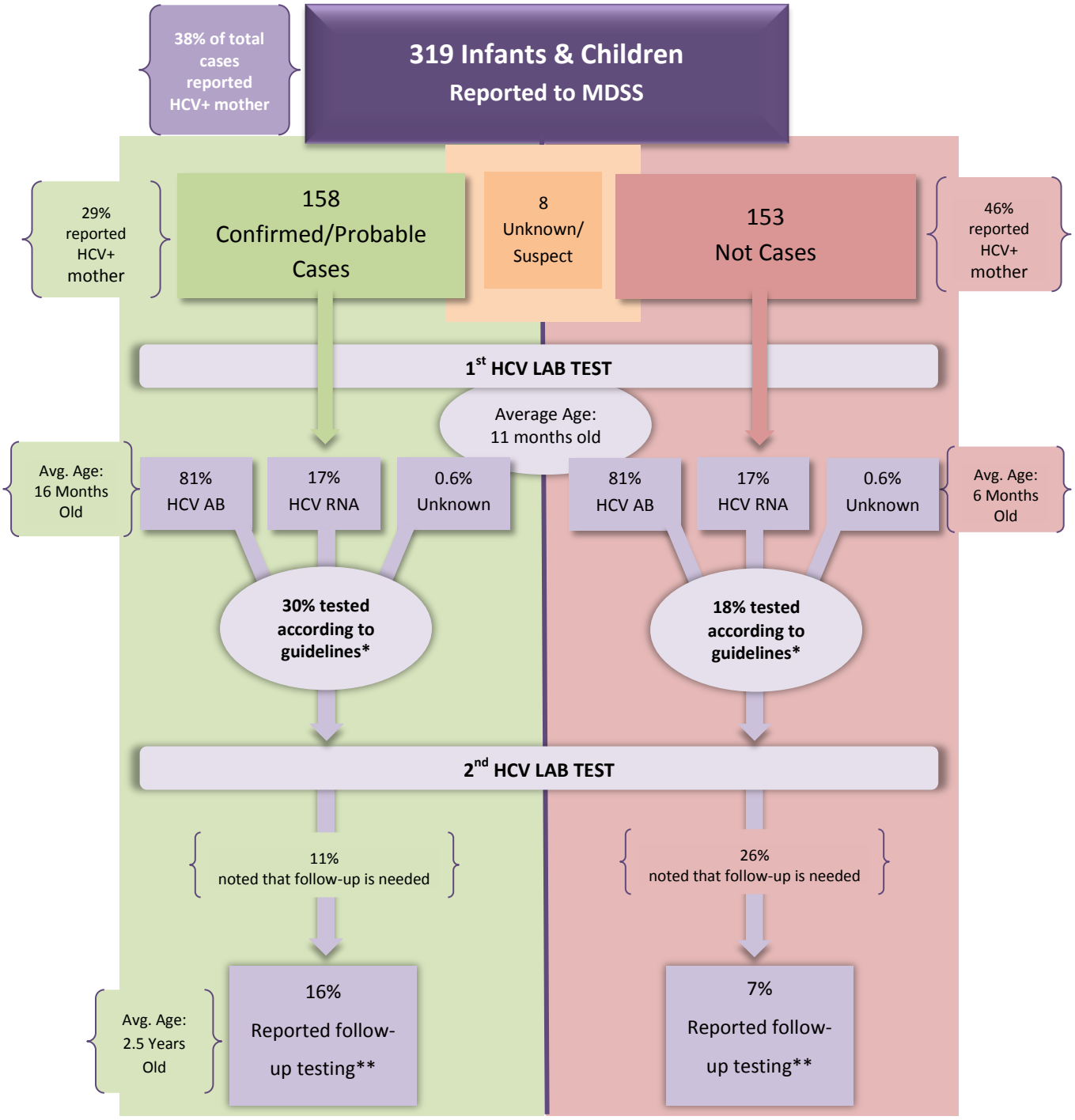
Of the *confirmed/probable* cases, the average age of the infants tested was 16 months old. Approximately 81% used anti-HCV AB test and 17% used the HCV RNA test as the first lab for confirming HCV status (see Figure 8). Of those classified as *non-cases*, the average age at testing was 6 months old, which is below the recommended age for any HCV confirmatory test. Despite this, 82% of *non-cases* were tested using the HCV AB and 17% used the HCV RNA. Meanwhile, 81% of those classified as *non-cases* were tested below the recommended age for first HCV test. It is likely that these were classified as *non-cases* because the diagnostic tests were conducted when the infants were below the minimal age for HCV testing. However, the concern is that confirmatory follow-up testing may not have occurred later in life.

In total, approximately 25% of all cases were appropriately tested in accordance to AASLD recommendations for testing infants and children. The remaining 75% were tested at an inappropriate

[b] CDC Guidelines for HCV Laboratory Testing and Result Reporting 2012: http://wwwn.cdc.gov/nndss/conditions/hepatitis-c-past-or-present/case-definition/2012/

age making them diagnostically meaningless and therefore may require follow-up. Since the State of Michigan does not require reporting of negative HCV labs, it is unclear if the non-cases have had follow-up labs to confirm their negative HCV statuses.

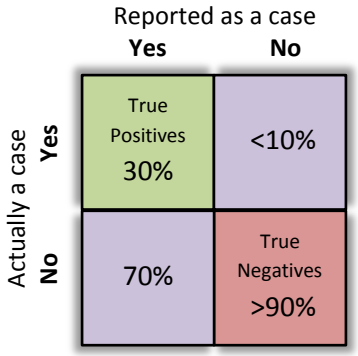
Figure 8. Flowchart of infants and children reported to MDSS for HCV testing, January 2005-July 2015



*In accordance to AASLD guidelines for testing of infants/children using appropriate HCV test at recommended age
**Michigan does not require reporting of negative HCV tests

Classification. Based on the available data and lab results, only 30% of *confirmed/probable* cases actually met the case definition for HCV (see Figure 9). This entails that these cases properly classified the case status based on recommended testing and test results that confirm HCV positivity. There was a high level of misclassification among *confirmed/probable* cases. Over 70% were misclassified as they did not report recommended testing or test results that can confirm HCV and therefore should not be classified as a *confirmed/probable* case. Over 90% of *non-cases* were correctly identified as not meeting the case definition. Approximately 88% of *non-cases* tested positive for HCV, which may indicate that the infants/children were carrying the mother's antibodies. Nearly all these cases were tested before 18 months of age. For this reason, they were properly classified as *non-cases*.

Figure 9. Percent of cases that comply with case definition for HCV in Infants/Children



Follow-Up Testing. Overall, approximately 11% of all cases noted in the MDSS report that follow-up testing should be done when the child is older than 18 months of age. For confirmed cases, 16% reported follow-up testing, the majority of which were HCV RNA tests. For non-cases, 7% reported follow-up testing. For both types of cases, it is likely that confirmatory follow-up testing has occurred without the lab results being reported to MDSS.

Conclusions

These findings highlight the rising trend of HCV among women, infants and children in Michigan. Trends should be closely monitored as young women from the "Millennial" birth cohort age into childbearing years. Over the last decade, increasingly more infants and children have been reported for having positive HCV serological markers. In terms of testing, the majority of infants are not being tested in accordance to AASLD guidelines. Likewise, surveillance data indicates a high level of misclassification as the lab results are not confirmatory and do not meet the case definition. Therefore, infants and children born to HCV-positive mothers in Michigan should be tested appropriately and follow-up should confirm HCV status.

Table 3. Key Summary

➢ On average, new HCV cases amongst childbearing women (15-44 years of age) are steadily increasing and these women are contributing more cases to the total average than a decade before
➢ Infants and Children born to HCV+ women in the "Millennial" birth cohort should be closely monitored for potential HCV perinatal transmission
➢ There is an upward trend of reported infant and child HCV cases between 2005 and 2014, which may be

attributed to an actual increase in childhood HCV cases and/or greater awareness and testing of infants born to HCV-positive mothers

- 38% of suspected HCV in infants and children reported that the reason for testing was because the mother had confirmed or suspected HCV while the remaining did not report a reason for testing
- 75% of reported infant and child HCV were not tested in accordance with AASLD recommendations, which raises concerns over misdiagnoses and/or misclassification of these cases
- 30% of *confirmed/probable* infant and child HCV cases and over 90% of *non-cases* were correctly classified in MDSS
- Future testing and reporting throughout the State of Michigan should carefully follow recommended guidelines and case definitions for diagnosing HCV in infants and children.

Limitations

This report is one of the first comprehensive looks at childhood HCV in Michigan. However there are several limitations to the data presented. Data may not be reflective of the current number of childhood HCV cases in the State of Michigan for several reasons. MDSS was launched in 2004. Cases predating MDSS may not be in the system. In addition, the earliest cases reported through the system may not have provided detailed epidemiological information. Chronic HCV is largely asymptomatic and therefore under-reporting is highly likely and expected, especially amongst infants and children. Furthermore, HCV testing of pregnant women, particularly those with documented HCV risk factors may not be occurring. Finally, since negative lab results are not required to be reported, these findings are based on reporting of positive test results only. Therefore due to these limitations, conclusions should be made with caution and further studies should be conducted.

Future Research

There are countless gaps in knowledge regarding infant and childhood HCV. To start with, the means of vertical transmission are not well understood, which means preventing transmission through various modes of delivery is infeasible and fruitless. Further studies are needed to fully understand the long-term effects of perinatal and childhood HCV in adults, including potential effects on adults who underwent HCV therapy in childhood. In Michigan, more extensive studies should review and confirm HCV statuses of all children born to HCV-positive women in Michigan.

This report is meant to highlight what we know about reported testing practices for perinatal and childhood cases of HCV in the State of Michigan. Targeted efforts should be implemented to improve awareness among providers about the AASLD guidelines for HCV testing in infants and reduce the number of unnecessary tests being ordered by providers. Likewise, efforts should aim to minimize misclassification of HCV cases reported to MDSS that are less than 18 months of age and improve surveillance of infant/child HCV cases in the State of Michigan. Additional resources on perinatal HCV for patients, providers and health officials are available (see Table 4).

Table 4. Additional Resources

Related Publications:
Hepatitis C in Pregnancy: Guidelines from The American College of Obstetricians and Gynecologists http://www.acog.org/~/media/For%20Patients/faq093.pdf
Women and Hepatitis: An HCSP Guide www.hcvadvocate.org/hepatitis/factsheets_pdf/Women_Guide.pdf

Hepatitis C Resources:

- **American Liver Foundation Hep C Diagnosis, Treatment & Support**
  http://hepc.liverfoundation.org/
- **CDC Hepatitis C Information**
  http://www.cdc.gov/hepatitis/hcv/
- **HCV Guidelines: Recommendations for Testing, managing and Treating Hepatitis C**
  http://www.hcvguidelines.org/fullreport

The information in report is designed to inform as to the current information and recommendations on testing, treating and managing HCV in women and children in the State of Michigan. The information is not intended as medical advice and does not dictate an exclusive course of treatment or procedure to be followed. All persons with HCV should consult a medical practitioner for diagnosis and treatment of HCV.

This information is provided by
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Lansing, MI 48909
MDCH-Hepatitis@michigan.gov
517-335-8165

References:

[1] American Liver Foundation: http://www.liverfoundation.org/chapters/rockymountain/doctorsnotes/pediatrichcv/

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[3] *Being a positive mother.* HCSP Fact Sheet. HCV Advocate: http://hcvadvocate.org/hepatitis/factsheets_pdf/Wm_Mother.pdf

[4] Benova, L., Y.A. Mohamoud, C. Calvert, and L.J. Abu-Raddad. Vertical Transmission of Hepatitis C Virus: Systematic Review and Meta-analysis. *Clinical Infectious Diseases.* 2014; 59(6): 765-773.

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[9] 2013 Hepatitis B and C Surveillance Report, MDDHS.

[10] Young Adults with Hepatitis C Virus Summary Report. MDHHS. 2013. http://www.michigan.gov/documents/mdch/Young_Adult_Summary_Report_v6_412759_7.pdf

[11] 2014 Hepatitis B and C Surveillance Report, MDDHS. Draft.