

Expected and Actual Case Ascertainment and Treatment Rates for Children Infected with Hepatitis C in Florida and the United States: Epidemiologic Evidence from Statewide and Nationwide Surveys

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Objective To evaluate the rate of pediatric hepatitis C virus (HCV) case ascertainment relative to the estimated number of actual cases.

Study design Data from Florida and United States health departments were used to assess pediatric HCV case ascertainment rates in Florida and nationwide. The percentage of children infected with HCV from Miami-Dade County receiving medical care by a pediatric gastroenterologist was estimated based on data obtained from physician questionnaires.

Results From 2000 through 2009, 2007 children were identified as having positive HCV antibody tests in Florida, only 12% of the expected number ($n = 12\,155$). An estimated 1.6% of the expected children with HCV who tested Ab-positive (37 of 1935) were actively followed by a pediatric gastroenterologist in Miami-Dade County, Florida. Across the United States, only 4.9% of the expected cases have been identified.

Conclusions The identification of children infected with HCV in the nation as a whole is grossly inadequate. Only a small fraction of cases are identified. In Florida, less than 2% of children identified receive treatment. Lack of identification and lack of treatment of children infected with HCV constitute critical public health problems. Strategies to increase awareness of HCV infection and to screen at-risk individuals could substantially improve morbidity and mortality while reducing health care costs. (*J Pediatr* 2012; ■:■-■).

Hepatitis C virus (HCV) infection is a global health problem, affecting 170 million persons worldwide.¹ Over the next 10 years, approximately 120 000 people in the United States will die from end-stage liver disease or liver cancer associated with chronic HCV infection.² The projected worldwide cost associated with managing complications from chronic HCV in the next decade is \$10.7 billion.³ The direct medical costs of caring for children with chronic HCV infection over the coming decade is estimated to be between US\$168 million and 404 million.⁴ HCV infection is a silent disease that most often goes unnoticed until symptoms of advanced liver disease appear, at which point liver transplantation may be the only option for long-term survival.

The third National Health and Nutrition Examination Survey (NHANES)⁵ indicated that nearly 200 000 US children were exposed to HCV, with 75%-80% of them being chronically infected. The natural history of pediatric hepatitis C is still not clearly understood. Although a majority of infected children tend to have mild fibrosis,^{6,7} others have advanced fibrosis, cirrhosis, decompensated liver disease, and even hepatocellular carcinoma.⁸⁻¹³ Given the natural history of HCV in adults, an as yet unknown proportion of children with HCV are probably at risk for serious long-term complications.

Current antiviral therapies can achieve a sustained virologic response (SVR) in approximately 53% of children infected with HCV genotype 1 and in up to 90% with other genotypes.^{14,15} The recent US Food and Drug Administration approval of 2 protease inhibitors, telaprevir and boceprevir, for adults will substantially increase the efficacy of treatment potentially reaching SVR rates of up to 60%, 70%, and 80%.¹⁶⁻¹⁸ Although these protease inhibitors have not yet been approved for children, it is expected that they will increase pediatric SVR rates in the future. However, in order for these therapies to be considered effective in real life settings, it is crucial that they reach the population for which they are intended. Thus, identifying children infected with HCV and linking them to medical care are the essential first steps toward an effective management of this infection.

HCV	Hepatitis C virus
IOM	Institute of Medicine
MERLIN	Medical Emergency Relief International
NHANES	National Health and Nutrition Examination Survey
SVR	Sustained virologic response

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Insufficient health care utilization has been specifically recognized as an important factor responsible for poor control of adult HCV infection.¹⁹⁻²² What have yet to be established are the interventions that will lead to improved rates of treatment initiation among those infected. Important next steps for pediatric HCV infection involve improving our understanding of its natural history and developing treatments that are not only efficacious but that are made available to the majority of those who need them. We, therefore, sought to determine whether children with HCV are being adequately identified and whether they are being considered for antiviral therapy.

Methods

The study had 2 parts. The first was a statewide study in Florida; the second was a nationwide study in the United States.

The Florida Study

Ascertainment of Pediatric Cases of HCV in Florida.

Florida was selected because it mandates reporting of all acute and chronic cases of HCV infection by laboratories and health practitioners, and because it uses a powerful database (Medical Emergency Relief International [MERLIN]) for ascertainment of reported cases (http://www.doh.state.fl.us/disease_ctrl/epi/epi_updates/2002/attachments/0704att4.htm). This database is part of the national bioterrorism preparedness program and receives real-time data from all Florida counties 24 hours a day, 7 days a week. All cases that were HCV antibody-positive reported to the Florida Health Department for children 0-19 years of age between January 1, 2000 and December 31, 2009 and their associated demographic information were analyzed. Adult cases were included for comparison. Patient identifying information was excluded from the data pursuant to Florida statute. Reports were run several times over a 2-week period. MERLIN database excludes duplicate case reports. It is important to note that reporting of all identified HCV antibody-positive cases is ensured by automatic reporting directly from all laboratories in the state to the Health Department. Therefore, reported cases in Florida represent all identified HCV antibody-positive cases.

Identification and Management of Pediatric HCV in Miami-Dade County. Testing and reporting sources for each case identified in Miami-Dade County, the most populous in the state, in 2009 were reviewed. All pediatric gastroenterologists listed in the North American Society of Pediatric Gastroenterology Hepatology and Nutrition website (<http://www.naspghan.org/>) as working in Miami-Dade County in 2009 were contacted and asked to complete a brief online questionnaire. The list of pediatric gastroenterologists in the Miami-Dade area was corroborated through publicly available information from the Florida Board of Medicine. The questionnaire inquired about specific data including:

(1) duration of medical practice in Florida; (2) number of children infected with HCV currently being followed; and (3) number of children infected with HCV evaluated during the previous 5 years. No incentives were provided for their participation.

The Nationwide Study

Ascertainment of Pediatric Hepatitis C-Infected Cases in the United States. Hepatitis C coordinators from each of the 50 state health departments of the United States were contacted via e-mail, telephone, or both. These coordinators are part of a national Hepatitis Prevention Program, funded by the Centers for Disease Control in partnership with other nationwide and state agencies. All information about ascertainment of pediatric HCV from 2000 through 2009 was requested. Requested data included qualitative data, such as the regulations for reporting HCV infection in each of the states, and quantitative data, such as the number of reported cases and their associated demographic information.

Calculations and Statistical Analyses

The frequency of total reported pediatric cases was analyzed by year of report, case status, age, sex, race and ethnicity, testing, and reporting source. The primary statistic of interest was the percentage of expected cases that were identified, computed as:

$$\frac{\text{number of cases identified between} \\ (1/1/2000 \text{ and } 12/31/2009)}{\text{number of expected cases}} \times 100 \\ (\text{ie, prevalence} \times \text{population in 2009})$$

The published reported prevalence of pediatric HCV infection in the United States comes from NHANES III data, in which 0.2% of children 6-12 years old and 0.4% of children 13-18 years old were HCV antibody positive.⁵ Because the distribution of 0-12 and 13-18 year olds was equivalent in our study population, we calculated the average of the 2 resulting in an estimated prevalence of 0.3%. The number of expected pediatric cases was obtained by multiplying this prevalence times the pediatric population (0-18 years) in 2009.

For the Florida study, the number of cases identified among children was adjusted for individuals who had aged into adulthood during the 10-year data collection window by subtracting those who would be more than 18 years of age by 2009 from the total number of identified cases. The population for the State of Florida was obtained from the US Census Bureau. The number of adults identified with HCV infection in 2009 was calculated by adding the total number identified as adults plus those who were identified as children but who were older than 18 years by 2009.

More recent data is available for adults in a study by Armstrong et al based on NHANES (1999-2002).²³ This investigation revealed a weighted prevalence of 1% (20-29 years old), 2.1% (30-39 years old), 4.3% (30-49 years old), 1.6% (50-59 years old), 0.9% (60-69 years old), and 1.1% for adults older

than 70 years. Based on this information, we calculated the estimated prevalence for adults >19 years old (excluding children) to be 2.0% and this prevalence was used for calculations of the adult population. The number of expected adult cases was obtained by multiplying this prevalence times the adult population (>19 years old) in 2009. Of note, the Armstrong prevalence data of 1999-2000 was probably based on enzyme-linked immunosorbent assay 2.0 for which the false-positive rate may be high. This might lead to an overestimation of antibody-positive individuals. In addition, based on personal communication with Armstrong et al, the pediatric prevalence of HCV corresponding to NHANES 1999-2002 was approximately 0.1%. However, this estimate is unstable because of the small number of subjects and the relatively large confidence intervals. The report by Armstrong et al did not include details of the pediatric population.²³

For Miami-Dade County, the proportion of infected children who were receiving medical care for HCV by a pediatric gastroenterologist in 2009 was estimated by dividing the number of children actively followed by pediatric gastroenterologists (obtained from online questionnaires) by the expected number of infected children.

As described above for the Florida study, the ratio of identified-to-expected cases was evaluated nationwide. However, given the limitations of the data, we could not adjust for children aging into adulthood.

Results

The Florida Study

The expected number of children younger than 19 years of age positive for HCV antibodies in 2009 was estimated to be 12 311 ($4\ 103\ 700 \times 0.3\%$) (Table). During the 10-year study period, 2007 Florida children were reported to be HCV Ab-positive. Of those, 1444 were still children in 2009; the remainder (632) had aged into adulthood. Thus, only 11.7% (1444/12 311) of the expected pediatric cases had been identified.

In contrast, in 2009, the total number of adults in Florida was 14 434 290, of which 166 225 adults 19 years of age or

Table. Population and HCV-related statistics

Characteristic	Estimate
Total population of Florida in 2009	18 538 000
Total population of children (under 19 years old) in 2009	4103 700
Estimate population prevalence of HCV Ab-positive children	0.03
Expected number of HCV Ab-positive children in 2009	12 311
Number of HCV Ab-positive children identified between 1/1/2000 and 12/31/2010	2007
Number of HCV Ab-positive children 2009	1444
Proportion of expected HCV Ab-positive children identified	11.7%
Number of expected HCV Ab-positive children in Miami-Dade County in 2009	1935
Number of identified HCV Ab-positive children in Miami-Dade County in 2009	440
Number of identified HCV Ab-positive children under treatment in 2009 in Miami-Dade County	31
Proportion of identified HCV Ab-positive children under treatment in 2009 in Miami-Dade County	1.6%

older had been identified as being HCV Ab-positive. Adding the 632 children who had become adults by 2009 brings the total number of adults known to be HCV Ab-positive in 2009 to 166 857. Thus, 58% of the expected 288 685 (13 434 290 \times 2% seroprevalence) adults who were HCV Ab-positive in Florida were identified. In other words, the proportion of children with HCV who were identified to be Ab-positive (11.7%) was estimated to be only about one-fifth that of the proportion of adults with HCV who were identified to be Ab-positive (58%).

In Miami-Dade County, the expected number of children with HCV who were Ab-positive in 2009 was 1935, with 440 cases being reported between 2000 and 2009. There are 13 pediatric gastroenterologists in Miami-Dade County, and 100% of them responded to the online questionnaire. They reported a total of 31 children receiving care for hepatitis C infection in 2009. In addition, another 55 children had been evaluated or received care for HCV infection in the previous 5 years. Thus, only 1.6% of the children expected to be HCV Ab-positive were receiving care for this condition in 2009, and only 2.8% of expected children had received care over the previous 5 years. The Table summarizes the population and HCV-related statistics.

Of the 2007 children identified as HCV Ab-positive in Florida during the study period, 48% were girls. Most identified cases did not have racial information available (54.7%) and almost one-half of identified patients (49%) had missing ethnic information. Thirty-five percent were identified as white, 9.6% were African-American, and 0.3% Asian. Thirty-five percent were non-Hispanic and 16% were Hispanic. The age distribution was bimodal with peaks in the first year of life and between 16 and 18 years of age (Figure 1).

Of the 37 cases reported in Miami-Dade County for 2009, refugee health centers reported 16; physicians reported 11; hospitals, 4; blood banks and community-based organizations 2 each; and correctional facilities and public health clinics, 1 each.

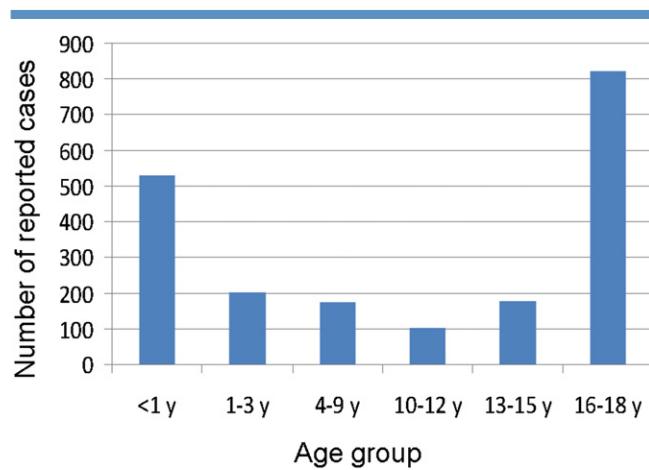


Figure 1. Age distribution of 2007 children with hepatitis C antibodies identified in Florida in 2009.

The Nationwide Study

Requirements for reporting HCV infection vary throughout the country and are depicted in **Figure 2**. New York, Minnesota, Connecticut, Colorado, and Oregon are funded by the Centers for Disease Control and Prevention to conduct enhanced HCV surveillance. Some mechanism for ascertaining chronic HCV is in place in 29 states where chronic HCV is a mandated reportable condition. Cases of chronic HCV are reportable in Alabama, Arkansas, Arizona, Delaware, Maryland, Nebraska, Nevada, and Virginia, but these states have no mechanisms for managing these data. The Pennsylvania Department of Health did not provide any information. The remaining states do not mandate reporting cases of chronic HCV infection.

Of the 35 states reporting information, 9 identified between 0% and 20% of total expected cases (children and adults), 15 identified between 20% and 40%, 8 identified between 40% and 60%, and only 3—New Mexico, Massachusetts, and Alaska—identified more than 60% of expected cases. Eight states reported that data were not available, and 7 others provided no information. In contrast, when pediatric cases were analyzed (**Figure 3**), 19 states identified 0%-20% of expected cases, Massachusetts identified 20%-40% of cases, New Hampshire identified 40%-60%, and the remaining states either did not have data available or did not respond to the survey. When estimating the percentage of children identified over those expected, it is noted that

in the nation as a whole, only 4.9% of the expected cases have been identified.

The prevalence of pediatric HCV antibody positivity used in this investigation was chosen because it is the only published NHANES-based prevalence available in children. However, we repeated all analyses using data from personal communication with Armstrong et al, which, as noted above, is higher (0.1) but may not be stable. Using the higher prevalence, we found that in Florida there were 35.1% of identified over expected HCV antibody-positive children and in the nation as a whole there were 14.7% of identified over expected pediatric cases. Using this higher prevalence we also found that some states with better surveillance exceeded greatly the expected number of subjects (ie, Massachusetts had identified 107% and Vermont had identified 167% of expected cases respectively), which suggested that 0.1% may be lower than the true prevalence at least in some locations.

Discussion

In this study, we report on the lack of adequate case-ascertainment of children with HCV in the State of Florida (which identified only 11.7% of expected cases, about one-fifth of the proportion of adults identified) and in the nation as a whole (in which only 4.9% of expected cases were identified). Even more concerning is the finding that only a small minority of identified children receive medical care for this condition (1.6% of the 1935 children in Miami-Dade

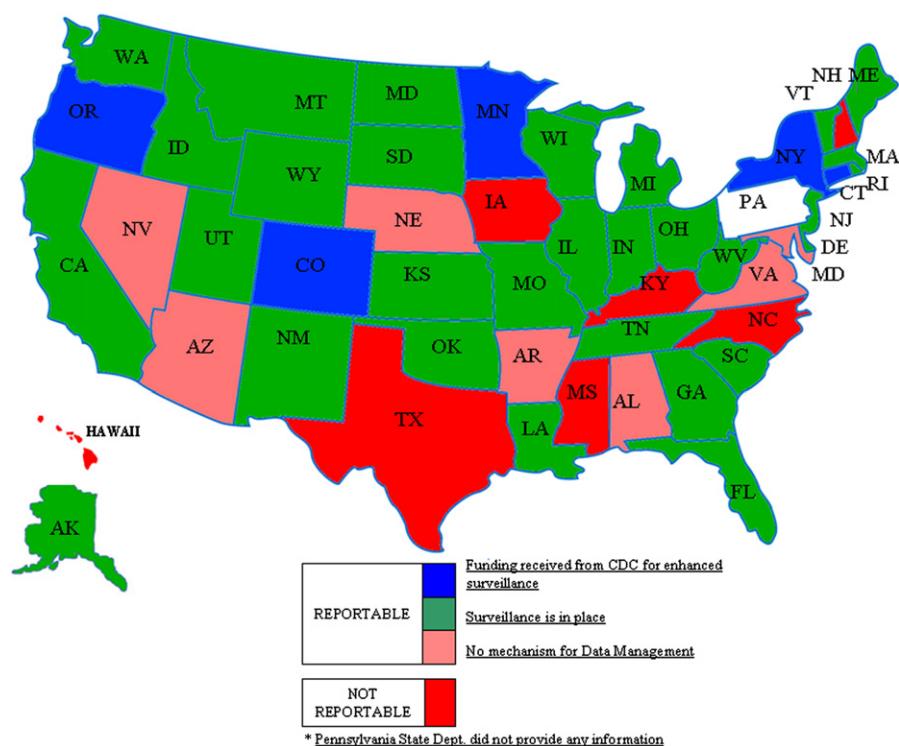


Figure 2. State requirements for reporting chronic cases of HCV infection. CDC, Centers for Disease Control and Prevention.

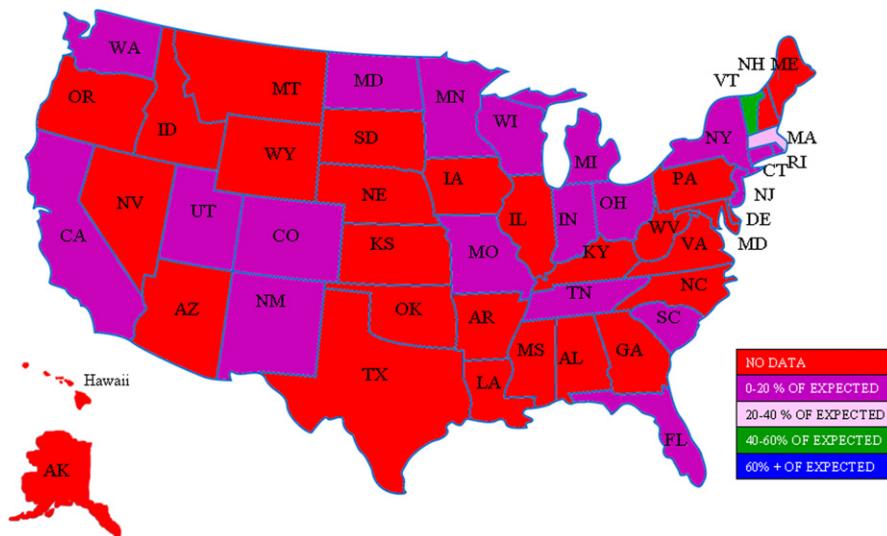


Figure 3. Case ascertainment rates of pediatric HCV infection in 2009, by state.

County). There was insufficient information about race and ethnicity to determine the distribution for the entire identified population, but among those with available information, most were identified as white and as non-Hispanic. There was a bimodal distribution with regards to age. This could depend on the age at which patients are more likely to be tested for HCV infection and/or it could represent true differences in prevalence with the earlier peak (below 1 year of age), possibly as a result of maternal antibodies and not a true infection.

Florida was selected for investigation because it is one of the few states that requires all acute and chronic cases of HCV to be reported to the Health Department and because its MERLIN database places it at the forefront of communicable disease reporting. HCV coordinators from the 3 states that identified the larger percentage of cases with HCV overall, including New Mexico, Massachusetts, and Alaska, reported a number of reasons that could account for their higher ascertainment rates. Among these were public funding to support efforts for more efficient reporting, robust disease surveillance systems, initiatives to screen inmates and other individuals at risk through structured programs.

Early identification of HCV can result in SVR in 53%-90% of infected children harboring HCV genotype 1 or non-1 infection, respectively.^{11,14} Achieving SVR may prevent chronic liver injury, including fibrosis, and, by extension, avert the development of liver failure, hepatocellular carcinoma, and premature death.^{24,25} Early identification and sustained treatment response may also reduce patient and family stress, social stigmatization, and the financial burden associated with HCV. Treatment of all infected persons in 2010 could reduce risk of cirrhosis, decompensation, cancer, and liver-related deaths by 16%, 42%, 31%, and 36% by 2020, given current response rates to antiviral therapy.²⁶

Natural history studies of patients who acquired HCV from transfusions as children have found that severe hepatic dam-

age usually occurs after the first 30 years of life.^{24,25} Natural history studies of perinatally acquired HCV with extended follow-up periods are not available. Several studies have found mild fibrosis in the majority of children infected with HCV (55%-97%).^{6,7} Others have reported pronounced fibrosis in 25%-75%, as well as cirrhosis in at least 8%.^{8,9} The only multicenter trial of pediatric HCV in the United States found mild, moderate, and severe liver inflammation in 60%, 38%, and 3% of the 121 children, respectively; 5 children had advanced fibrosis and 2 had cirrhosis.¹⁰ Among 332 children, Bortolotti et al found progression to decompensated cirrhosis in 6 (1.8%).¹¹ At least 4 children with HCV with hepatocellular carcinoma have been reported.^{12,13} However, most children with HCV infection are asymptomatic or present with vague, nonspecific symptoms.

Despite substantial research investment to achieve SVR among patients with HCV, the greatest improvement in therapeutic effectiveness may likely be accomplished simply by identifying infected individuals and referring them for proper medical management. The most important barriers to treatment of patients infected with HCV are insufficient diagnosis and referral.²⁷ Our results indicate that only 11.7% of expected pediatric cases are identified in Florida, and only 1.9% of expected cases are under the care of a trained physician for their infection. Given current treatment response rates, and assuming that all children followed by pediatric gastroenterologists were to undergo therapy and that SVR rate was about one-half, only 0.8% of expected cases are being treated successfully. The alarming difference between antiviral efficacy (in clinical trials) above 50% and an actual effectiveness (in real life situations) of as low as 0.8% must be addressed. Improving the efficacy of therapy is unlikely to improve the health of thousands of affected individuals until those with the disease are identified and considered for therapy.

The major factor responsible for impeding current efforts to prevent and control hepatitis B and C is lack of knowledge and awareness about these diseases among healthcare and social-service providers, members of the public, and policy makers.² According to the Institute of Medicine (IOM), resources allocated to prevention, control, and surveillance programs are inadequate, a situation that has led to continued transmission of these infections and inadequate case identification and medical management for chronically infected people. However, the IOM report did not address the disparity in identification and management between adult and pediatric cases, as noted in this study. The IOM provided recommendations to improve the identification and medical management of chronic HCV.² However, recommendations that specifically address infected children are needed.

An important limitation of this investigation is that the actual prevalence of pediatric HCV infection is not well established. It should be noted that estimates based on NHANES data did not include populations at greatest risk, such as children who are incarcerated or homeless, and they are not representative of certain populations that could be of high risk but have not been well studied. The prevalence used in this study is the only published NHANES-based pediatric prevalence, and it is possible that this prevalence may be higher based on unpublished data.²³ However, using a prevalence of 0.3 or 0.1 does not alter the important conclusion that only a minority of children with HCV have been identified and that even fewer are receiving medical attention for this condition. An additional limitation is that practitioners other than pediatric gastroenterologists could be treating children for HCV infection. However, we believe this possibility is unlikely. This was the only specialty chosen because, in Miami-Dade County, pediatric gastroenterologists care for the majority of children infected with HCV (based on personal experience, and confirmed through personal communication about referrals with the Miami-Dade Public Health Department and local pediatricians). Moreover, assuming that an equal number of children were being treated for HCV infection by nonpediatric gastroenterologists, only 3.8% of identified children would be receiving care for HCV infection instead of the estimated 1.9%.

It could be argued that case identification is not critical in children because advanced symptomatic liver disease from HCV occurs rarely in childhood and because exposure to treatment regimens with protean adverse effects in asymptomatic children may not be well accepted by care providers.²⁸ However, we argue strongly that a meaningful portion of children surprisingly have more advanced fibrosis, despite the brevity of disease duration.⁸⁻¹⁰ In addition, with decades of chronic HCV infection, many patients progress to pronounced fibrosis and often to end-stage liver disease,^{24,25} and the burden of chronic viral infection has also been associated with other morbidities.²⁹⁻³¹ Halting the progression of disease in early life may potentially result in better overall outcomes. Furthermore, the improving array of treatment options is likely to leave us with attractive treatment

choices within the next decade that spare important adverse effects and preserve efficacy.

Our findings suggest that current practices in the ascertainment and linkage to medical care for pediatric HCV infection need urgent improvement. The substantially lower identification rates among children compared with adults illustrate the need for diagnostic strategies specific to pediatrics. The barriers to diagnosis and linkage to medical care for children with HCV need to be targeted. Once children infected with HCV are in treatment, even existing therapies will substantially improve their outcomes, decrease morbidity, prevent unnecessary early deaths, and reduce costs.

An important next step to improve identification and medical referral of children with HCV is to educate the public at large, specifically parents infected with HCV and healthcare providers, about this disease. The importance of early identification and consideration for treatment need to be emphasized. The establishment of electronic databases and support for infrastructures to adequately ascertain cases and handle relevant data are also important elements in the control of this infection. Communication between the referring clinician and the subspecialist who will care for the child infected with HCV should start at the time of referral as an added measure to optimize evaluation and follow-up. Finally, legislative support would ensure that all individuals at risk for this condition, including all children of mothers infected with HCV, are adequately evaluated and followed. ■

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