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## UNDIAGNOSED HEPATITIS C INFECTION IN AN URBAN EMERGENCY DEPARTMENT

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**UNDIAGNOSED HEPATITIS C INFECTION IN AN URBAN EMERGENCY  
DEPARTMENT**

**CAPSTONE PROJECT PAPER**

A paper submitted in partial fulfillment of the  
Requirements for the degree of  
Master of Public Health in the  
University of Kentucky College of Public Health

By  
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Final Examination:  
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**Abstract**

**Aim:** To evaluate the prevalence of previously undiagnosed hepatitis C virus and associated patient risk factors in an urban ED through a universal, integrated screening program, to contextualize results found in terms of gaps in existing HCV screening models and to inform future sustainable and effective screening models.

**Methods:** ED patients, ages 18-71, that were medically stable, hadn't had a prior HCV test, and were having blood drawn as part of routine clinical care, were offered (n=2,726) an anti-HCV test, of whom 1,945 accepted. An assessment of correlates to anti-HCV positivity was completed using a binomial logistic regression model.

**Results:** Approximately, 12.5% (n=241) of patients tested (n=1,923) were anti-HCV positive. Among birth-cohort patients, 18.7% (n=154) tested positive. Specifically, holding all else constant, patients within the birth-cohort were associated with odds of having anti-HCV positivity 13.1 (CI: 7.5-22.9) times higher than those born outside the birth-cohort. Notably, approximately 5.8% (n=14) of patients who were anti-HCV positive had no documented risk factors. After controlling for all other variables, anti-HCV positivity was associated with patients within the birth-cohort, males, PWID, and persons living with HIV (PLWH).

**Conclusion:** The anti-HCV prevalence found in the JHBMC ED was high and comparable to that documented in other urban EDs throughout the country. This study demonstrates the unique capacity of EDs to reach previously missed or unacknowledged cases of hepatitis C. ED HCV screening models should be further piloted and evaluated throughout the country, as they might serve as critical safety-nets in the effort to curb this silent, costly epidemic.

**Keywords:** Hepatitis C; HCV; HCV testing, disease prevalence; undiagnosed infection; emergency medicine; epidemiology; universal screening; targeted screening; CDC recommendations; guidelines.

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## List of Abbreviations

Ab	Antibody
ACA	Patient Protection and Affordable Care Act
AASLSD	American Association for the Study of Liver Diseases
CDC	Centers for Disease Control and Prevention
CMIA	Chemiluminescent Micro-particle Immunoassay Technology
CMS	Centers for Medicaid and Medicare Services
ED	Emergency department
ESLD	End-stage liver disease
EMR	Electronic medical record
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IDSA	Infectious Diseases Society of America
IDU	Injection drug use
JHBMC	Johns Hopkins Bayview Medical Center
JHH	Johns Hopkins Hospital
MSM	Men who have sex with men
NHANES	National Health and Nutrition Examination Surveys
PLWH	Persons living with HIV
PMD	Primary medical provider
PWID	Persons who inject drugs
STI	Sexually transmitted infection
QALY	Quality adjusted life-year
US	United States
USPSTF	United States Preventive Services Task Force

## INTRODUCTION

The mounting economic and societal burden caused by two distinct epidemics of hepatitis C virus (HCV) infection poses a significant challenge in the United States (U.S.). Over 4.1 million persons in the U.S. are estimated to be infected with HCV, of whom 3.5 million are predicted to be chronically HCV-infected.<sup>1-3</sup> Established, chronic infections mostly include persons born during the years 1945 to 1965, and account for three-fourths (75%) of total HCV infections.<sup>4-6</sup> This population, previously known as the post-transfusion population, is now referred to as the baby boomer, birth-cohort and is characterized by a low risk of ongoing transmission.<sup>4,6,7</sup> New infections represent a markedly different epidemiologic profile and predominantly include persons who inject drugs (PWID) and HIV-infected men who have sex with men (MSM).<sup>4,6,8,9</sup>

A new, acute HCV infection will spontaneously clear within roughly six months for approximately 15%-25% of cases; thus, only 75%-85% of infections progress to a chronic state.<sup>10-13</sup> Once infection reaches a chronic state, disease path both varies in time and stage and greatly depends a variety of fixed factors related to the host, virus, and environment (see Table 1).

<b>Table 1. Natural history of chronic HCV infection: Host, viral and environmental factors<sup>11</sup></b>		
Host Factors	Viral Factors	Environmental Factors
Age at infection, gender, race, obesity, steatosis, insulin resistance, diabetes, genetics, ALT levels, exercise	Viral load (RNA), genotype, coinfection with HIV, coinfection with HBV	Caffeine, alcohol, smoking, cannabis

Roughly 60%-70% of cases will progress from chronic HCV infection to chronic liver disease, while 5%-20% will advance further to cirrhosis, and 1%-5% will die from hepatocellular carcinoma (HCC), end-stage liver disease (ESLD), or due to complications arising from a liver transplant.<sup>10,12</sup>



Chronic HCV infection is the leading indication for HCC and the leading cause for both liver transplants and liver failure in the U.S.<sup>14-17</sup> Morbidity and mortality attributable to HCV infection is expected to increase considerably over the next 50 years – so much so that at the current rates of treatment, roughly 1.76 million people will develop cirrhosis and mortality from HCV-associated complications will surpass 1 million.<sup>18</sup> In fact, HCV-associated mortality eclipsed that of HIV almost a decade ago, in 2007.<sup>19</sup> A high HCV prevalence combined with the severity of complications caused by chronic, long-term infection, constitutes a public health crisis that demands attention.<sup>4,19-24</sup>

The increasing burden of HCV on the healthcare system coupled with recent breakthroughs in the treatment of HCV infection have revitalized efforts to confront the HCV epidemic both in the U.S. and globally and stimulated much enthusiasm for a long under-recognized and unacknowledged patient population. Historically, HCV infection received little attention from the public and government authorities. Less than 3% of funding allotted to HIV-related initiatives is annually earmarked by the Centers for Disease Control and Prevention (CDC) for viral hepatitis.<sup>25</sup>

HCV infection gained notoriety in 2014, when the U.S. Food and Drug Administration (FDA) approved three effective, short-term (3-month) oral regimens that demonstrated sustained virologic response in over 90% of cases across varying patient demographics.<sup>26,27</sup> Now, only two years later, upwards of 10 similarly promising drugs have either now been approved for hepatitis C treatment or are currently being channeled through the drug approval pipeline.<sup>26,28,29</sup>

The concurrent passage and implementation of the Patient Protection and Affordable Care Act (ACA), which mandated full coverage for recommended preventative services, such as HCV screening, and eliminated payer ability to deny coverage to patients because of preexisting health conditions, presented an opportunity to transform the HCV care cascade.<sup>30,31</sup> Despite these advances, treatment remains elusive for the vast majority of the population due to pronounced barriers within a fragmented care system.<sup>27,28,32-34</sup>

Low rates of HCV screening and diagnosis remain one of the more significant barriers. Studies have estimated that approximately 45%-85% of those infected with chronic HCV are unaware of their serostatus.<sup>4,6,7</sup> Limited, spotty screening also contributes to countless missed opportunities for medical evaluation, counseling and education, care, and treatment.<sup>21,33,35,36</sup> In fact, increased HCV-related morbidity and mortality have been partially attributed to historically low screening rates and a lack of patient education surrounding the disease.<sup>34,37-39</sup>

Episodic care settings, specifically emergency departments (EDs), could be a valuable point of intervention, given the high proportion and visit frequency of patients that are high-risk for HCV infection and from medically underserved populations (PWID, uninsured persons, mentally-ill, homeless, Medicaid recipients).<sup>38,40-43</sup> Thus, urban EDs might serve as a critical safety net in reaching individuals unaware of their infection.<sup>42,44,45</sup> Prevalence of HCV antibody seropositivity in some urban EDs has been demonstrated to be as high as 13% - 18%.<sup>44,46-48</sup>

Further characterizing the population affected by HCV within EDs is a critical first step that can be used to analyze, guide, and motivate screening and policy efforts. In this study, we evaluated the prevalence of previously undiagnosed hepatitis C virus and associated patient risk factors in an urban ED through a universal, integrated screening program. The results of this study will serve to more accurately assess community need and gaps in existing screening models, investigate the feasibility of screening implementation in an ED setting, and inform future sustainable and effective screening models.

## METHODS

### *Setting*

This study was conducted in the adult ED of Johns Hopkins Bayview Medical Center (JHBMC) in Baltimore, Maryland. JHBMC serves a socioeconomically-disadvantaged, diverse population with a high prevalence of HIV and injection drug use (IDU).<sup>49,50</sup> Among all urban cities, Baltimore has the highest per capita prevalence of PWID of persons aged 15-64 years.<sup>50</sup> Annual ED census averages approximately 60,000 patients. Of those patients JHBMC serves, 35%

identify as black, 55% identify as white, 7% identify as Hispanic, and 53% identify as female. With respect to payer mix, approximately 13.2% of the population was uninsured, 30.2% had private insurance, and 53.6% had public insurance. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board.

### *Study Design*

This was a descriptive analysis of the results of an integrated, non-targeted (universal) HCV screening program from August 2016 to October 2016 at a single-center ED. The study was cross-sectional in design with retrospective analysis of the EMR for demographics and an assessment of risk factors for HCV. Hepatitis C screening, instituted through the EMR as a recommended clinical policy, was both triage-based and nursing-driven.

ED patients ages 18-71 were eligible for HCV screening if (1) they were having blood drawn as part of their clinical visit, (2) had never been previously tested for hepatitis C within the Johns Hopkins Health System, and (3) by triage nurse assessment. Patients unable to provide informed consent due to altered mental status or severe, debilitating illness were excluded. Patient consent was obtained utilizing an opt-out approach and documented in the EMR. The opt-out consent policy required patients to verbally inform nursing staff if they did not want a test. This screening strategy was demonstrated to be less stigmatizing and more effective in routine HIV screening programs implemented across various health settings.<sup>51,52</sup>

Tests were electronically ordered by the triage nurse for consenting patients and then cosigned by physicians. ED nursing and technician staff obtained blood specimens along with other clinical samples and submitted them to the hospital laboratory for processing. All screening tests were analyzed on the Abbott Architect with an anti-HCV assay using chemiluminescent microparticle immunoassay (CMIA) technology, which has a specificity of 99.6% and sensitivity of 99.1%.<sup>53</sup> Laboratory staff phoned research program personnel in the event of a positive result. If still receiving care in the ED, patients were informed at bedside by the clinical team in cooperation with research staff. Discharged patients were called, notified of the result, and where appropriate, offered help in following-up with a specialist or primary medical provider (PMD).

### *Data Collection*

Basic demographic and clinical data were abstracted from administrative, programmatic, or clinical datasets to establish a comprehensive study-related database by trained research staff. Any patients screened were assigned a unique study code. Patient identifiers were permanently removed to adhere to protected health information standards. Source documentation, including paper laboratory reports and documents containing identifiable patient information, was kept in a locked filing cabinet in a secluded departmental research suite. All research staff received standardized training both in chart review and related to EMR (Epic Systems) navigation prior to collecting any data. Research staff conducted periodic systematic reviews of data to ensure validity, and any discrepancies were corrected and verified by both senior research staff and the principal investigator.

### *Data Management*

The primary outcome of the study was HCV antibody (Ab) seropositivity, which was defined as a positive antibody test result performed between August and October 2016. Major independent variables were HIV seropositivity and IDU, established risk factors of HCV Ab positivity, and year of birth, specifically those born between 1945 and 1965. HIV seropositivity was defined by a positive HIV laboratory result or confirmatory provider note documented within the medical record. IDU was defined as having ever injected drugs. Gender was characterized as male or female. Race was accounted for as Black or non-Black. Risk factors such as transfusion history, transplant, tattoos, ALT elevation, and incarceration were not reliably available within the EMR and were not included in this analysis.

### *Statistical Analysis*

Descriptive statistics characterized the study population. Proportions were tabulated using chi-square tests, and a binary logistic regression model captured factors associated with HCV Ab seropositivity. Any P-value <0.05 (95% confidence) was considered to be significant and

included within the final model. Results were analyzed using the SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Mac, version 20.0. Armonk, NY, USA).

## RESULTS

During the three months of the study period, total ED visits were 13,261. Of the population, 3,468 (~26%) patients were excluded based on age criteria (under 18: 344, ~2.6%; 72+: 3,124, ~23.6%). Of patients between 18-71 years of age, approximately 34.6% (3,384) were excluded because no blood was drawn as part of routine clinical care during the patient's ED visit. Of patients within the eligible age-range and having blood drawn as part of routine clinical care, nearly 44.4% (2,844) were excluded because they a prior HCV test [HCV antibody screening or HCV Quantitative PCR (RNA)] documented within the EMR, while roughly 13.1% (839) of patients were excluded due to having an altered mental status or being medically unstable during time of test offer.

In all, 2,726 patients, or 20.6% of the total ED population, were offered HCV screening. Only 781 (28.6%) declined the test offer, and 1,945 (71.4%) accepted. Approximately 22 tests were cancelled because the blood sample was either not collected or determined insufficient for analysis. In total, 1,923 patients, 70.5% of those offered screening, received a HCV Ab test (anti-HCV test). All tests were free of charge.

Of those who received tests, 50.5% were female and 49.5% were male; 39.3% were black and 60.4% were non-black. Among the 1,923 patients tested, 241(12.5%) were anti-HCV positive. For patients born during the years 1945-1965, known as the birth cohort, 154 of 822 (18.7%) patients tested positive. Prevalence among patients born before or after the birth cohort years was 7.8% (87 of 1106). Of patients who had ever injected drugs, 92.7% were found to be anti-HCV positive. Of patients with HIV, 83.3% were found to have reactive test results.

Table 1 presents results from both univariate analyses as well as adjusted binomial regression model. In the univariate analysis, being born in the birth-cohort was associated with a 2.7 (CI: 2.0-3.6) increase in the odds of anti-HCV positivity. Ever having injected drugs was associated

with a 170.2 (CI: 84.3-343.4) higher odds of anti-HCV positivity. Having a HIV infection was associated with a 38.1 (CI: 12.9-112.4) increase in odds of anti-HCV positivity. Being male was associated with a 4.1 (CI: 3.0-5.7) increase in odds of HCV antibody infection.

In the final model, controlling for all variables, anti-HCV positivity was associated with patients within the birth-cohort, males, PWID, and persons living with HIV (PLWH). Specifically, holding all other covariates constant, patients within the birth-cohort were associated with odds of having anti-HCV positivity 13.1 (CI: 7.5-22.9) times higher than those born outside the birth-cohort. Only 14 of the 251 (5.8%) of patients who were anti-HCV positive had no risk factors documented, including IDU, age, or HIV seropositivity. Within the final model, 51% of the variance within the results was explained. The Hosmer-Lemeshow test verified goodness of fit.

## DISCUSSION

### *HCV Prevalence*

The overall undocumented HCV prevalence found in this study (12.5%) is significantly higher than national prevalence estimates, but mirrors the findings of several studies conducted locally in Baltimore and in academic EDs across the country.

National prevalence estimates of chronic HCV infection predominantly rely on the data from the U.S.-based National Health and Nutrition Examination Surveys (NHANES). The most recently released analysis, from the years 2003 through 2010, estimated that 3.2 million individuals, 1.3% of the total U.S. population, are currently living with chronic HCV.<sup>7,54</sup> HCV prevalence was reported by previous NHANES studies to be 1.6% between 1999 and 2003 and 1.8% between 1988 and 1994, and appeared to be declining.<sup>1,55</sup>

Yet, NHANES analyses are widely considered to be underestimates of the true HCV prevalence in the U.S, due to limitations related to sampling bias. The NHANES HCV prevalence survey only collects blood serum samples from the non-institutionalized population in the U.S, thereby excluding certain high-risk, transient populations, which include the incarcerated, the homeless,

nursing home residents, persons on active military duty, and immigrants.<sup>6,7</sup> Moreover, studies have shown that chronic HCV disproportionately affects some of these very populations: it has been documented at elevated rates in the mentally ill (19%)<sup>56-58</sup>, the incarcerated (23%-41%)<sup>6,59,60</sup>, PWID (58%)<sup>6</sup>, and the homeless (22%-53%).<sup>6</sup>

Thus, a more accurate prevalence is projected to be between 5.2 and 7.1 million chronically HCV-infected persons (~3% of the U.S. population).<sup>6,61</sup> However, even this updated prevalence estimate is noticeably lower than the one found in our study.

Comparatively, many studies conducted locally in Baltimore, as well as analyses undertaken in urban EDs across the country, found similarly high prevalence rates of HCV infection. A screening program in sexually-transmitted infection (STI) clinics run by the city health department in Baltimore, Maryland recently found a 7% overall HCV prevalence and a 30% prevalence among persons in the birth cohort.<sup>62</sup> Another Baltimore study reported an overall anti-HCV prevalence of 15% with age, IDU history and male sex associated with HCV Ab positivity.<sup>63</sup> In EDs across the country, prevalence rates have been documented across a relatively wide range: 1.6% (RHI, Providence); 11.6% (UAB, Birmingham); 12% (BMC, Boston); 14% (UC, Cincinnati); 7.3% (NYU, New York); and 10.3% (AHS, Oakland).<sup>64-69</sup>

Our study found a HCV infection prevalence of 18.7% within the birth cohort. Nationally, the birth cohort's HCV prevalence is estimated to be 3%-4%, or three to five-fold any other age or age-group.<sup>7,70</sup> Further, published studies demonstrate HCV antibody positive prevalence among this age-group to be upwards of 10% and as high as 30%.<sup>59,62,71-74</sup> A recent study in an Alabama emergency department found an 11.1% seropositivity in the baby boomer birth-cohort via an opt-out screening program<sup>73</sup>, while a study on U.S. male veterans living in Atlanta reported a 15% seropositivity among birth-cohort veterans that had not previously been screened for HCV.<sup>71</sup> Another study on veterans indicated an overall 10.3% seropositivity rate among the birth-cohort compared to 1.2% among veterans born after 1965.<sup>72</sup> Further, an analysis of a screening program in New York jails found a 22.5% seropositivity in the birth-cohort compared to 18.5% seropositivity in those born after 1965.<sup>59</sup> Thus, similar to the rate of total undocumented HCV

seropositivity within the JHBMC ED, our prevalence finding for the birth-cohort was higher than in most published studies.

Among PWID, we found a slightly higher HCV prevalence of 92.7%. Previously published studies on HCV infection among PWID report prevalence rates ranging from 38% to as high as 85%, with as many as 75% of injection drug users unaware of their anti-HCV seropositivity.<sup>48,62,67,75-78</sup> In the JHBMC adult ED, IDU prevalence is estimated to be 6.9%+, while HCV seroprevalence is estimated to be roughly 15%. These estimates parallel what has been reported at our sister institution's ED, Johns Hopkins Hospital (JHH) ED, in terms of IDU prevalence (7%+) and HCV seroprevalence (13.8%, 2013 and 18%, 1992).<sup>47,48</sup> Hence, a minimum of 12.6% (115/ [6.9% of 13,261]) of anti-HCV positive, documented PWID are unaware of their status in our ED. This projection is reported as a minimum, as any number of anti-HCV positive PWID that previously tested negative within the Hopkins system are excluded from the assessment, along with those who present to the ED with a drug overdose and are consequently indicated to be medically unstable and ineligible for testing. Further, this study relies on IDU history of the patient population to be accurately documented within the medical record, increasing the likelihood that this projection is an underestimate.

### *HCV Screening Recommendations*

The most recent guidelines from the CDC were issued in 2012 and recommend risk-based hepatitis C testing, which includes: PWID or having ever injected drugs; hemodialysis patients; the post-transfusion population; transplant patients; persons with clotting disorders; persons subject to occupational exposures; PLWH; those with an abnormal alanine aminotransferase level; and those born to a HCV-infected mother, and targeted, once-in-a-lifetime testing for persons born during the years 1945-1965, the birth-cohort.<sup>4</sup> From 1998-2011, the CDC had only advised a risk-based testing strategy.<sup>79</sup> A year later in 2013, the U.S. Preventive Services Task Force (USPSTF) assigned a B-grade recommendation to targeted, once-in-a-lifetime HCV testing for the birth-cohort.<sup>20,21</sup> This rating allowed PMDs and providers within episodic care settings, such as hospitals, to receive reimbursements for HCV screening and fortified the need for prevention-focused, patient-centered HCV care.



Following the release of the new CDC guidelines and associated-USPSTF policy, much discussion focused on (1) effective implementation of these screening recommendations and (2) the healthcare system's infrastructure and capacity to manage and sustain HCV-related care for newly diagnosed or informed populations. Accordingly, questions on which healthcare settings were most appropriate and capable of establishing effective, integrated HCV screening protocols arose. PMDs, rehabilitation and detoxification programs for persons suffering from substance use disorders, and STI clinics were widely determined to be acceptable practices for HCV screening initiatives.<sup>61</sup>

### *Feasibility of HCV Screening Implementation in the ED Setting*

Mandates for public health, preventive-care focused initiatives, such as HCV screening, piloted in the ED setting remain highly controversial at both the provider and policy level. As demonstrated with HIV testing interventions, EDs are uniquely capable of reaching high-risk (PWID, homeless, formerly incarcerated, mentally ill) or underserved, socioeconomically-disadvantaged populations with previously undiagnosed infections who could seek treatment once aware and educated about their serostatus.<sup>40,41,45,80,81</sup> Moreover, these populations disproportionately affected by HCV are less likely to be consistently monitored in by a PMD or other outpatient care provider, and more apt to sporadically visit emergent or high-acuity care settings.<sup>30,82,83</sup>

Urban EDs across the country have demonstrated the success and feasibility of differing integrated HCV screening models, ranging from targeted, birth-cohort screening, to universal screening paradigms, to risk-based only screening. These EDs have also reported varying levels of success in identifying undocumented or undiagnosed infection and pursuing subsequent linkage-to-care efforts for anti-HCV positive patients.

Our study implemented universal, once-in-a-lifetime screening and discovered a previously undocumented 12.5% anti-HCV positivity. If we had only implemented targeted screening in the birth cohort, 36% of cases would have remained undetected. Even when combining targeted,

birth-cohort screening and risk-based screening models, 5.8% of cases would have been missed. These findings are similar to those found by a mid-western ED, where 28% of reactive cases were outside of the birth cohort and 7% had no apparent, documented risk factors.<sup>67</sup> Likewise, an ED in Oakland, Calif. found a similarly high prevalence (2.6%) among persons at no perceived risk, and one in Rhode Island found that half of cases would have been missed if only current screening recommendations were implemented.<sup>64,68</sup>

The changing epidemiologic profile of HCV infection, especially within the context of both acute cases and incident cases of chronic HCV, also impacts the relative success and cost-effectiveness of screening models. In fact, incidence of acute HCV infection has been increasing since 2006 and as of 2014, is estimated to reach ~30,500 cases annually.<sup>5,70,77,84</sup> These incident cases are predominantly among PWID and HIV-infected MSM.<sup>8,9,29,77,84,85</sup> Given the worsening epidemic of PWID, especially among white persons who have previously used opioid agonists, acute HCV incidence is expected to continue increasing.<sup>10,77,86-88</sup> If these trends endure, EDs employing a targeted, birth-cohort screening strategy would miss these new cases. This becomes increasingly worrisome when considering over two-thirds of PWID are unaware of their anti-HCV positive status.<sup>76,89-91</sup>

Further, EDs that choose to implement targeted screening for patients within the birth-cohort alone might also find lower acceptance rates as persons within this age group have been found to misunderstand or unreliably report risk.<sup>4,7,38</sup> Similarly, risk-based screening initiatives that single out PWID might result in patients inaccurately reporting risk, due to fears of societal stigma that surrounds these populations.<sup>8,76</sup>

Despite the successful, routine adoption of HCV screening in various academic, urban EDs, support for these types of initiatives among emergency providers is mixed. EDs are already chronically overcrowded, overburdened, and struggle to provide time-sensitive care for patients presenting with acute illness.<sup>92-94</sup> Recently, the Centers for Medicare and Medicaid Services (CMS) sided against HCV testing models implemented in the ED setting, releasing a thorough policy that precluded secondary care settings, with specific reference to EDs, from receiving reimbursement for HCV screening.<sup>95</sup> 53.6% of the patient population that JHBMC's ED serves

has public or government-sponsored insurance; therefore, implementing any sustainable screening program would warrant CMS reimbursement. The same proves true for EDs across the country.

Even if EDs are able to implement a screening methodology, patients are likely to require resource-intensive assistance in navigating care and accessing treatment options.<sup>28</sup> Many patients infected with HCV are likely to have alcohol and substance use disorders, competing health priorities such as mental illness or homelessness, and limited social support; thus, linkage-to-care might prove time-intensive and difficult.<sup>96–98</sup> Linkage to specialty care rates vary widely, with some programs reporting levels as low as 25% and others reporting levels as high as 80%.<sup>28,62</sup>

Higher linkage-to-care rates were seen by hospitals, primary care centers, and EDs with additional staff support, often in the form of a program coordinator, financial assistance counselor, or nurse case manager.<sup>62,99–102</sup> Without financial assistance in the form of external funding, similar to the Ryan White comprehensive care model for HIV-infected persons, ancillary staff dedicated to this type of initiative would not be feasible for the common ED, and any additional workload heaped upon existing personnel might prove overwhelming.

### *Importance of Investing in Enhanced HCV Screening Models*

Expert healthcare economists note HCV-related burden to be of increasing concern.<sup>56–58</sup> Because of the decades-long, asymptomatic incubation period of the virus, the healthcare system has only begun to feel the true impact of the large prevalence of chronic HCV.<sup>18</sup> As the HCV-infected baby boomer population ages, liver disease severity increases substantially, resulting in more complications and increased healthcare utilization.<sup>17,18,42,58,103</sup> Hospital diagnoses of HCV-related complications, such as cirrhosis and HCC, have increased along with HCV-related inpatient mortality.<sup>56–58</sup> Several studies have also noted that both lack of insurance or government-sponsored insurance are indicators of higher ED utilization, increased disease severity, length-of-stay and inpatient mortality.<sup>103–105</sup> This is significant because chronic HCV is widely considered to be “a disease of the marginalized”.<sup>106,107</sup>

Total burden of disease in the U.S. is estimated to be \$6.5 billion, and is anticipated to peak at \$9.1 billion in 2024.<sup>56,58</sup> Peak costs are largely attributable to complications and care of persons with advanced liver diseases such as decompensated cirrhosis (46%), compensated cirrhosis (20%), and HCC (16%).<sup>56</sup> Lifetime cost per patient was calculated as \$64,490 (\$46,780-\$73,190) in 2011, and is estimated to increase to \$205,760 (\$154,890-\$486,890) in coming years due to the influence of medical inflation.<sup>61</sup>

Hospitalizations and mortality are also increasing.<sup>42,90,103,108</sup> Total hospitalizations for HCV-related disease increased 190% from 2004 to 2011 alone.<sup>90</sup> Annual HCV-related mortality has been reported to be anywhere from 19,000<sup>109</sup> to 80,000<sup>34</sup> and is forecasted to increase to over 36,000 between 2022 and 2035.<sup>18,19,56</sup>

Increasing annual treatment of patients four-fold, to 400,000 – from the 100,000 that have been treated historically – has been estimated to prevent over half a million cases of cirrhosis and over 250,000 HCV-associated deaths over the next decade.<sup>33</sup> Most health economists agree that as long as HCV prevalence is >0.84 and total costs amount to less than \$50,000 per quality adjusted life year (QALY), screening is cost-effective.<sup>22</sup> Screening adults aged 20-69 (60% of persons) on a population level was shown to be cost-effective by a recent analysis as 7.1% of liver-related deaths were averted. This is an additional 3.8% of deaths averted than if only risk-based screening was implemented.<sup>110</sup> This expanded on previous cost-effectiveness analyses that have demonstrated the value of a targeted, birth-cohort screening model.<sup>22,111</sup>

### *Notable Barriers to HCV Treatment*

Numerous barriers along the cascade of HCV care prevent patients from receiving treatment, in addition to challenges related to screening and diagnostics. The general inaccessibility and rationing of treatment, an insufficient body of trained providers and a marginalized patient population are the most enumerated barriers impeding progress.<sup>25,112</sup>

Drug prices are perhaps the most publicized barrier. Gilead Sciences and AbbVie, the two pharmaceutical companies responsible for developing the first HCV drugs released, established high fee structures for standard (12-week) regimens that ranged from \$51,000 to \$147,000.<sup>113-</sup>

<sup>115</sup> Proprietary licensing on their discoveries provided them with limited market competition, and federal oversight on pharmaceutical drug pricing allowed them to inflate rates. While government payers such as Medicaid and Medicare and private insurers do not pay ‘list’ prices for treatment, cost per patient is still estimated to be high, at a minimum of ~\$40,000 in 2014 and ~\$30,000 in 2015.<sup>114–116</sup>

Payers overwhelmingly responded to these pricing models by severely rationing care in the U.S. Eligibility for HCV treatment is primarily limited to those with either advanced stages of cirrhosis (stage F4) or fibrosis (stage F3) and those without ongoing substance use problems.<sup>26,115,116</sup> Criteria for coverage vary considerably among payers and do not conform to the treatment guidelines developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA).<sup>26,117,118</sup> Medicaid is especially limiting, with 88% of states authorizing specific eligibility criteria related to substance use; 50% of these state policies required patients to remain abstinent for over 1 year in order to receive treatment. These restrictions were neither mandated by the FDA nor supported by scientific evidence.<sup>107,116</sup> Moreover, in two-thirds of states, Medicaid demands that treatment be provided by a specialist in infectious disease or gastroenterology. The result of these policies is a growing bottleneck of patients without access to an already limited pool of specialists.

Payers have also introduced a broad range of other policy barriers that include requiring clinically irrelevant laboratory standards, denial of coverage to HIV co-infected patients, an evaluation of a patient’s pharmacy refill records to assess ‘patient readiness’ for care, contracts for a once-in-a-lifetime course of therapy, and restrictive limits on enrollment volumes at company-sponsored patient assistance programs.<sup>114,116,119</sup> Ultimately, only a small minority of patients are eligible for and eventually complete HCV-treatment. One systematic review, analyzing recent studies on HCV treatment, concluded that treatment was prescribed to only 16% of HCV-infected persons among the non-institutionalized U.S. population.<sup>28,106</sup>

Furthermore, only 56% of the individuals who underwent HCV-treatment achieved a sustained virologic response (SVR), which is considered to be a functional cure.<sup>28</sup> In response to criticism and payer rationing, Gilead’s Sovaldi and Harvoni wholesale acquisition costs were reduced by

nearly half in early 2015, resulting in a net \$54,000 and \$45,000 per treatment regiment, respectively.<sup>113,114</sup> Even with these price reductions, completing a full course of therapy still can cost \$100,000 per patient, given physician, facility and other care-related fees. Luckily, there is hope for the future, as several new competitors have recently entered or are expected to enter the market.<sup>113</sup>

Moreover, patient and provider-related beliefs, education, and practices profoundly impact whether a patient pursues and completes treatment. Studies have found that most PMDs have insufficient knowledge regarding screening for anti-HCV and chronic HCV infection and a limited understanding of disease progression to HCC and ESLD.<sup>25,96</sup> Additionally, many healthcare professionals providing preventative services to patients have misconceptions of HCV risk factors and natural history, and a limited awareness of the screening recommendations for HCV infection.<sup>96,112,120</sup>

Additionally, in one study, more than half of physicians surveyed in the primary care setting neglected to discuss stigmatized, high-risk behaviors such as IDU with their patients.<sup>120</sup> Finally, despite the availability of PMD training programs on HCV therapies, few primary care centers actively offer HCV treatment to their patients, choosing instead to refer out to a limited pool of overburdened specialists.<sup>121,122</sup>

Patient-level factors are also significant barriers to receiving treatment. Limited patient knowledge and understanding of the disease, concerns related to side-effects, duration, and cost of treatment, and lack of provider trust have all been documented as great obstacles for treatment.<sup>27,121</sup> These studies reinforce the need for additional staffing resources and government-facilitated training initiatives for settings implementing HCV screening programs to assure thorough and accurate counseling of anti-HCV positive patients and their respective PMDs.

### *Limitations*

While there is no certainty that the high HCV prevalence found in this study and in other studies discussed is generalizable to EDs across the country or even within similar regions, evidence suggests HCV prevalence remains high and endemic in all EDs, with the exception of those in extremely rural areas.<sup>67</sup> Because our study evaluated prevalence among a specific subset of patients (individuals between 18-71 having blood drawn as part of routine clinical care, medically stable, with no prior HCV test in their medical history) the results are not generalizable to other EDs. Limitations of this study include potential sampling bias as the population inherently likely to visit an ED is more likely to be sick and have multiple comorbidities.<sup>40,43</sup> Participation bias is also a possibility as those at risk may have been less likely to report risk or accept screening when offered. Moreover, the presence or absence of risk factors included within the study was dependent on documentation in the form of a lab result or provider note in the EMR; thus, the rates reported may be underestimates. Further, the sample size of this study may be too small to fully assess the association of IDU and HIV with anti-HCV positivity. As mentioned above, the generalizability of this study is uncertain, as other EDs may serve differing demographics. Baltimore is particularly noted for its high prevalence of HIV, HCV, and IDU. Finally, the prevalence findings of the study do not reflect total ED HCV seroprevalence, as persons with HCV infection already documented within the EMR as well as those who were previously screened were not offered a test.

### *Conclusion*

In summary, HCV screening initiatives in EDs may prove particularly adept at identifying previously undiagnosed HCV infection and help close the gap between persons infected and persons accessing treatment. The high documented prevalence (1.6%-12%) and seroprevalence (13-18%) in EDs, as well as the high prevalence of undiagnosed infection (12.5%) characterized in this ED-based study, demonstrate the benefit of adopting an HCV screening strategy, more specifically a universal or targeted, birth-cohort screening model. Universal screening models are likely to be perceived as less stigmatizing and have been demonstrated to be cost-effective at the population-level.

However, in order for HCV screening initiatives to be sustainable in the long-term in the ED setting, CMS regulations must be amended to include reimbursement for secondary, episodic care settings. Further, health care systems and providers must advocate for public funding umbrellas, similar to the Ryan White comprehensive care model developed for HIV services, so that hospitals, PMDs, and EDs may invest in ancillary personnel that can subsequently be trained to educate patients and provide linkage to primary or specialty care assistance. Without enhanced and more comprehensive screening, the economic and societal burden of HCV-related disease will continue to increase, a fact especially troubling given the availability of an effective, tolerable cure.



## APPENDIX

<b>Table 1. Factors associated with HCV antibody positivity</b>						
<b>Characteristic</b>	<b>Number Screened:</b>	<b>HCV Prevalence (%)</b>	<b>OR</b>	<b>(95% CI)</b>	<b>Adjusted OR</b>	<b>(95% CI)</b>
<b>Age</b>						
Non-Birth Cohort	1106	87 (7.86)	2.70	(2.04-3.57)	13.12	(7.52-22.90)
Birth Cohort	822	154 (18.73)				
<b>Gender</b>						
Female	973	54 (5.55)	4.14	(3.02-5.69)	0.37	(0.25-0.54)
Male	955	187 (19.58)				
<b>Race</b>						
Black	758	111 (14.64)	0.73	(0.56-0.96)	2.13	(1.46-3.12)
Non-Black	1170	130 (11.11)				
<b>HIV Status</b>						
Negative	1904	221 (11.61)	38.10	(12.90-112.42)	0.13	(0.02-0.87)
Positive	24	20 (83.33)				
<b>Ever IDU</b>						
No	1804	126 (6.98)	170.17	(84.32-343.41)	0.002	(0.001-0.005)
Yes	124	115 (92.74)				

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