Received: 6 April 2022 | Revised: 26 July 2022 | Accepted: 19 August 2022

DOI: 10.1002/emp2.12819

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
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BRIEF RESEARCH REPORT

Infectious Disease

Non-targeted hepatitis C virus screening in acute care healthcare settings in the Southern Appalachian region

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Funding information
Gilead Sciences

Abstract

Objectives: The objective of this study was to evaluate the performance of non-targeted hepatitis C virus (HCV) screening in emergency departments (EDs) and other healthcare settings in terms of patients identified with HCV infection and linked to HCV care.

Methods: In the Southern Appalachian region of the United States, we developed non-targeted HCV screening and linkage-to-care programs in 10 institutions at different healthcare settings, including EDs, outpatient clinics, and inpatient units. Serum samples were tested for HCV antibodies, and if positive, reflexed to HCV ribonucleic acid (RNA) testing as a confirmatory test for active infection. Patients with positive RNA tests were contacted to link them to HCV care.

Supervising Editor: Christian Tomaszewski, MD, MS.

Results: Between 2017 and 2019, among 195,152 patients screened for HCV infection, 16,529 (8.5%) were positive by antibody testing, 10,139 (5.2% of screened patients and 61.3% of patients positive by antibody test) were positive by RNA testing, and 5778 (3.0% of screened patients and 57.0% of patients positive by RNA test) were successfully linked to HCV care. Among 83,645 patients screened in EDs, 9060 (10.8%) were positive by HCV antibody, and 5243 (6.3%) were positive by RNA test. Among patients positive by RNA testing, linkage to care was lower for patients screened in the ED (44.1%) compared with outpatient clinics (67.6%) ($P < 0.01$) and inpatient units (50.9%) ($P < 0.01$).

Conclusions: Non-targeted HCV screening in acute care settings can identify large numbers of people with HCV infection. To optimize the utility of these screening programs, future work is needed to develop best practices that consistently link these patients to HCV care.

KEYWORDS
epidemiology, hepatitis c virus, injection drug use, preventive care, surviellance, viral hepatitis

1 | INTRODUCTION

1.1 | Background

Hepatitis C virus (HCV) infection is a major cause of liver-related morbidity and mortality.[1–4] Nearly all cases of HCV infection are curable with direct-acting antiviral medications.[2] Thus, identifying people with HCV infection before the onset of liver-related morbidity and successfully linking them to HCV treatment are keys to optimizing patient outcomes.[5] In recognition of this need to improve the early detection of HCV infection, the Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force (USPSTF) updated HCV screening guidance in 2020 to include screening for all adults aged ≥18 years at least once in their lifetimes.[6,7]

1.2 | Importance

Many potential methods have been proposed to achieve broad screening of the US adult population, including routine, non-targeted HCV testing in emergency departments (EDs), inpatient hospital units, and outpatient clinics.[5,8–11] However, the utility of non-targeted HCV screening, defined as testing for HCV infection regardless of the patient's symptoms and known risk factors for HCV infection, in these settings remains incompletely understood.

1.3 | Goal of this investigation

We developed non-targeted HCV screening programs in EDs, outpatient acute care clinics, and inpatient units at 10 institutions in Southern Appalachia, an area with a high burden of HCV infection,[3,11,12] to evaluate the prevalence of positive HCV results and the success rate for linking patients who screen positive to HCV care.

2 | METHODS

2.1 | Study design, setting, and selection of participants

We conducted a multicenter, multiyear surveillance program for HCV infection by implementing HCV screening at the time of patients accessing healthcare. The program used non-targeted screening methods, meaning patients were offered HCV testing without regard to clinical symptoms or risk factors for HCV infection. The program included 10 institutions in 5 US states within Southern Appalachia (Table 1) that implemented non-targeted screening as part of the Frontlines of Communities in the United States HCV screening program[13] funded by Gilead Sciences before the 2020 CDC/USPSTF recommendation for universal 1-time HCV screening. Locations of HCV screening in these institutions included EDs, inpatient hospital units, outpatient medical clinics, health department clinics, syringe service programs, correction facilities, and federally qualified health centers (FQHCs). Patients screened between January 1, 2017, and December 31, 2019, were analyzed. Each participating institution received a non-research determination from their governing institutional review board for this work. Deidentified data were transmitted from participating institutions to Vanderbilt University Medical Center for analysis.

2.2 | Interventions

Each participating institution developed protocols for non-targeted, opt-out HCV screening for adults aged ≥18 years. In these protocols,

clinicians offered HCV testing as an additional procedure on top of providing care for the reason the patient sought acute medical attention. Patients who self-reported prior positive HCV testing were eligible for entry into the screening program because positive testing in this setting could enhance linkage to HCV care (as screening programs had dedicated personnel for assisting patients with linkage to care if they tested HCV positive as part of the screening program). Patients who were offered HCV testing and did not opt out had blood collected for HCV testing. The initial HCV test in the program was an HCV antibody (serology) test using a third-generation enzyme immunoassay. Patients who had an HCV antibody test completed were considered to have entered the screening program. Positive antibody results could represent a prior infection that had cleared or an active infection.[14] Thus, samples positive by antibody testing underwent reflex molecular testing for HCV ribonucleic acid (RNA). RNA-positive results were interpreted as confirmed (active) HCV infection. Results were typically not available in real time and were reported to screening program personnel in a delayed fashion (days to weeks after blood sample collection).

Screening program personnel, which included healthcare personnel at each site, attempted to contact patients with positive HCV RNA results to disclose positive results, counsel them regarding HCV infection, and link them to HCV care. Each site developed its own protocol for contacting patients; common elements of the protocols included serial phone calls, and for patients who could not be reached by phone, sending certified letters. Once contacted, personnel coordinated linkage to local HCV resources and treatment options for patients who expressed an interest in linkage. In this analysis, patients were considered successfully linked to care if they attended any appointment for education about or evaluation of HCV infection or an addiction care program if HCV infection coexisted with injection drug use.

2.3 | Analysis

We described the prevalence of positive HCV antibody and RNA test results. For these prevalence calculations, the denominator was the total number of patients tested as part of the screening program and the numerator consisted of the number of patients who tested positive for HCV by antibody test (first prevalence reported) and by RNA test (second prevalence reported). The prevalence results were reported for the entire population and stratified by location of screening and the patient's birth year (categorized as 1945–1965, which has historically been identified as a "birth cohort" with increased risk for HCV,[15] vs not 1945–1965). We also described the proportion of patients with positive HCV RNA tests successfully linked to HCV care. For these calculations on linkage to care, the denominator was the number of patients with a positive HCV RNA test, and the numerator was the number of patients with a positive HCV RNA test successfully linked to care. Among patients with a positive HCV RNA test not successfully linked to care, we reported the primary reason for not being linked. In a secondary analysis to understand the number of screening antibody tests that resulted in a new diagnosis of HCV seropositivity, patients were considered to have a newly diagnosed positive antibody test if the HCV antibody test was positive, the patient reported no prior positive HCV testing, and the local medical record had no evidence of a prior positive HCV test. In this analysis, the denominator consisted of the total number of patients tested for HCV in the screening program, and the numerator was the number of patients with a newly diagnosed positive HCV antibody test. Proportions were compared using the chi-squared test, with a P value < 0.05 considered statistically significant. Analyses were completed using R (Version 3.5.2; www.R-project.org).

The Bottom Line

Emergency departments (EDs) are potentially well positioned for early recognition of asymptomatic hepatitis C virus infection, thereby facilitating timely linkage to treatment. A pharmaceutical company sponsored study of nontargeted testing at 10 sites throughout Southern Appalachia between 2017 and 2019 discovered 16,529 (8.5%) of 195,152 patients were positive for hepatitis C virus antibodies.

3 | RESULTS

3.1 | Characteristics of study participants

Across all screening locations, 195,152 HCV antibody tests were completed, including 66,354 in 2017, 80,707 in 2018, and 48,091 in 2019 (Table 1). The largest number of screening tests were completed in EDs (83,645), outpatient medical clinics (76,163), and health department clinics (20,876). Among screened patients, 78,765 (40.4%) were born 1945–1965, and 116,387(59.6%) were born outside the 1945–1965 birth cohort.

3.2 | HCV antibody tests

Among 195,152 antibody tests completed, 16,529 (8.5%) were positive, including 6.0% among patients born 1945–1965 and 10.1% among those born outside the 1945–1965 birth cohort ($P < 0.01$). Screening tests in EDs resulted in the highest number of positive antibody tests (9060/83,645 [10.8%] antibody tests from EDs were positive), whereas screening in syringe service programs yielded the highest proportion of positive tests (22/44 [50.0%] antibody tests from syringe service programs were positive) (Table 2). Most positive antibody tests identified in the program were the first known positive HCV test for a patient; 10,189 positive antibody tests occurred in patients with no self-report or local medical record evidence of a prior positive HCV test, representing 61.6% of positive antibody tests and 5.2% of all antibody tests completed.

TABLE 1 Prevalence of positive HCV antibody and RNA test results and proportion of patients successfully linked to HCV care by institution and location of screening in the institution

Institution	City, state	Dates of screening	Screening location	Total patients screened for HCV, n	HCV antibody positive, n (% of total screened)	HCV RNA positive, n (% of total screened | % of antibody positive)	Successfully linked to HCV care, n (% of total screened | % of RNA positive)
Appalachian Regional Healthcare	Hazard, Kentucky, and surrounding	January 2017–December 2019	ED	26,799	4298 (16.0)	2790 (10.4 | 64.9)	1037 (3.9 | 37.2)
			Syringe service programs	44	22 (50.0)	11 (25 | 50)	5 (11.4 | 45.5)
Blue Ridge HealthCare	Morganton, North Carolina, and surrounding	April 2017–September 2019	FQHC	8092	652 (8.1)	436 (5.4 | 66.9)	406 (5.0 | 93.1)
Carilion Clinic	Roanoke, Virginia	April 2018– December 2019	Inpatient units	1529	186 (12.2)	97 (6.3 | 52.2)	36 (2.4 | 37.1)
			Outpatient clinics	7102	319 (4.5)	192 (2.7 | 60.2)	101 (1.4 | 52.6)
Knox County Health Department	Knoxville, Tennessee, and surrounding	January 2017–September 2019	Health departments	19,901	2316 (11.6)	1571 (7.9 | 67.8)	1229 (6.2 | 78.2)
University of Louisville	Louisville, Kentucky	January 2018–September 2019	Inpatient units	439	15 (3.4)	11 (2.5 | 73.3)	5 (1.1 | 45.5)
University of Kentucky	Lexington, Kentucky	July 2018–March 2019	ED	13,836	1772 (12.8)	909 (6.6 | 51.3)	468 (3.4 | 51.5)
Madison County Health Department	Marshall, North Carolina, and surrounding	April 2017–June 2019	Health departments	975	92 (9.4)	64 (6.6 | 69.6)	50 (5.1 | 78.1)
			Correction facilities	477	128 (26.8)	89 (18.7 | 69.5)	72 (15.1 | 80.9)
			FQHC	1277	58 (4.5)	32 (2.5 | 55.2)	30 (2.3 | 93.8)
Norton Healthcare	Louisville, Kentucky	January 2017–December 2018	ED	86	24 (27.9)	21 (24.4 | 87.5)	7 (8.1 | 33.3)
			Inpatient units	2199	816 (37.1)	707 (32.2 | 86.6)	351 (16.0 | 49.6)
			Outpatient clinics	65,244	2729 (4.2)	1618 (2.5 | 59.3)	1120 (1.7 | 69.2)
Vanderbilt University Medical Center	Nashville, Tennessee	January 2017–December 2018	ED	18,621	1541 (8.3)	713 (3.8 | 46.3)	211 (1.1 | 29.6)
West Virginia University	Morgantown, West Virginia	July 2017–December 2019	ED	24,303	1425 (5.9)	810 (3.3 | 56.8)	590 (2.4 | 72.8}
			Inpatient units	411	96 (23.4)	62 (15.1 | 64.6)	54 (13.1 | 87.1)
			Outpatient clinics	3817	40 (1.0)	6 (0.2 | 15)	6 (0.2 | 100)
Total				195,152	16,529 (8.5)	10,139 (5.2 | 61.3)	5778 (3.0 | 57.0)

Abbreviations: ED, emergency department; FQHC, federally qualified health center; HCV, hepatitis C virus.

TABLE 2 Prevalence of positive HCV antibody and RNA test results and linkage-to-care results by location of HCV screening

Location of HCV screening	Total patients screened for HCV, n	HCV antibody positive, n (% of total screened)	HCV RNA positive, n (% of total screened | % of antibody positive)	Successfully linked to HCV care, n (% of total screened | % of RNA positive)	HCV RNA positive and unable to be reached to establish HCV care, n (% of total screened | % of RNA positive)
Emergency departments	83,645	9060 (10.8)	5243 (6.3 | 57.9)	2313 (2.8 | 44.1)	2406 (2.9 | 45.9)
Inpatient hospital units	4578	1113 (24.3)	877 (19.2 | 78.8)	446 (9.7 | 50.9)	181 (4.0 | 20.6)
Outpatient medical clinics	76,163	3088 (4.1)	1816 (2.4 | 58.8)	1227 (1.6 | 67.6)	308 (0.4 | 17.0)
Health department clinics	20,876	2408 (11.5)	1635 (7.8 | 67.9)	1279 (6.1 | 78.2)	282 (1.4 | 17.2)
Syringe service programs	44	22 (50.0)	11 (25.0 | 50.0)	5 (11.4 | 45.5)	4 (9.1 | 36.4)
Correction facilities	477	128 (26.8)	89 (18.7 | 69.5)	72 (15.1 | 80.9)	2 (0.4 | 2.2)
FQHCs	9369	710 (7.6)	468 (5.0 | 65.9)	436 (4.7 | 93.2)	29 (0.3 | 6.2)
Total	195,152	16,529 (8.5)	10,139 (5.2 | 61.3)	5778 (3.1 | 57.0)	3212 (1.6 | 31.7)

Note: In this table, the results were collapsed across institutions into categories representing the healthcare setting of HCV screening.
Abbreviations: FQHC, federally qualified health center; HCV, hepatitis C virus.

3.3 | HCV RNA tests

Overall, among 16,529 antibody-positive samples, 10,139 were positive by RNA testing, representing 61.3% of samples positive by antibody testing and 5.2% of all samples tested. The percentage of positive antibody samples that tested positive by RNA varied by screening location from 50.0% in syringe service programs to 78.8% in inpatient settings.

3.4 | Linkage to HCV care

Among 10,139 RNA-positive samples, 5778 (57.0%) patients were successfully linked to HCV care through the screening program. Screening in EDs led to the highest number of patients successfully linked to care (2313/5243 [44.1%] positive RNA tests in EDs led to linkage of care), whereas screening at FQHCs led to the highest percentage of patients with RNA-positive tests being linked (436/468 [93.2%] positive RNA tests in FQHCs led to linkage of care). Among patients with a positive RNA test, linkage to care was lower for patients screened in the ED (44.1%) compared with outpatient clinics (67.6%) ($P < 0.01$) and inpatient units (50.9%) ($P < 0.01$).

Among the 4361 positive RNA tests that did not lead to linkage to HCV care, 3212 (73.7%) were unable to be reached to establish follow-up, 415 (9.5%) were incarcerated, 345 (7.9%) died before follow-up or were terminally ill, 313 (7.2%) declined HCV care, and 76 (1.7%) stated that they had previously been evaluated for HCV care and thus declined linkage via the program.

4 | LIMITATIONS

The results of this study should be interpreted in the context of its limitations. First, data were pooled from 10 institutions to report HCV prevalence across the Southern Appalachian region; the methods for executing a screening program varied somewhat across institutions, including approaches to discussing the screening program with patients and contacting patients for linkage to care. Thus, this study reported results for multiple screening programs implemented based on local context. Second, HCV screening was dependent on clinical personnel offering HCV testing and patients not opting out. Hence, the population reported in this report was a convenience sample, and the number of patients who were not offered testing and who refused testing are not known. Third, participating institutions designed non-targeted screening programs, but adherence to the non-targeted approach was not measured, and personnel differentially offering screening tests to patients with overt HCV infection risk factors at times cannot be ruled out. Fourth, data collection ended at the time of linkage to HCV care; we did not collect data on HCV treatments. Fifth, this study was conducted in a US region with a high burden of HCV, and the results may not be generalizable to other regions.

5 | DISCUSSION

This study demonstrated a high burden of HCV infection among adults who underwent non-target HCV screening at the time of seeking healthcare in the Southern Appalachian region within the US states of Kentucky, Tennessee, West Virginia, Virginia, and North Carolina; 8.5% of nearly 200,000 HCV antibody screening tests completed between 2017 and 2019 were positive. High HCV positivity rates were observed across a variety of settings in which patients routinely seek acute healthcare, including EDs (10.8%), inpatient hospital units (24.3%), and health department clinics (11.5%), and among those both within (6.0%) and outside (10.1%) the HCV birth cohort. The screening program provided the first diagnosis of HCV infection in 61.6% of patients who screened positive. Reflexing positive HCV antibody tests immediately

to RNA testing allowed screening programs to consistently confirm ongoing infection and determine who may benefit from subsequent linkage to care. In this program, 38.7% of samples with a positive antibody result were negative by RNA testing, illustrating the need to confirm ongoing infection before further efforts related to linkage to care. Finally, this study demonstrated that although many people can be newly diagnosed with HCV infection via non-targeted screening programs, linking these patients to HCV care can be challenging. Despite dedicated personnel committed to contacting patients who tested positive for HCV by RNA testing, we successfully linked only 57.0% of these patients to HCV care, and a wide range of successful linkage to care was reported across different care environments.

HCV infection is a major cause of cirrhosis, hepatocellular carcinoma, and mortality in the United States and globally.[1–4] Although the precise burden of chronic HCV infection is unknown, at least 58 million people worldwide and 2.4 million people in the United States likely have chronic HCV infection.[3,4,16] During the past decade, direct-acting antiviral agents have revolutionized HCV treatment, with sustained virological response now achievable with oral medication therapy in nearly all patients, and complete eradication efforts have been proposed.[2,4,5] However, it has been estimated that only 50% of people in the United States with chronic HCV are aware of their infection,[17] highlighting that screening, diagnosis, and linkage-to-care efforts in the United States must increase in scale and effectiveness.

Historically, HCV infection in the United States was concentrated among people with defined risk factors and those born between 1945 and 1965.[15] Recently, opioid use disorder and associated injection drug use has been a major contributor to new HCV cases, resulting in the rapid evolution of a syndemic between opioid use disorder and HCV infection.[1,12] The Appalachian region of the United States has been particularly affected by opioid use–associated HCV transmission.[1,12] In recognition of shifts in HCV epidemiology, the CDC and USPSTF recently updated HCV screening guidance to recommend that all adults aged ≥18 years undergo 1-time lifetime screening in addition to screening based on risk factors.[6,7] Now, innovative approaches are needed to embed these HCV screening recommendations into US healthcare delivery.

In this study, we evaluated non-targeted HCV screening among adults in several healthcare settings that have historically not been used for screening efforts, including EDs and inpatient hospital units. Our results demonstrated that HCV screening in these acute care settings can be successfully implemented and identify large numbers of patients with undiagnosed HCV infection. However, contacting patients who screen positive and linking them to HCV care appears more challenging from these acute care settings than from traditional screening settings, such as health departments and FQHCs. The rate of successful linkage to care ranged widely among both screening location and institution, likely reflecting the contributions of personnel, protocols, care environments, and patient populations in different settings. Furthermore, linkage-to-care opportunities were available in the same location as screening in some cases (ie, outpatient clinic), whereas others necessitated external referral and subsequent follow-up (ie, ED). Among patients with RNA-confirmed infection not linked to HCV care in this study, 73.7% were not successfully contacted after initial positive testing during the study period. These findings are consistent with prior studies noting low linkage-to-care rates for patients diagnosed with HCV infection in other ED screening programs.[17,18] Further development of real-time interventions, such as point-of-care molecular testing, early multidisciplinary assessments, and rapid initiation of HCV treatment after confirmation of infection may be considered to improve the impact of screening by elimination of barriers to subsequent care. Optimal approaches for HCV screening in and linkage-to-care strategies from EDs are currently being studied in the DETECT Hep C trial.[19]

In conclusion, non-targeted HCV screening among adults seeking acute care in EDs, clinics, and inpatient units in the Southern Appalachian region can identify a large number of people with previously undiagnosed HCV infection. Future efforts are needed to develop processes and identify best practices that consistently link these patients to HCV care.

AUTHOR CONTRIBUTIONS

Cody A. Chastain, Michelle Rose, Daniel Moore, Diana Parker, Barbra Cave, Jane Crowe, Sarah Adams, Marrieth G. Rubio, Rachel Potter, Kimberly Quedado, Ian D. Jones, Jin H. Han, and Wesley H. Self contributed to the methodological design and data collection. Cathy A. Jenkins and Wesley H. Self contributed to the data analysis. Cody A. Chastain, Cathy A. Jenkins, Michelle Rose, Daniel Moore, Diana Parker, Barbra Cave, Jane Crowe, Sarah Adams, Marrieth G. Rubio, Rachel Potter, Kimberly Quedado, Ian D. Jones, Jin H. Han, and Wesley H. Self contributed to the interpretation of results. Michelle Rose, Daniel Moore, Diana Parker, Barbra Cave, Jane Crowe, Marrieth G. Rubio, Rachel Potter, Kimberly Quedado, and Wesley H. Self obtained funding. Wesley H. Self drafted the initial manuscript. Cody A. Chastain, Cathy A. Jenkins, Michelle Rose, Daniel Moore, Diana Parker, Barbra Cave, Jane Crowe, Sarah Adams, Marrieth G. Rubio, Rachel Potter, Kimberly Quedado, Ian D. Jones, Jin H. Han, and Wesley H. Self contributed to the critical revision of the manuscript.

ACKNOWLEDGMENT

Funding for this project was provided by Gilead Sciences through the Frontlines of Communities in the United States (FOCUS) program. Each participating site received funds from Gilead Sciences to establish a hepatitis C virus screening program. FOCUS funding supports HIV, hepatitis B virus, and hepatitis C virus screening and linkage to a first appointment. Gilead Sciences provided approval for pooling data from multiple FOCUS sites but had no role in the design, analysis, interpretation, or dissemination of the study.

CONFLICTS OF INTEREST

Each author reports funding from Gilead Sciences to develop hepatitis C virus screening programs described in this work. None of the authors report any other potential conflicts of interest.

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How to cite this article: Chastain CA, Jenkins CA, Rose M, et al. Non-targeted hepatitis C virus screening in acute care healthcare settings in the Southern Appalachian region. *JACEP Open*. 2022;3:e12819. https://doi.org/10.1002/emp2.12819