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Screening for hepatitis C virus among adolescents and emerging adults in federally qualified health centers in the United States, 2012–2017

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BOSTON UNIVERSITY
SCHOOL OF PUBLIC HEALTH

Thesis

**SCREENING FOR HEPATITIS C VIRUS AMONG ADOLESCENTS AND
EMERGING ADULTS IN FEDERALLY QUALIFIED HEALTH CENTERS
IN THE UNITED STATES, 2012–2017**

by

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requirements for the degree of
Master of Science

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ABSTRACT

Introduction: Despite rising hepatitis C virus (HCV) incidence in the United States in recent years among young adults, little data describe HCV testing in youth. My objective was to characterize the HCV care cascade in adolescents and emerging adults in a large US sample and to describe the association between diagnosed substance use disorders (SUDs) and HCV testing.

Methods: In this retrospective cohort study, I describe HCV care cascade outcomes for youth 13–21 years old seen at least once from 1/2012–9/2017 at an OCHIN-participating federally qualified health center. Using electronic health record data, I analyzed odds of HCV testing by number of concurrent diagnosed SUDs associated with HCV risk (those associated with injection or intranasal use: opioids, amphetamines, and cocaine).

Results: Among 269,124 youth who met inclusion criteria, (54.7% female, 62.5% non-white, mean age [SD] at testing 18.5 [2.2] years), 6812 (2.5%) were tested for HCV antibody, 122/6812 (1.8%) of those tested were anti-HCV positive, and of anti-HCV positive youth, 75.4% had additional diagnostic testing. Only 1 had documented HCV treatment. Each additional HCV risk-associated SUD was associated with higher odds of HCV testing, particularly in younger (OR 9.12,

95% CI 6.78, 12.4 in 13–15 year-olds, and OR 8.37, 95% CI 7.48, 9.36 in 16–18 year-olds) compared with older youth (OR 3.9, 95% CI 3.59, 4.24 in 19–21 year-olds).

Conclusion: This study highlights important gaps in recommended HCV testing during the current opioid crisis. As the first step in the care cascade, addressing missed testing opportunities is critical for reducing hepatitis C burden.

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List of Abbreviations:

ADVANCE	Accelerating Data Value Across a National Community Health Center Network
CDC	Centers for Disease Control and Prevention
CHC	Community Health Center
FQHC	federally qualified health center
HCV	hepatitis C virus
EHR	electronic health record
ICD-9/10	International Classification of Diseases, 9th and 10th Edition
OR	odds ratio
RNA	ribonucleic acid
SUD	Substance Use Disorder
U.S.	United States

Objectives:

1. To characterize the hepatitis C virus (HCV) care cascade in a large national sample of adolescents and emerging adults 13–21 years old seen in an OCHIN-participating federally qualified health center.
2. To determine the association between diagnosed substance use disorders, namely opioid, amphetamine and cocaine use, and screening for HCV antibody in this cohort.

Hypotheses:

1. Substantial loss to follow-up will be observed at each step in the cascade.
2. Adolescents and emerging adults who have substance use disorders, in particular opioid, amphetamine, and cocaine use disorders, those most commonly injected or used intra-nasally, will be more likely to have been screened for HCV antibody.

Background:

Although the co-occurring opioid and hepatitis C virus (HCV) epidemics in the United States (U.S.) have most notably affected young adults 18–39 years old, overdose deaths and self-reported substance use have also increased sharply in adolescents (13–19 year-olds).^{7,9,26} However, HCV incidence in adolescents has not been well-described to date. The prevalence of HCV among individuals admitted to children’s hospitals across the U.S. has risen over the

past decade, particularly in adolescents with diagnosed substance use disorders.⁵ Overall HCV testing has also increased in both adults and children in recent years, although based upon national and statewide laboratory reporting data, these levels still fall far short of guideline-recommended screening for both adults and children.^{4,12,15–17,28} The United States Department of Health and Human Services National Viral Hepatitis Action Plan has set forth respectable goals for HCV elimination over the next few decades,²⁷ but in order to meet these goals, significant ramp up of testing, linkage, and treatment must be accomplished. Community health centers represent a key venue in the cascade to cure for HCV in general adult populations, and could serve an important role in screening adolescents and children, but few studies examine outpatient HCV screening and linkage practices in pediatrics.^{2,8,12,14,18,20,29} Additionally, to my knowledge, no published studies in the era of the current opioid crisis have specifically described adolescent HCV screening practices.

National guidelines recommend HCV screening for any adult or child, who is currently injecting or has in the past injected drugs (and less strongly recommend screening if any past or current intranasal drug use).^{1,11,23} HCV screening is also recommended for individuals with certain medical conditions (such as long-term hemodialysis, human immunodeficiency virus [HIV] infection), receipt of an unregulated tattoo, incarceration, and anyone who has had exposure to a potentially HCV-infected source via healthcare or other percutaneous or mucous membrane exposure, organ transplant, blood

transfusion, long-term sexual partner, or mother with HCV.^{11,23} Additionally, for adults, birth cohort screening has been recommended since 2012 for individuals born between 1945–1965 due to the high HCV prevalence noted in this age group.²¹ Studies examining uptake of birth cohort screening have shown increased screening rates following the 2012 and 2013 Centers for Disease Control and Prevention (CDC) and United States Preventative Services Task Force recommendations.^{4,6,12,22} However, even with rapid uptake of the recommendations, fewer than 50% of eligible birth-cohort individuals across the country have been HCV-tested.²² Multiple studies have also demonstrated geographic variation of birth-cohort screening and increased rates of HCV screening in African American and Hispanic adults^{6,8,22}.

Investigations into HCV prevalence and screening rates in the outpatient setting for other risk-factor groups are more limited. Mayer and colleagues examined HCV prevalence and provider perceptions about individual screening rates and barriers among a multi-state community health center (CHC) cohort.¹⁸ They report estimated clinic HCV prevalence rates (among all ages combined) of 0.1–3.7% for individual CHCs with an overall prevalence of 1.0%. Although 81% of providers reported regularly screening individuals with injection drug use for HCV, only 44.4% reported screening for HCV in individuals in the 1945–1965 birth cohort. In pediatrics, one study conducted in the 1990s revealed low prevalence of HCV in a Boston adolescent outpatient population (0.1%) and several in that era describe higher prevalence (approximately 2%) among

incarcerated youths.^{3,10,14,19,24} More recent studies demonstrate that routine screening of all 15–30 year-olds is predicted to be cost-effective when prevalence of injection drug use in a community is at least 0.59% (a level below estimates from national survey data),^{2,7} and showed increased linkage to care for 18–30 year-olds compared with older adults.²⁹ Furthermore, individuals under age 30 are those most likely to transmit HCV and therefore should be central in elimination efforts.³⁰ However, to my knowledge, no studies describe adolescent HCV screening, prevalence or care cascade outcomes during the current opioid crisis.

In this analysis, I therefore aim to characterize the HCV care cascade for adolescents and emerging adults, aged 13–21 years old, in a large, diverse, national sample of federally qualified health centers (FQHCs). My primary aim is to describe the proportion of youth tested for HCV in this cohort and to determine the association between the primary exposure, an identified substance use disorder (opioid, amphetamine, or cocaine use disorder) (SUD) that is potentially associated with direct HCV risk through injection or intranasal drug use, and the primary outcome, proportion HCV-tested, adjusting for demographic factors: age, sex, and race/ethnicity. As a secondary aim, I will describe the association between identified substance use disorders and HCV seropositivity, in other words, exposure to HCV.

My hypotheses are 1) that screening rates for HCV in 13–21 year olds in US FQHCs are low with substantial loss-to-follow-up at each step of the care

cascade and 2) that opioid, amphetamine, and cocaine use disorders diagnoses predict a higher odds of screening, but with persistent gaps remaining in youth with this recorded risk. Injection drug use is the risk factor noted most frequently in acute reported cases of HCV.^{20,26} I isolate this age group (13–21 year-olds) as it represents the population most likely to be seen by pediatricians and most likely to be HCV-tested for an injection drug-related risk factor. Children HCV-tested before the age of 13 are more likely screened for either evidence of perinatal HCV transmission or other (non-injection-related) blood or bodily fluid exposures. In youth 13–21 years old, however, with rising prevalence of substance use, testing for HCV is likely to represent screening in the presence of a recognized substance-related risk factor.^{7,9} In fact, in a recent study of patients admitted to children’s hospitals in the US with diagnosed HCV infection, diagnosed SUDs increased from co-occurring in 25% of children with diagnosed HCV in 2006 to 41% of children with HCV in 2012.⁵ In this study, I will use International Classification of Diseases, 9th and 10th edition (ICD-9/10) codes for substance use disorders, primarily those for opioid, amphetamine, and cocaine use, as a proxy for risk of injection or intranasal drug use, as these are substances that can be injected or used intra-nasally in various forms. Not all individuals with a diagnosed opioid, amphetamine or cocaine use disorder inject or intra-nasally use drugs, but these disorders do indicate that an individual is at higher risk of potential injection or intranasal drug use. Additionally, ICD-9/10 codes for substance use and dependence have been shown to have high

sensitivity (albeit poorer specificity) for detecting injection drug use.¹³

Design and Methods:

Study Population

OCHIN, formerly the Oregon Community Health Information Network prior to its expansion across many states and health systems, is a subset of the Accelerating Data Value Across a National Community Health Center Network (ADVANCE) cohort. OCHIN is a multisite, electronic health record (EHR) based data registry, that at the time of our data procurement in September 2017, included 549 individual FQHCs (98 health systems) across 19 states (Alaska, California, Colorado, Florida, Georgia, Indiana, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Mexico, North Carolina, Ohio, Oregon, Texas, Utah, Wisconsin, and Washington). Of the more than 2 million individual patients across the U.S. included in this cohort, 28% are under 19 years old, and 66% have either public insurance or are uninsured. For this analysis, we requested and analyzed data for all individuals with at least one visit to a participating OCHIN FQHC between January 1st, 2012 and March 31st, 2017, who were 13–21 years old at study end.

Data Collection

As an EHR-based cohort, data is retrospectively abstracted from the clinical data input into the OCHIN EHRs, and de-identified by the OCHIN team.

Substance use disorders are determined by ICD-9/10 codes for substance abuse or dependence entered into the EHR, and include alcohol, amphetamines, barbiturates, cannabis, cocaine, hallucinogens, and opioid abuse or dependence (Supplementary Table 1). I combined codes for dependence and abuse for each individual substance and categorized them jointly as the particular substance use disorder. Race/ethnicity and sex are abstracted directly from the EHR. Year of birth is included for all individuals, and dates for all laboratory values and visit dates are de-identified to a date within a similar time period. HCV antibody (anti-HCV), nucleic acid (RNA), and genotype as well as HIV antibody and RNA results are directly obtained from the EHR as well as ICD-9/10 codes for HCV (Supplementary Table 1) with associated de-identified first date of diagnosis. Finally, pharmacy records from the EHR for all HCV therapies with dates of initiation and completion were obtained as well. All individuals included in the dataset have complete data for each variable; anyone missing key demographic variables was excluded by OCHIN prior to data abstraction. For substance use variables, anyone without recorded substance use in the social history or by ICD-9/10 code for a SUD is considered not to have an *identified* SUD.

For HCV-tested individuals only (n=6812), each visit date and the insurance type (public, private, or self-pay) at the time of visit is also available as is HIV testing occurring over the study period.

Measures

Outcomes: The primary outcome was the proportion of youth in the cohort who were screened at least once for HCV over the study period. To isolate incident HCV screening from prevalent HCV diagnoses already made in the cohort, I excluded individuals with an HCV diagnosis by ICD-9/10 code that pre-dates (occurs prior to the exact date of) any HCV Ab testing occurring during the study period. Excluding these individuals yielded a study population size of N=269,124. An HCV screening event was defined by the presence of a completed HCV Ab test in the EHR. The secondary outcome will be positive HCV antibody testing.

Primary Exposure: The primary exposure, diagnosed opioid, amphetamine or cocaine use disorders, were determined by either ICD-9/10 coding for use or dependence as described above or by presence of substance use listed in the social history of the EHR. Each SUD was examined individually for independent effects on HCV testing in univariate analysis, however for the primary multivariable analysis, to account for collinearity between multiple SUDs and to account for the number of co-existing SUDs, I categorized individuals by the combined number of SUDs present that could be associated with injection or intranasal route (opioid, amphetamine, and cocaine use). This categorical variable has a range of 0–3, with 3 representing individuals with diagnosed opioid, amphetamine and cocaine use disorders, 2 representing youth with any

combination of 2 of these diagnoses, 1 indicating a single diagnosis, and zero indicating none of these diagnoses identified.

Care Cascade:

Cascade of care outcomes are be described as follows:

1. HCV tested (completed HCV antibody)
2. HCV seropositive (positive HCV antibody testing)
3. HCV RNA-tested (HCV RNA testing completed)
4. HCV viremic (HCV RNA positive)
5. HCV genotype completed
6. HCV treatment initiated (determined by HCV medication start date)
7. HCV treatment completed (determined by HCV medication stop date)
8. Sustained viral remission (cure, demonstrated by negative HCV RNA at least 12 weeks after completion of HCV treatment)

Each cascade outcome is conditional on the prior cascade outcome; in other words, all those with an HCV genotype completed are eligible for HCV treatment. This will exclude individuals who may have completed earlier cascade steps in other care locations or prior to study start, but will allow for clear categorization of individuals along the care cascade.

Potential Confounders: Year of birth was converted to age and examined along with race/ethnicity and sex as potential confounders of the association between diagnosed SUD and HCV testing and seropositivity. I categorized age

as 13–15 years, 16–18 years, or 19–21 years at study end as younger and older age groups may be approached differently by clinicians in determining risk factors, addressing testing, and considering the possibility of HCV treatment.

Analysis:

Cascade of care: Descriptive statistics were used to describe the cascade of care outcomes and the overall cohort, showing the proportion of participants receiving HCV screening, evaluation, and treatment over the study period.

Factors associated with screening: Again, using descriptive statistics, I describe the population HCV-screened and HCV seropositive by demographics, and single and combined SUDs. I then employed multivariable logistic regression analysis to explore factors associated with HCV testing (primary outcome), namely the number of identified substance use disorders (primary exposure), adjusting for potential confounders: race/ethnicity, age, and sex. Variables causing at least a ten percent change in estimate of odds of HCV screening to the univariate odds ratio were selected step-wise for inclusion in the multivariable model, and two-way interaction terms were evaluated as well, with stratified analysis completed in the case of significant interactions. For my original objectives, I considered evaluating each SUD individually, or opioid use disorder primarily; however, given significant associations and interactions between each individual SUD, as they are not mutually exclusive, and as shown, many individuals had polysubstance use, in order to isolate the effect of specifically the

SUDs associated with potential HCV risk, I therefore categorized the number of these SUDs occurring together. Institutional Review Board approval was obtained from Boston Medical Center, with exempt status given the fully de-identified data set. All analyses were performed using SAS version 9.4 (Cary, North Carolina).

Results:

In total, 269,287 individuals age 13–21 years old at study end (2017) visited an OCHIN FQHC from January 2012 through September 2017 (Figure 1). Excluding 163 with evidence of HCV by ICD-9/10 coding preceding any HCV testing observed, 269,124 met inclusion criteria and were analyzed; 147,198 (54.7%) were female, 101,014 (37.5%) white non-Hispanic, 47,476 (17.6%) Black non-Hispanic, 90,203 (33.5%) Hispanic, and 30,431 (11.3%) other race (Alaskan Native, American Indian, Asian, Native Hawaiian, other Pacific Islander, or no race reported) (Table 1). Altogether, 23,237 youth (8.6%) had a diagnosed substance use disorder (SUD), with cannabis use disorder being most common (20,058, 7.4%). Eight hundred seventy-five (0.3%) had a diagnosed opioid use disorder, 1738 (0.6%) a diagnosed amphetamine use disorder, and 2204 (0.8%) either a diagnosed opioid or amphetamine use disorder. By number of diagnosed SUDs with potential for injection or intranasal use, 1830 (0.7%) had one of these SUDs listed, 563 (0.2%) had two, and 180 (0.07%) had all three identified.

HCV Care Cascade

Over the study period, 6812 (2.5%) individuals were tested for HCV (Table 2), and of those tested 122 (1.8%) were HCV seropositive (Table 3). Of the 122 seropositive, 92 (75.4%) had confirmatory HCV RNA testing completed, of whom, 41 (44.6%) had positive HCV RNA, or in other words, evidence of chronic HCV infection (Figure 2). Fifteen (36.6%) of those with evidence of chronic infection had HCV genotype testing completed, and only one individual was treated for HCV during the study period. This individual was treated in 2017, and did have evidence of return for confirmation of cure (at least 12 weeks after therapy completion) before the end of the study period, but did have negative HCV RNA testing at 6 weeks into therapy (Figure 1).

HCV Testing by Diagnosed Substance Use

Of youth with diagnosed opioid use disorder, 311 (35.5%) were tested for HCV, and of those, 33 (10.6%) were HCV seropositive (Tables 2–3). Similar proportions of individuals with amphetamine and cocaine use disorder were also tested for HCV (33.4% and 37.4%, respectively), and of those tested, 34 (5.9%) youth with amphetamine use disorder and 11 (3.3%) with cocaine use were HCV seropositive (Table 3). Of youth with all three of these SUDs diagnosed, 118 (65.6%) were HCV-tested.

Multivariable Analysis

Unadjusted analysis examining individual covariates and the primary

exposure (diagnosed SUDs) revealed associations between each variable and the primary outcome (HCV antibody testing). Older age, male sex, Black non-Hispanic race, and individual SUDs were each associated with increased crude odds of HCV testing (Table 2). For age, this trend increased from an unadjusted odds ratio [OR] for HCV testing of 3.54 (95% confidence interval [95% CI] 3.21–3.90) for 16–18-year-olds compared with 13–15-year-olds, to an odds of HCV testing of 6.86 (95% CI 6.24–7.52) for 18–21 year-olds compared with 13–15 year-olds. Opioid and amphetamine use were associated with the highest univariate ORs for testing, 22.2 (19.3–25.6) and 21.0 (18.9–23.3) respectively. Examining associations between the number of diagnosed SUDs with potential direct HCV risk and HCV testing, the odds of HCV testing increased in a dose-dependent manner with the number of diagnosed SUDs (Table 2).

Model building was conducted using the 10% change in estimate rule, without including any variables a priori, and with the number of SUDs with potential for direct HCV risk (amphetamine, cocaine, and opioids) as the primary exposure. I first adjusted for age group given younger adolescents are likely generally perceived to have fewer risk factors for HCV given less reported substance use in these age groups.⁷ Adding this covariate indeed changed the estimate of the OR for HCV testing by 12.5%, decreasing the OR from 6.15 (95% CI 5.76, 6.56) unadjusted to 5.38 (5.05, 5.72) adjusted for age category (Table 4). I examined next race/ethnicity given reported bias in HCV testing in adults, with higher testing rates in Black and Hispanic individuals, controlling for risk

factors.^{6,8,22} Here I did not find a greater than 10% change in the odds of HCV testing for individuals by additional potential injection or intranasal route SUDs. Continuing stepwise selection by 10% change in estimates, sex did not meet criteria for entry into the regression model either. Next, I checked for the two-way interaction term between age category and ordinal number of potential injection or intranasal route SUDs, and indeed this interaction term was significant and increased the adjusted OR. Therefore, I decided to stratify by age to better evaluate for potential effect measure modification at different age categories. Repeating the 10% change in estimate rule with each age group, no additional covariates (neither race/ethnicity nor sex) were selected for the model. The final model, therefore, reflects age-stratification only (Table 5), and reveals higher odds of HCV testing by additional SUD diagnoses in younger (OR 9.12, 95% CI 6.78, 12.4 in 13–15-year-olds, and OR 8.37, 95% CI 7.48, 9.36 in 16–18-year-olds) compared with older age categories (OR 3.9, 95% CI 3.59, 4.24 in 19–21-year-olds).

Discussion:

In this large, national sample of youth seen at US FQHCs, 2.5% of youth were tested for HCV, and 1.8% were HCV seropositive. Each SUD examined was associated with increased screening for HCV, in particular opioid and amphetamine use disorders and the presence of more than one diagnosed SUD that is associated with potential HCV risk. Yet still only 22.9% of those with a

single SUD associated with potential HCV risk and only 65.6% of those with all three *diagnosed* SUDs associated with potential HCV risk were tested for HCV despite an HCV seroprevalence of 1.1–3.6% in individuals with any of these SUDs HCV-tested, and of 11% in those with opioid use disorder in particular, who were HCV-tested.

To our knowledge, this study is the first to provide estimates of outpatient HCV testing rates specifically in youth 13–21 years of age amidst the opioid epidemic. The only recent study to also examine this question, but across all children younger than 19 years of age and in a large commercially insured population, revealed a testing rate of less than 0.5%.¹² Other seroprevalence studies in youth were published prior to the current opioid epidemic or do not distinguish youth from young adults.^{3,29} More recent evidence exists for increased HCV diagnoses among pediatric hospitalizations in the U.S. and another among youth in Massachusetts.^{5,20} Consistent with this recent data, this study demonstrates substantial HCV test positivity in youth and emerging adults at FQHCs across the U.S. With direct acting antivirals now available for youth as young as 12 years old and increased linkage to care in 15–30 year-olds, expanding testing programs for HCV in adolescents and emerging adults represents a cost-effective strategy to initiating the cascade to cure.^{2,5,29}

Testing in this cohort appropriately occurred more frequently in youth with diagnosed SUDs, in particular opioid, amphetamine, and cocaine use disorders, those most likely to be injected or used intranasally therefore associated with

direct risk of HCV acquisition. Individuals with co-occurring SUDs had higher odds of being HCV-tested, but the identification of even one of these diagnoses should prompt appropriate risk assessment and screening. Increased testing also occurred for Black, Hispanic, and other race and for cannabis and alcohol use in unadjusted analyses without corresponding associations with increased HCV seropositivity. Although race/ethnicity was not found to confound the relationship between number of diagnosed SUDs and HCV testing, Black non-Hispanic race remained significantly associated with increased odds of HCV testing in all models evaluated (data not shown). This raises concern for bias in testing practices consistent with evidence in adult studies indicating increased testing associated with Black and Hispanic race in the absence of other risk factors compared to White non-Hispanics.^{6,25}

Limitations and Strengths:

I was able to utilize a large dataset that should be representative of the population seen at community health centers around the U.S. and is balanced in regards to age, sex, and race/ethnicity. The sample size (with no missing data) afforded power to find significant associations if they indeed exist, but also increased the chance of determining significance where it may not represent true findings. I therefore aimed to focus on associations with large effect sizes that persisted even with adjustment for the demographics that likely have an effect on the outcome based on provider biases in screening practices.

Another strength of the study is the quality of data obtained. HCV diagnoses and screening were determined directly from laboratory testing done within the OCHIN EHR, as opposed to utilization of billing or diagnosis data alone, which can be misrepresentative. The OCHIN FQHC sites, as primary care venues, represent the primary location where HCV and HIV screening should be occurring per guidelines. However, I was not able to capture any screening that occurred elsewhere, such as in an emergency department, during inpatient hospitalizations, at previous primary care locations outside the OCHIN FQHC network, or at specialty offices not part of the participating FQHCs. Additionally, as I only had laboratory testing completed during the study period, I may have missed anyone screened just prior to the study period. However, given the five-year time period captured and that youth were unlikely to be screened at an age younger than 13 for substance use related-risk factors, and as observed, occurred less frequently in younger age groups overall, it is likely few instances of previous testing were missed.

Another important limitation is that I did not have visit data or person-time contributed for those youth not screened for HCV over the study period. I could not therefore adjust for the number of visits as a variable to in the primary analysis or conduct a time-to-event analysis. Visit frequency and time followed could be important confounders – individuals with fewer visits within the system may be less engaged in healthcare, may not be continuing to pursue care within the particular FQHC, and regardless provide fewer opportunities for screening to

occur. These individuals could also be less likely to develop a relationship with a healthcare provider and disclose a risk factor for HCV such as substance use. Additionally, I did not have objective data such as toxicology screens, patient-reported substance use outcomes, or variables to represent substance use in the absence of ICD-9/10-coded abuse or dependence or social history documentation. However, the aim of the analysis was not to determine the likelihood of HCV screening by presence of substance use at all but rather by *identified* substance use disorders. Furthermore, coding data does not differentiate injection drug use from non-injection drug use disorders, and therefore I am using opioid, amphetamine and cocaine use disorders as a proxy for risk of injection (or intranasal use). Although not all individuals with these diagnoses has ever injected, the diagnoses provide a measure of risk for injection and therefore HCV risk. In addition, ICD-9/10 coding for SUDs likely significantly underestimates the true burden of disease. In fact, the proportion of youth in this sample with a diagnosed opioid or amphetamine use disorder (0.8%) approximates the overall age-adjusted proportion of youth reporting ever injection use (of any type) in the 2016 National Survey on Drug Use and Health (0.7%).⁷ Therefore, likely even fewer than 35.5% of individuals with any opioid use or than the 22.9% with any of opioid, cocaine, or amphetamine use for example, were HCV-tested.

Finally, additional information such as concurrent HIV testing, insurance status or geographic information such as U.S. region would have been useful to

evaluate as predictors of HCV screening, especially given geographic variation in substance use patterns and demonstrated differences in HCV screening in adults by region.^{12,22} I unfortunately did not have access to these variables for individuals not HCV-tested, however, or access to U.S. region on any individuals, and therefore could not adjust for these factors. Future studies examining the impact of region, HIV testing, and insurance status on HCV testing occurring in youth could be very helpful.

Conclusion:

In this analysis, I aimed to describe HCV screening and linkage occurring in youth 13–21 years old in this large, national US FQHC population and to determine factors that predict higher HCV screening rates to help identify where additional education and policy change around testing and referral support may be most beneficial. In the absence of prior studies demonstrating successes or failures in HCV screening in adolescents, especially amidst the current opioid and HCV syndemics, this study represents an area requiring heightened attention. Although the presence of opioid, amphetamine and cocaine use disorders were associated with increased HCV testing, still fewer than one third of individuals with any of these *identified* risks for HCV were tested, highlighting a need to improve screening programs in youth in order to achieve HCV elimination goals.

Master's Degree Candidate Role in Project:

I designed the analysis plan with help from my mentors in this project, Dr. Sabrina Assoumou, Dr. Benjamin Linas, and Dr. C. Robert Horsburgh, Jr., as well as input from my master's degree advisor, Dr. Ann Aschengrau, and from Dr. Scott Hadland and Dr. Alex Walley. Dr. Assoumou initially proposed the project of characterizing the HCV cascade to cure for adults in the OCHIN cohort as data to be utilized in a cost-effectiveness analysis, and she wrote the initial IRB and obtained the data, including the data for the associated pediatric cohort in order to later evaluate the pediatric cascade. I cleaned and operationalized variables from the raw pediatric data, and I planned and performed all data analysis for the project and drafted the thesis and manuscripts. I also performed the background literature search. Jenny Wang, MS, assisted with pulling the pediatric data from the larger cohort and oversaw my data cleaning and analysis. Mr. John Puro and Dr. Kenneth Mayer assisted with the data request through OCHIN and contributed to critical revision of the manuscripts.

Table 1: Demographic characteristics, youth seen at a participating federally qualified health center (FQHC), United States, 1/2012–9/2017^a

Characteristic	Total No. (%)
All	269,124
Age at Study End	
13–15 years	78,427 (29.1)
16–18 years	92,353 (34.3)
19–21 years	98,344 (36.5)
Sex	
Female	147,198 (54.7)
Male	121,926 (45.3)
Race	
White Non-Hispanic	101,014 (37.5)
Black Non-Hispanic	47,476 (17.6)
Hispanic	90,203 (33.5)
Other/Not Reported ^b	30,431 (11.3)
Diagnosed Substance Use Disorders (SUDs) associated with potential direct HCV-Risk ^c	
0 Diagnosed HCV-Risk SUDs	266,551 (99.0)
1 Diagnosed HCV-Risk SUD	1830 (0.7)
Amphetamines only	1070 (0.4)
Opioids only	391 (0.2)
Cocaine only	369 (0.1)
2 Diagnosed HCV-Risk SUDs	563 (0.2)
Amphetamine & Cocaine	259 (0.1)
Opioids & Amphetamine	229 (0.1)
Opioids & Cocaine	75 (0.03)
3 Diagnosed HCV-Risk SUDs	180 (0.07)
Substance Use By Agent ^d	
Alcohol	1591 (0.6)
Amphetamine	1738 (0.6)
Barbiturate	52 (0.02)
Cannabis	20,058 (7.4)
Cocaine	883 (0.3)
Hallucinogen	70 (0.03)
Opioids	875 (0.3)

Abbreviations: FQHC, federally qualified health center, HCV hepatitis C virus, SUD substance use disorder

^a FQHCs were located in the following states: Alaska, California, Colorado, Florida, Georgia, Indiana, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Mexico, North Carolina, Ohio, Oregon, Texas, Utah, Wisconsin, and Washington

^b Other includes Alaskan Native, American Indian, Asian, Native Hawaiian, other Pacific Islander, or no race reported

^c Amphetamine, cocaine or opioid use disorders

^d Individually listed SUD diagnoses are not mutually exclusive and include individuals with multiple co-occurring SUD diagnoses

Table 2: Association between HCV antibody testing and diagnosed substance use disorders, youth seen at a participating federally qualified health center, United States, 1/2012–9/2017, unadjusted analysis

Characteristic	Tested for HCV Antibody No. (%) ^a	Unadjusted Odds Ratio: HCV Antibody Testing (95% CI)
All	6812 (2.5)	--
Age at Study End		
13–15 years	509 (0.6)	Ref
16–18 years	2085 (2.3)	3.54 (3.21, 3.90)
18–21 years	4218 (4.3)	6.86 (6.25, 7.52)
Sex		
Female	3637 (2.5)	Ref
Male	3175 (2.6)	1.06 (1.01, 1.11)
Race		
White Non-Hispanic	2293 (2.3)	Ref
Black Non-Hispanic	1743 (3.7)	1.64 (1.54, 1.75)
Hispanic	2077 (2.3)	1.02 (0.96, 1.08)
Other	699 (2.3)	1.01 (0.93, 1.10)
Diagnosed Substance Use Disorders (SUDs) associated with potential direct HCV-Risk ^b		
0 Diagnosed HCV-Risk SUDs	6051 (2.3)	Ref
1 Diagnosed HCV-Risk SUD	419 (22.9)	12.8 (11.4, 14.3)
2 Diagnosed HCV-Risk SUDs	224 (39.8)	28.4 (24.0, 33.7)
3 Diagnosed HCV-Risk SUDs	118 (65.6)	81.9 (60.2, 112)
Substance Use By Agent ^d		
Alcohol	172 (10.8)	4.76 (4.06, 5.59)
Amphetamine	580 (33.4)	21.0 (18.9, 23.3)
Cannabis	1758 (8.8)	4.64 (4.38, 4.91)
Cocaine	330 (37.4)	24.1 (21.0, 27.7)
Opioid	311 (35.5)	22.2 (19.3, 25.6)

Abbreviations: HCV, hepatitis C virus, SUD, substance use disorder

^a Denominator for HCV antibody testing percentage is all youth in the sample with the individual characteristic (i.e. row percentages)

^b Amphetamine, cocaine or opioid use disorders

^c Using diagnosed HCV-Risk associated SUDs as a continuous variable (0–3)

^d Substance use disorder diagnoses are not mutually exclusive

Table 3: Anti-HCV seropositivity with diagnosed substance use disorders, youth seen at a participating federally qualified health center, United States, 1/2012–9/2017

Characteristic	Anti-HCV Positive No. (%) ^a
All	122 (1.8)
Age at Study End	
13–15 years	6 (1.2)
16–18 years	22 (1.1)
18–21 years	94 (2.2)
Sex	
Female	72 (2.0)
Male	50 (1.6)
Race	
White Non-Hispanic	57 (2.5)
Black Non-Hispanic	19 (1.1)
Hispanic	28 (1.4)
Other	18 (2.6)
Diagnosed Substance Use Disorders (SUDs) associated with potential direct HCV-Risk ^b	
0 Diagnosed HCV-Risk SUDs	68 (0.03)
1 Diagnosed HCV-Risk SUD	32 (1.8)
2 Diagnosed HCV-Risk SUDs	20 (3.6)
3 Diagnosed HCV-Risk SUDs	2 (1.1)
Substance Use By Agent ^c	
Alcohol	4 (2.3)
Amphetamine	34 (5.9)
Barbiturate	1 (12.5)
Cannabis	36 (2.0)
Cocaine	11 (3.3)
Hallucinogen	1 (10.0)
Opioid	33 (10.6)

Abbreviations: HCV, hepatitis C virus, SUD, substance use disorder

^a Denominator for anti-HCV seropositive is of all HCV antibody-tested youth with the individual characteristic

^b Amphetamine, cocaine or opioid use disorders

^c Substance use disorder diagnoses are not mutually exclusive

Table 4: Model-Building Process, Primary analysis

Variables in Model	Odds Ratio Estimate	95% Confidence Interval	Change in Odds Ratio Estimate by adding selected variable:
Crude OR for HCV Testing with primary exposure: ordinal 'injection' risk (0–3 for number of co-existing substance use disorders (SUDs) that are associated with injection or intranasal use and therefore HCV risk) ^a	6.15	5.76, 6.56	
Adding Age Category (13–15 years, 16–18 years, 19–21 years at study end)	5.38	5.05, 5.72	12.5%
OR Estimate for HCV testing, adjusting for injection risk category and age category	5.38	5.05, 5.72	
Adding Race/Ethnicity	5.75	5.40, 6.13	7.0%
OR Estimate for HCV testing, adjusting for injection risk category and age category	5.38	5.05, 5.72	
Adding Sex	5.34	5.01, 5.68	8.0%
OR Estimate for HCV testing, adjusting for injection risk category and age category	5.38	5.05, 5.72	
OR Estimate for HCV testing, with injection risk category, age category, & interaction term: age category * injection risk ^b	9.18	6.79, 12.4	81%

Abbreviations: HCV, hepatitis C virus, SUD, substance use disorder, OR odds ratio

^a Amphetamine, cocaine or opioid use disorders

^b p-value for interaction term <0.001

Table 5: Final models, association between HCV antibody testing and number of diagnosed substance use disorders associated with HCV risk, youth seen at a participating federally qualified health center, United States, 1/2012–9/2017

Stratum / Characteristic	Stratified Odds Ratio: HCV Antibody Testing ^b (95% CI)
<hr/>	
Age 13–15 years, at Study End	
Each Additional Substance Use Disorder, Associated with HCV Risk via Injection or Intranasal Use ^a	9.12, (6.78, 12.4)
<hr/>	
Age 16–18 years, at Study End	
Each Additional Substance Use Disorder, Associated with HCV Risk via Injection or Intranasal Use ^a	8.37 (7.48, 9.36)
<hr/>	
Age 19–21 years, at Study End	
Each Additional Substance Use Disorder, Associated with HCV Risk via Injection or Intranasal Use ^a	3.9 (3.59, 4.24)

Abbreviations: HCV, hepatitis C virus

^a Amphetamine, cocaine or opioid use disorders

^b Unadjusted as no covariates met the 10% change in estimate criteria

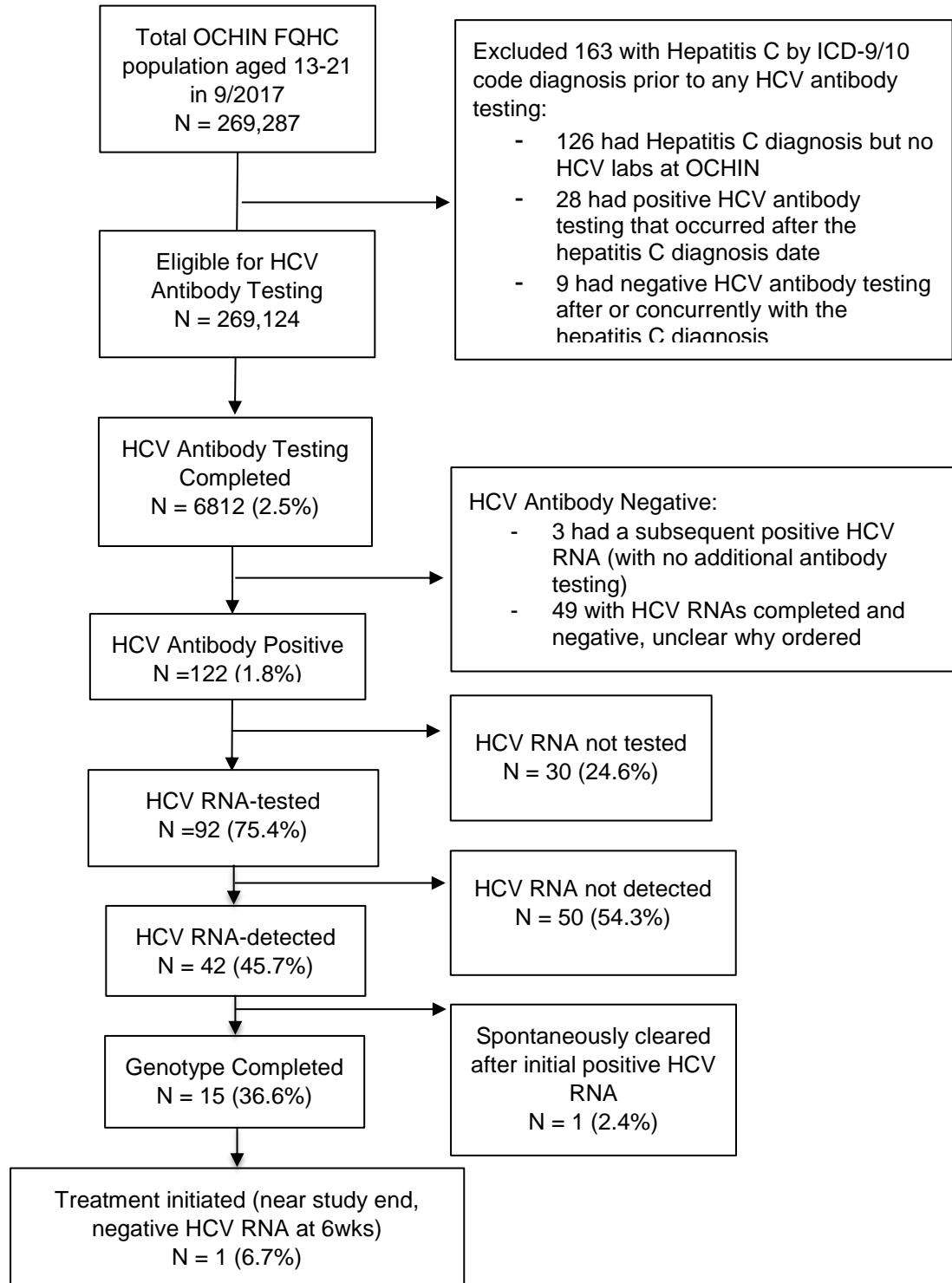
Supplementary Table 1: ICD-9/10 codes used for hepatitis C virus infection and substance use disorders^a

Hepatitis C Diagnoses	ICD-9 Code	ICD-10 Code(s)
Acute hepatitis C, without hepatic coma	070.51	B17.10
Chronic hepatitis C, without hepatic coma	070.54	B18.2
Unspecified viral hepatitis C, without hepatic coma	070.70	B19.20
Substance Use Disorders		
Drug dependence	304	F11, F12, F13, F14, F15, F16, F18, F19
Alcohol dependence	303	F10.2
Alcohol abuse	305	F10.1
Amphetamine dependence	304.4	F15.2
Amphetamine abuse	305.7	F15.1
Barbiturate dependence	304.1	F13.2
Cannabis dependence	304.3	F12.2
Cannabis abuse	305.2	F12.1
Cocaine dependence	304.2	F14.2
Cocaine abuse	305.6	F14.1
Hallucinogen dependence	304.5	F16.2
Hallucinogen abuse	305.3	F16.1
Opioid dependence	304.0	F11.2
Opioid abuse	305.5	F11.1

Abbreviations: ICD-9/10, International Classification of Diseases, 9th and 10th Edition

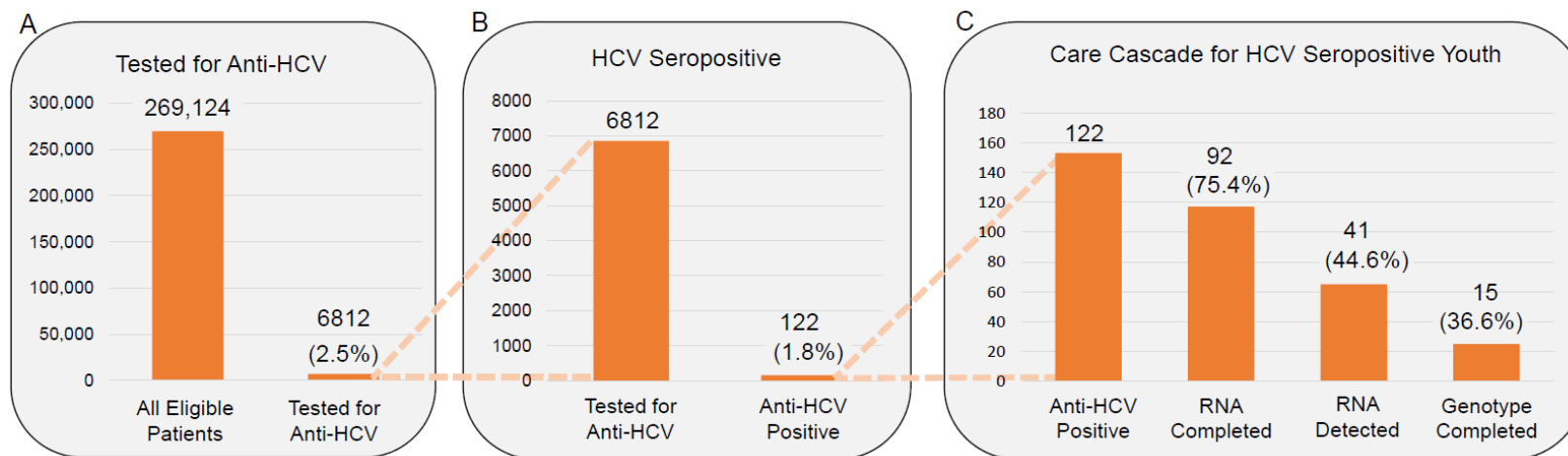
^a Abuse and dependence categories were combined to indicate an individual substance use disorder, and 'Any Substance Use' denotes the presence of any of the listed codes.

Figure 1: Study Flow Diagram



Abbreviations: HCV, hepatitis C virus; FQHC, federally qualified health center; RNA, ribonucleic acid; ICD-9/10, International Classification of Diseases, 9th and 10th Edition.

Figure 2: Hepatitis C care cascade for youth 13–21 years old seen at a participating FQHC, 1/2012–9/2017, United States



Legend: Outcomes along the Hepatitis C Care Cascade: Patients tested for anti-HCV (HCV antibody), seropositive (anti-HCV positive), those with HCV RNA completed and detected, and those with HCV genotype completed. Percentages in (C) are conditional.

Abbreviations: HCV hepatitis C virus; FQHC federally qualified health center; RNA ribonucleic acid.

Bibliography:

1. AASLD-IDSA. Key Populations: Identification and Management of HCV in People Who Inject Drugs. Recommendations for testing, managing, and treating hepatitis C. HCVGuidelines.org. <https://www.hcvguidelines.org/unique-populations/pwid>.
2. Assoumou SA, Tasillo A, Leff JA, et al. The cost-effectiveness of one-time hepatitis C screening strategies among adolescents and young adults in primary care settings. *Clinical Infectious Diseases*. September 2017. doi:10.1093/cid/cix798.
3. Bair RM, Baillargeon JG, Kelly PJ, et al. Prevalence and Risk Factors for Hepatitis C Virus Infection Among Adolescents in Detention. *Archives of Pediatrics & Adolescent Medicine*. 2005;159(11):1015–1018. doi:10.1001/archpedi.159.11.1015.
4. Barocas JA, Wang J, White LF, et al. Hepatitis C Testing Increased Among Baby Boomers Following The 2012 Change To CDC Testing Recommendations. *Health Affairs (Millwood)*. 2017;36(12):2142–2150. doi:10.1377/hlthaff.2017.0684.
5. Barritt AS, Lee B, Runge T, Schmidt M, Jhaveri R. Increasing Prevalence of Hepatitis C among Hospitalized Children Is Associated with an Increase in Substance Abuse. *Journal of Pediatrics*. 2018;192:159–164. doi:10.1016/j.jpeds.2017.09.016.
6. Bourgi K, Brar I, Baker-Genaw K. Health Disparities in Hepatitis C Screening and Linkage to Care at an Integrated Health System in Southeast Michigan. *PLoS ONE*. 2016;11(8). doi:10.1371/journal.pone.0161241.
7. Center for Behavioral Health Statistics and Quality (CBHSQ), Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services (HHS), and by RTI International. Results from the 2016 National Survey on Drug Use and Health: Detailed Tables. September 2017. <https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.htm>. Accessed July 23, 2018.
8. Cook N, Turse EP, Garcia AS, Hardigan P, Amofah SA. Hepatitis C Virus Infection Screening Within Community Health Centers. *Journal of the American Osteopathic Association*. 2016;116(1):6–11. doi:10.7556/jaoa.2016.001.

9. Curtin SC, Tejada-Vera B, Warmer M. Drug Overdose Deaths Among Adolescents Aged 15–19 in the United States: 1999–2015. *NCHS Data Brief*. 2017;(282):1–8.
10. Feldman GM, Sorvillo F, Cole B, Lawrence WA, Mares R. Seroprevalence of hepatitis C among a juvenile detention population. *Journal of Adolescent Health*. 2004;35(6):505–508. doi:10.1016/j.jadohealth.2004.02.007.
11. Final Recommendation Statement: Hepatitis C: Screening - US Preventive Services Task Force. U.S. Preventive Services Task Force. <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening#consider>. Published June 2013. Accessed May 15, 2018.
12. Isenhour CJ, Hariri SH, Hales CM, Vellozzi CJ. Hepatitis C Antibody Testing in a Commercially Insured Population, 2005–2014. *American Journal of Preventive Medicine*. 2017;52(5):625–631. doi:10.1016/j.amepre.2016.12.016.
13. Janjua NZ, Islam N, Kuo M, et al. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. *International Journal on Drug Policy*. 2018;55:31–39. doi:10.1016/j.drugpo.2018.02.001.
14. Jonas MM, Robertson LM, Middleman AB. Low prevalence of antibody to hepatitis C virus in an urban adolescent population. *Journal of Pediatrics*. 1997;131(2):314–316.
15. Koneru A, Nelson N, Hariri S, et al. Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission – United States and Kentucky, 2011–2014. *MMWR: Morbidity and Mortality Weekly Report*. 2016;65(28):705–710. doi:10.15585/mmwr.mm6528a2.
16. Kuncio DE, Newbern EC, Johnson CC, Viner KM. Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus-Infected Women. *Clinical Infectious Diseases*. 2016;62(8):980–985. doi:10.1093/cid/ciw026.
17. Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. Hepatitis C Virus Infection Among Reproductive-Aged Women and Children in the United States, 2006 to 2014. *Annals of Internal Medicine*. May 2017. doi:10.7326/M16–2350.

18. Mayer KH, Crawford P, Dant L, et al. HIV and Hepatitis C Virus Screening Practices in a Geographically Diverse Sample of American Community Health Centers. *AIDS Patient Care and STDs*. 2016;30(6):237–246. doi:10.1089/apc.2015.0314.
19. Murray KF, Richardson LP, Morishima C, Owens JWM, Gretch DR. Prevalence of hepatitis C virus infection and risk factors in an incarcerated juvenile population: a pilot study. *Pediatrics*. 2003;111(1):153–157.
20. Onofrey S, Church D, Kludt P, et al. Hepatitis C Virus Infection Among Adolescents and Young Adults – Massachusetts, 2002–2009. *MMWR: Morbidity and Mortality Weekly Report*. 2011;60(17):537–541.
21. Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965. *MMWR: Morbidity and Mortality Weekly Report*. 2012;61:1–18.
22. Sarkar S, Esserman DA, Skanderson M, Levin FL, Justice AC, Lim JK. Disparities in hepatitis C testing in U.S. veterans born 1945–1965. *Journal of Hepatology*. 2016;65(2):259–265. doi:10.1016/j.jhep.2016.04.012.
23. Testing Recommendations for Hepatitis C Virus Infection | HCV | Division of Viral Hepatitis | CDC. <https://www.cdc.gov/hepatitis/hcv/guidelinesc.htm>. Accessed May 15, 2018.
24. Thomas AR, Keene WE, Cieslak PR. Seroprevalence of hepatitis B and C in juvenile detention entrants, Oregon, 1994–1996. *Journal of Adolescent Health*. 2005;37(5):410–413. doi:10.1016/j.jadohealth.2004.11.129.
25. Trooskin SB, Navarro VJ, Winn RJ, et al. Hepatitis C risk assessment, testing and referral for treatment in urban primary care: Role of race and ethnicity. *World Journal of Gastroenterology: WJG*. 2007;13(7):1074–1078. doi:10.3748/wjg.v13.i7.1074.
26. U.S. 2016 Surveillance Data for Viral Hepatitis, Statistics & Surveillance, Division of Viral Hepatitis, CDC. <https://www.cdc.gov/hepatitis/statistics/2016surveillance/commentary.htm>. Published April 17, 2018. Accessed June 22, 2018.
27. U.S. Department of Health and Human Services O of H and IDP, Office of the Assistant Secretary for Health. National Viral Hepatitis Action Plan (2017–2020). January 2017. <https://www.hhs.gov/sites/default/files/National%20Viral%20Hepatitis%20Action%20Plan%202017–2020.pdf>. Accessed June 5, 2017.

28. Watts T, Stockman L, Martin J, Guilfoyle S, Vergeront JM. Increased Risk for Mother-to-Infant Transmission of Hepatitis C Virus Among Medicaid Recipients — Wisconsin, 2011–2015. *MMWR: Morbidity and Mortality Weekly Report*. 2017;66. doi:10.15585/mmwr.mm6642a3.
29. Young KL, Huang W, Horsburgh CR, Linas BP, Assoumou SA. Eighteen- to 30-year-olds more likely to link to hepatitis C virus care: an opportunity to decrease transmission. *Journal of Viral Hepatitis*. 2016;23(4):274–281. doi:10.1111/jvh.12489.
30. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤ 30 years – Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. *MMWR: Morbidity and Mortality Weekly Report*. 2015;64(17):453–458.

Curriculum Vitae

