Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus–Infected Women

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Background. Vertical transmission of hepatitis C virus (HCV) is the most common route of pediatric HCV infection. Approximately 5% of children born to HCV-infected mothers develop chronic infection. Recommendations employ risk-based HCV testing of pregnant women, and screening children at a young age. This study assesses testing rates of children born to mothers tested HCV-positive in a major US city with a high burden of HCV infection.

Methods. HCV surveillance data reported to the Philadelphia Department of Public Health are housed in the Hepatitis Registry. Additional tests, including negative results, were retrospectively collected. HCV data were matched with 2011–2013 birth certificates of children aged ≥20 months to identify mothers tested HCV-positive and screened children. The observed perinatal HCV seropositivity rate was compared to the expected rate (5%).

Results. A total of 8119 females aged 12–54 years tested HCV-positive and in the Hepatitis Registry. Of these, 500 (5%) had delivered ≥1 child, accounting for 537 (1%) of the 55 623 children born in Philadelphia during the study period. Eighty-four (16%) of these children had HCV testing; 4 (1% of the total) were confirmed cases. Twenty-three additional children are expected to have chronic HCV infection, but were not identified by 20 months of age.

Conclusions. These findings illustrate that a significant number of women giving birth in Philadelphia test positive for HCV and that most of their at-risk children remain untested. To successfully identify all HCV-infected children and integrate them into HCV-specific care, practices for HCV screening of pregnant women and their children should be improved.

Keywords. perinatal; hepatitis C; prenatal screening; vertical transmission; pediatric hepatitis C.

Vertical transmission (mother to infant) is the primary route of hepatitis C virus (HCV) infection in children. An estimated 40 000 children are born annually to HCV-infected women, resulting in up to 4000 new perinatally infected children each year [1–3]. As the HCV infection rate among young people continues to increase as a result of the rise in injection drug use, a concomitant increase in the number of perinatally infected children may be expected [2, 4, 5]. Pediatric HCV can impact cognitive development and the overall health of children, and may lead to more severe adverse outcomes including cirrhosis, hepatocellular carcinoma, and liver failure [6–9].

The mechanism and risk factors of vertical transmission are poorly understood; however, extended exposure to maternal blood, elevated HCV viremia during pregnancy, and coinfection with human immunodeficiency virus (HIV) are shown to increase the risk of transmission [10–14]. While some infants spontaneously clear HCV infection before 18 months of age, the proportion of children who develop chronic infection after vertical transmission from mothers who test HCV-positive/HIV-negative is thought to be approximately 5%, although study results range from 1% to 11% [10, 12–14].

Prenatal screening for HCV is not routine, in part because there are no proven clinical interventions that prevent or minimize vertical transmission, including elective cesarean section and treatments that are not approved for use during pregnancy (ribavirin is contraindicated, and direct-acting antivirals are not approved) [1, 11, 14, 15]. Although the American Congress of Obstetricians and Gynecologists recommends HCV screening for pregnant women who have risk factors such as a history of injection drug use and/or HIV infection, many patients remain unidentified using risk-based testing criteria [3, 16]. Failure to capture all HCV-infected pregnant women through risk-based screening has driven other countries, including Australia in 2013, to adopt universal prenatal HCV screening [17, 18].

Because pediatric cases of disease are often asymptomatic, all children born to women who test HCV-positive should be tested to rule out vertical transmission [19]. Current guidelines from the American Association for the Study of Liver Diseases (AASLD) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommend that children born to women who test HCV-positive be tested for anti-HCV antibody (HCV-Ab) after 18 months of age; screening before this age is less reliable due to the possible presence of maternal antibodies. Any positive HCV-Ab result...
should be followed by a HCV RNA test to confirm that the child is infected [19, 20]. HCV RNA tests may also be performed after 2 months of age, with retesting after an additional 2 months, or performed once after 12 months of age [21]. Multiple tests may be needed because viral titers can fluctuate in the first year of life, though testing for HCV RNA earlier may assuage parental anxiety [20].

Children who test positive for HCV RNA should be evaluated by a pediatric HCV specialist and considered for treatment (interferon-α and ribavirin are currently approved for children ≥3 years of age) [20]. Treating HCV infection during childhood can prevent liver damage caused by long-term chronic HCV infection, has the advantage of improved adherence with parental supervision, and can limit secondary transmission that may occur as a result of risk behaviors initiated during adolescence. However, adverse consequences of the current pediatric treatment regimen should be considered and may lead physicians to warehouse patients for improved regimens in the pipeline [7, 20, 22, 23]. Although direct-acting antivirals have not yet been approved for use in children, they are more tolerable and more effective in curing HCV infection in adults and will likely become available for children within a few years [22].

The public health impact of perinatal HCV infection remains largely unexplored. In both Australia and Europe, studies have been conducted to assess effects of HCV in pregnant women, policies on perinatal HCV screening, and vertical transmission risks [1, 14, 24–26]. A 2012 analysis of National Health and Nutrition Examination Survey (NHANES) data found that only 4.9% of expected perinatally HCV-infected children were identified in the United States, and medical record review of the pediatric HCV cases in Florida revealed that <2% of known cases had received follow-up care [27]. Given the uncertain generalizability of NHANES estimates when used to approximate populations at high risk for HCV, the 2012 study likely underestimated the true burden of perinatal HCV infections [1–3, 27]. This study uses population-based surveillance data to estimate both the scale of perinatal exposures and the success of current testing recommendations for children born to women who test HCV-positive.

METHODS

Data Sources
All positive HCV-Ab, HCV RNA, and HCV genotype laboratory tests and all negative HCV RNA tests performed on Philadelphia residents are routinely reportable to the Philadelphia Department of Public Health (PDPH). They are stored in an electronic Hepatitis Registry and de-duplicated to the person level. For this study, additional negative HCV laboratory test results from 2011 to 2015 were obtained from major commercial laboratories and hospital systems in the Philadelphia region. Women with positive HCV-Ab, HCV RNA, and/or HCV genotype results were included as having tested HCV-positive, and those with a negative HCV RNA result were considered HCV-uninfected.

PDPH receives birth certificates for all births occurring within Philadelphia or to a Philadelphia resident. For this study, birth certificates were limited to children who were born to a Philadelphia resident during January 2011–July 2013 and were at least 20 months of age (study period is January 2011–February 2015). This age restriction allowed at least 2 months for HCV testing to be performed and results to be reported to PDPH following the American Academy of Pediatrics’ recommended 18-month well visit. Additional demographic and contact information for children included in the study was obtained from the Philadelphia Immunization Registry, a database housing all vaccinations performed in Philadelphia.

Data Matches
All matching methodology in this study utilized name and date of birth comparisons using the “spedis” function in SAS version 9.3 (SAS Institute, Cary, North Carolina). Address information and manual review were used to verify matches.

To measure the number of children born to women testing HCV-positive, 2011–2013 birth records were matched to the Hepatitis Registry. The match yielded women who tested HCV-positive and gave birth during the time period. After the initial match, children listed as deceased or adopted on the birth certificate were excluded from the analysis due to the limitations in assessing the HCV testing they received.

Children born to mothers testing HCV-positive were subsequently matched to the Hepatitis Registry to assess whether they had been tested for HCV according to current guidelines. The final dataset was then matched to the Immunization Registry to obtain recent contact information. Children who were no longer Philadelphia residents were excluded from the analysis, as their HCV laboratory results would not be reported to PDPH.

Case Definitions
Children with an HCV-Ab test performed after 18 months of age or an RNA test performed after 12 months of age were adequately tested according to current guidelines, and were defined as confirmed perinatal cases if the result was positive [21]. Children who received 1 positive HCV-Ab test before 18 months, or 1 positive HCV RNA test before 12 months and no follow-up tests after an additional 2 months, were inadequately tested and defined as probable perinatal cases. Children with a positive HCV-Ab test and a negative HCV RNA test after 12 months were defined as uninfected. An infant with no test results was considered untested. Those children who were tested, but whose testing did not follow AASLD/NASPGHAN guidelines, were considered inadequately tested.

Statistical Analysis
The expected number of confirmed perinatal cases in Philadelphia was calculated by applying the predicted proportion of children with perinatal HCV born to women who test HCV-positive/HIV-negative (5%) to the number of women tested HCV-positive who gave birth. Because mothers' HIV status was unknown...
in this study, the more conservative HIV-uninfected vertical transmission estimate was used. The number of undiagnosed children with perinatal HCV infection was calculated by subtracting the number of confirmed perinatal cases from the expected number of cases. Given that approximately 30% of HCV-Ab-positive women who lack a reported HCV RNA test may be HCV RNA negative, a lower limit of perinatally infected children was calculated using 70% of the women with unknown HCV RNA status.

Maternal demographic and clinical information, including race/ethnicity, marital status, education history, insurance, and child sex was extracted from the birth certificates. Univariate analysis was used to compare demographic and testing information for mothers who gave birth during 2011–2013 and matched with the HCV Registry (known HCV infected) with those who did not match or had a negative RNA result (unknown HCV infection status or HCV uninfected). Variables found to be associated with HCV positivity in univariate analyses (with \( P < .20 \)) were included in an initial multivariate model. The final model was adjusted for potential confounding and variables were retained via backward selection using likelihood ratio tests significant at \( P < .05 \). All odds ratios were weighted for hospital of birth to adjust for geographic and provider-specific variations. All analyses were conducted using SAS software (version 9.3).

**Ethical Considerations**

This study was reviewed and approved by the PDPH Institutional Review Board.

**RESULTS**

From 1 January 2011 to 1 July 2013, Philadelphia residents gave birth to 55,623 children (Figure 1). The maternal age at birth ranged from 12 to 54 years (Table 1). The Hepatitis Registry contained 8,119 women in the same age range with a positive HCV infection status (Figure 1). Date of first laboratory report for these women ranged from 1998 to the study period. The original match between these data sources yielded 5,687 children (537/55,623) of births to mothers who tested HCV-positive, of whom 5.5% (n = 31) had died or moved at the time of analysis and were subsequently excluded (Figure 1). The final match indicated that 4.6% (n = 500) of women in the Hepatitis Registry gave birth to 537 children during the study period (Table 1; Figure 1), 57% of whom had no known HCV RNA result.

Births during the study period to women who did not test HCV-positive were significantly different than the 1% (537/55,623) of births to mothers who tested HCV-positive. In both univariate and multivariate models, mothers with positive HCV testing had higher adjusted odds of being white, older, less educated, publicly insured, and unmarried than were mothers without a positive HCV test result (Table 1). Retention of multiple births (sequential or nonsingleton) by mothers did not significantly change the results of these analyses (data not shown). Of the mothers known to test positive for HCV, 20.3% (n = 109) had received an HCV test during their pregnancy, although testing in pregnancy had no effect on the likelihood of their child being tested for HCV (data not shown).

At the time of this analysis, PDPH had received an HCV test result for 84 children (16%) who were born to women who tested HCV-positive in the Registry (Table 1; Figures 1 and 2). Of these, 38 (45%) were adequately tested and 4 (5%) were identified as confirmed perinatal cases (all HCV-Ab and HCV RNA positive) (Figure 2). An additional 4 children were identified as probable perinatal cases (all tested HCV-Ab positive before 6 months of age with no follow-up testing) that will require further testing to confirm infection. Two of the confirmed perinatal children were born to women with no reported RNA result, 3 were born to mothers who were not tested for HCV during pregnancy, and 1 was born to a woman who was reported for the first time after childbirth (data not shown). Thirty-four adequately tested children were classified as uninfected, including 4 with HCV-Ab-positive and HCV RNA-negative test results after 18 months of age, who are thought to have spontaneously cleared the infection.

Using the 5% vertical transmission rate, an estimated 27 children of the 537 births to mothers tested HCV-positive are expected to be chronically infected with HCV (Figure 1). Given that 4 (15%) are confirmed perinatal children, 23 (85%) children remain unidentified and may be living with chronic HCV infection (Figure 1). The lower limit for the estimate of children perinatally infected with HCV is 22 (4%), which would leave 18 (82%) of children unidentified.

**DISCUSSION**

This study demonstrates that a notable number of women testing HCV-positive are giving birth in a major US city, and the majority...
of their children, 84% (n = 181 per year), are not being adequately tested for HCV infection. As a result, most chronically infected children are unidentified and therefore unable to be linked to specialty care. These findings support the 2012 analysis that highlighted a nationwide failure to identify HCV-Ab–positive children [27]. The delay in identifying pediatric HCV infections can elevate a child’s risk of developing adverse health consequences of prolonged infection, increase secondary transmission, and result in higher healthcare costs [7, 23].

Mothers tested HCV-positive in this study show evidence of being socioeconomically disadvantaged—that is, more likely to be unmarried, less educated, and publicly insured than mothers without a reported HCV-positive result. Mothers with positive HCV testing were also nearly 8 times as likely to be white, an observation that correlates with the nationwide increase in HCV infection among young non-Hispanic white injection drug users [4]. Barriers to HCV-specific care within this population have been well identified and include a lack of knowledge about the severity of the infection, inadequate insurance coverage, limited access to HCV care, and ineligibility for treatment [28, 29]. As a result of these barriers and the limits of risk-based testing, it is likely that there are many more HCV-infected mothers in Philadelphia who have not yet been identified [16, 30]. Although there are currently no interventions that can prevent a woman with HCV from perinatally transmitting to her children, screening pregnant women for HCV infection is critical to ensuring that exposed children are tested for HCV infection. Prenatal care also provides an opportunity to identify HCV-infected women not regularly engaged in the healthcare system.

There are multiple explanations for the considerable gap in the testing of children born to women tested HCV-positive. First, screening of pregnant women for HCV is not routine in

<table>
<thead>
<tr>
<th>Maternal Characteristic</th>
<th>Mother Tested HCV-Positive in Hepatitis Registry</th>
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<th>Multivariate Analysis</th>
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<td>Yes (n = 537)</td>
<td>AOR (95% CI)</td>
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<td>18 497 (34)</td>
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<td></td>
<td>36–45 y</td>
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Data are presented as No. of births (%) unless otherwise specified. Percentages may not sum to 100% due to rounding.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HCV, hepatitis C virus.
prenatal care, and HCV-related risk factors may not be regularly ascertained; thus, opportunities for an active dialogue between infected mothers and their healthcare providers are missed. Indeed, there is a need for increased physician education about HCV infection in general, including prevention, early detection, and current therapies [30, 31]. Second, women may be unaware of the severity and transmissibility of their HCV infection and therefore not disclose their status to their obstetrician. Education about the importance of HCV-related medical care for mother and child must be effectively communicated to women at all points of care. Third, pediatricians may not be alerted to a mother’s HCV infection status from the obstetrician, birthing hospital, or mother, therefore preventing adequate testing from being initiated [19, 20]. Moreover, pediatricians may be waiting until a later age to test children for HCV; however, children in this study born in 2011 were tested at statistically the same rate as those born in 2013 (data not shown). Last, many pediatricians may be unaware or skeptical of the guidelines for testing children exposed to HCV. This study showed that even when performed, testing often did not adhere to current guidelines. Widespread education of pediatricians on the adequate testing recommendations and a review of the national guidelines may be warranted. Without improved communication between primary care providers, obstetricians, pediatricians, and HCV-infected mothers, children are likely to remain untested.

This study has a few limitations. Surveillance-based research relies on the reporting of laboratory test results. Although additional data were obtained to more accurately assess HCV testing among both mothers and children, it is likely that there are still some missing data. Another limitation is the absence of maternal HIV status in this study. Because HCV/HIV coinfection increases the risk of perinatal transmission, our analysis likely underestimates the number of children perinatally infected with HCV during the study period. It is also likely that there are women infected with HCV who were unreported to PDPH or who remain untested, as evidenced by children identified in this study with no PDPH record of maternal infection (data not shown). Inclusion of these women would further increase the number of potential children with perinatal HCV infection. Given the wide range of published perinatal transmission rates resulting from differences in study design and populations [10], it is possible that the true expected number of HCV-infected children may differ from study estimates. Finally, the up to 30% of HCV-infected mothers with unknown RNA status may include some women who would have tested HCV RNA negative. Inclusion of HCV-Ab–positive mothers with unknown RNA status was important because many high-risk groups may only be tested in environments where HCV RNA testing is not offered, such as methadone clinics and drug rehabilitation facilities. Two of the confirmed perinatal cases were born to women with unknown RNA status, and the perinatal transmission estimate adjusted for HCV RNA–negative mothers was still noteworthy.

It is important for both patients and providers to be aware of the risks of vertical HCV transmission and to understand the steps required to identify children perinatally infected with HCV. This study showed that a notable number of births are occurring to women who tested HCV-positive but that a gap exists in testing of perinatally exposed children. As a part of standard healthcare, women should be encouraged to communicate their HCV infection statuses to relevant providers. In addition, healthcare providers of mother and child must communicate with each other and adequately test every child who is exposed to HCV. Identifying children with perinatal HCV infection and introducing them to specialty care and eventual treatment

Figure 2. Hepatitis C testing and testing results for children born to women tested Hepatitis C virus (HCV)-positive and the testing adequacy according to the American Association for the Study of Liver Diseases and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition national guidelines. Chart shows inadequately tested/uninfected (n = 42); probable perinatal HCV (n = 4); confirmed perinatal HCV (n = 4); adequately tested/uninfected (n = 34); and untested (n = 453) groups.
and cure is imperative to their comprehensive well-being. Further efforts should ascertain the reasons for the gap in testing of children born to women with HCV infection and guide future research and policy discussions surrounding the care of HCV-infected women and their children.

**Notes**

**Disclaimer.** The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention (CDC).

**Financial support.** This work was supported by the CDC (cooperative agreement U51PS004045-02).

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**