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Hepatitis A Person-to-Person Outbreaks: Epidemiology, Morbidity Burden, and Factors Associated With Hospitalization —Multiple States, 2016–2019

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Abstract

Background.—Since 2016, the United States has experienced person-to-person hepatitis A outbreaks unprecedented in the vaccine era. The proportion of cases hospitalized in these outbreaks exceeds historical national surveillance data.

Methods.—We described the epidemiology, characterized the reported increased morbidity, and identified factors associated with hospitalization during the outbreaks by reviewing a 10% random sample of outbreak-associated hepatitis A cases in Kentucky, Michigan, and West Virginia —3 heavily affected states. We calculated descriptive statistics and conducted age-adjusted log-binomial regression analyses to identify factors associated with hospitalization.

Results.—Participants in the random sample (n = 817) were primarily male (62.5%) with mean age of 39.0 years; 51.8% were hospitalized. Among those with available information, 73.2%

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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reported drug use, 14.0% were experiencing homelessness, 29.7% were currently or recently incarcerated, and 61.6% were epidemiologically linked to a known outbreak-associated case. Residence in Michigan (adjusted risk ratio [aRR] = 1.8), being a man who has sex with men (aRR = 1.5), noninjection drug use (aRR = 1.3), and homelessness (aRR = 1.3) were significantly ($P <$ .05) associated with hepatitis A-related hospitalization.

Conclusions.—Our findings support current Advisory Committee on Immunization Practices recommendations to vaccinate all persons who use drugs, men who have sex with men, and persons experiencing homelessness against hepatitis A.

Keywords

hepatitis A; disease outbreaks; hospitalization; United States; vaccine-preventable diseases

Hepatitis A is typically acquired through fecal-oral transmission, either from direct person-to-person contact or consumption of contaminated food or water. Hepatitis A virus (HAV) infection is typically mild and self-limited; however, symptomatic illness, jaundice, hospitalization, and complications are more frequent among adults [1, 2].

Effective hepatitis A vaccines were first licensed in the United States in 1995. In 1996, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination for people at increased risk for HAV infection or adverse consequences of infection (eg, people who use drugs, men who have sex with men [MSM], and people with chronic liver disease) [3]. In 2006, ACIP recommended routine vaccination of all children 12–23 months of age; and in 2019, ACIP recommended routine hepatitis A vaccination of people experiencing homelessness [4, 5]. Although hepatitis A vaccination coverage is low, particularly among adults, the overall incidence of hepatitis A declined substantially in the United States after widespread vaccination of children [6, 7]. As a result, the proportion of susceptible adults has increased. Based on data from the National Health and Nutrition Examination Survey, the proportion of US-born adults aged ≥20 years who were susceptible to HAV infection increased from 70.5% during 1999–2006 to 74.1% during 2007–2016, with >80.0% of US-born adults aged 30–49 years susceptible to HAV infection during the latter period [8, 9].

According to the National Notifiable Diseases Surveillance System (NNDSS), hospitalization for reported cases of hepatitis A in the United States increased from 7.3% in 1999 to 24.5% in 2011 to 41.6% in 2016 [7, 10]. Since 2016, the United States has experienced unprecedented person-to-person hepatitis A outbreaks in the vaccine era, with infections spreading primarily through close contact among people who use drugs, people experiencing homelessness, and MSM. During July 1, 2016 through July 25, 2020, state health departments publicly reported >33 500 outbreak-associated cases, >20 500 hospitalizations, and >330 deaths [11]. Overall, the proportion of outbreak-associated hepatitis A cases hospitalized in these person-to-person outbreaks has been higher (61%; range by affected state 43%–88%) than hospitalization historically associated with HAV infection [11]. In this study, we sought to describe the epidemiology of the ongoing person-to-person hepatitis A outbreaks, characterize the increased morbidity reported in the outbreaks, and identify factors associated with hospitalization during the outbreaks.

METHODS

We performed a retrospective, cross-sectional observational study of hepatitis A outbreak-associated cases with onset between July 1, 2016 and June 10, 2019. Individuals eligible for study participation were residents of Kentucky, Michigan, or West Virginia and had been designated by the respective state health department as a person-to-person outbreak-associated hepatitis A case. These states were selected because they accounted for 40% of the publicly reported person-to-person hepatitis A cases nationally at the end of the study period. We obtained deidentified hepatitis A outbreak records from the Kentucky Department for Public Health, the Michigan Department of Health and Human Services, and the West Virginia Bureau for Public Health, current as of June 11, 2019, August 16, 2019, and June 13, 2019, respectively. The state outbreak records were populated with data gathered by public health staff during case investigations. Case investigations involved patient interviews about demographics, risk factors, signs and symptoms of hepatitis A, and clinical outcomes; they were sometimes supplemented by information extracted from patient medical records. After utilizing the state health department outbreak records to determine eligibility, we generated a 10% random sample of hepatitis A outbreak-associated cases in each of the participating states for the study. We requested medical records from hospitals and reviewed all available records, along with the state outbreak records, for study participants using a standardized data abstraction instrument.

We obtained demographic (age, sex, race, ethnicity, county and state of residence), risk factor (drug use [injection and noninjection], homelessness, unstable housing, transient living, MSM status, incarceration, international travel, epidemiological linkage), clinical (comorbid medical conditions, pregnancy status, signs or symptoms consistent with hepatitis A, laboratory results), and outcome (hospitalization, fulminant hepatitis, liver transplant, death) data for study participants. Risk factors for acquiring hepatitis A were assessed based on their presence or absence during a participant's exposure period (ie, the 15–50 days before symptom onset). Drug use included, but was not limited to, marijuana use (regardless of state legalization status) as well as misuse of prescription opioids. International travel was defined as travel outside of the United States or Canada. Epidemiological linkage was defined as being a close contact (eg, household or sexual) of a known hepatitis A outbreak-associated case.

We assessed comorbid medical conditions: history of hepatitis B (laboratory evidence of prior exposure or current infection, or hepatitis B diagnosed in the medical record); history of hepatitis C (laboratory evidence of prior exposure or current infection, or hepatitis C diagnosed in the medical record); other pre-existing liver disease (eg, alcoholic liver disease, non-alcoholic fatty liver disease, cirrhosis); diabetes; immunosuppression (eg, human immunodeficiency virus [HIV]/acquired immune deficiency syndrome, hemodialysis, recipient of solid organ, bone marrow, or stem cell transplant, recipient of high-dose steroids, chemotherapy, or immunomodulators at the time of hepatitis A diagnosis, primary immunodeficiency condition); and cardiovascular disease (eg, coronary artery disease, hypertension, congestive heart failure, valvular heart disease, dyslipidemia, arrhythmia, peripheral artery disease, stroke). For laboratory results, we abstracted the result most

temporally proximal to the collection time of the specimen that yielded the HAV immunoglobulin M (IgM) positive result.

We categorized participants as having been hospitalized if they had evidence of an inpatient hospital admission, evidence of an admission order from an emergency department physician for those patients who left against medical advice, or evidence of >24 hours observation at a medical facility. Participants who were evaluated in an outpatient clinic, those discharged to home from the emergency department with a duration of stay ≤24 hours, or whose hospitalization status was unknown, were not considered hospitalized. We categorized participants as having fulminant hepatitis if the diagnosis was documented in the medical record or there was evidence of coagulopathy and hepatic encephalopathy in a patient with previously stable liver function.

Abstracted data were entered into a REDCap database [12, 13]. A second author independently reviewed and verified the accuracy of each participant record in the database. For participants with available information, we calculated descriptive statistics detailing the distribution of characteristics among hospitalized and nonhospitalized participants. We conducted multiple log-binomial regression analyses to estimate the relative risk and assess the association of individual factors with hospitalization. We adjusted the regression models by age (as a continuous variable). We conducted all analyses using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). The study was designated not human subjects research by the Centers for Disease Control and Prevention and the Michigan Department of Health and Human Resources Institutional Review Board (IRB) and was exempt from IRB review.

RESULTS

Demographic, Behavioral Risk, and Clinical Characteristics

We identified 817 hepatitis A outbreak-associated cases via generation of the 10% random sample; 472 participants were included from Kentucky, 92 from Michigan, and 253 from West Virginia. Study participants were residents of 63.3% of Kentucky counties, 19.3% of Michigan counties, and 54.5% of West Virginia counties (see Supplementary Figure 1 for epidemic curves). Overall, participants were primarily male (62.5%) with a mean age of 39.0 years. Among those with available risk factor information, 73.2% (459 of 627) reported drug use, whereas 14.0% (92 of 656) were experiencing homelessness, unstable housing, or transient living, 29.7% (94 of 317) were currently or recently incarcerated at the time of hepatitis A diagnosis, and 61.6% (141 of 229) were epidemiologically linked to a known hepatitis A outbreak-associated case (Table 1). Among male participants with available information, 10.1% (15 of 149) reported having sexual contact with men (Table 1).

Nausea (81.7%), jaundice or icterus (78.3%), and abdominal pain (70.4%) were the most frequently reported signs and symptoms among those with available data (Table 1). Of the participants with viral hepatitis coinfection data, 12.5% (83 of 662) had evidence of past or current hepatitis B virus (HBV) infection and 51.2% (370 of 723) had evidence of past or current hepatitis C virus (HCV) infection (Table 1). Among 134 participants with documented HIV testing, 0.7% (1 of 134) had evidence of HIV infection (Supplementary Table 1).

Outcomes and Hospitalization Burden

Of the 817 participants, 423 (51.8%) were hospitalized for a median of 4 days (range 1–59). Among hospitalized participants, 93.9% (397 of 423) experienced a single hepatitis A-related hospitalization; 9.8% (40 of 407) were in the intensive care unit at some point during their hospitalization (Supplementary Table 1). Among participants with available information, fulminant hepatitis occurred in 4.3% (20 of 460) of participants. One participant (0.2%, 1 of 466) underwent liver transplantation. Of the 719 (88.0%) study participants with available information, 7 (1.0%) died (Supplementary Table 1). Demographic, risk factor, clinical, and outcome characteristics of study participants stratified by state are described in the accompanying Supplementary Material.

Factors Associated With Hospitalization

Sociodemographic and risk factors were significantly ($P < .005$) associated with hospitalization among hepatitis A outbreak-associated cases in the log-binomial regression analyses after adjusting for age. Residence in Michigan (adjusted risk ratio [aRR] = 1.8, 95% confidence interval [CI] = 1.5–2.0, compared with residence in Kentucky), being a man who reported sexual contact with men (aRR = 1.5; 95% CI, 1.2–1.9), noninjection drug use (aRR = 1.3; 95% CI, 1.1–1.5), and homelessness, unstable housing, or transient living (aRR = 1.3; 95% CI, 1.1–1.5) were associated with higher relative risk of hospitalization, whereas incarceration was associated with lower relative risk of hospitalization (aRR = 0.7; 95% CI, 0.5–0.9) (Table 1).

Clinical factors were also significantly ($P < .05$) associated with hospitalization after adjusting for age. Signs and symptoms of hepatitis A that were associated with higher relative risk of hospitalization included the following: vomiting (aRR = 2.1; 95% CI, 1.8–2.4), abdominal pain (aRR = 1.8; 95% CI, 1.5–2.2), anorexia (aRR = 1.6; 95% CI, 1.4–1.9), dark urine (aRR = 1.6; 95% CI, 1.4–1.8), malaise (aRR = 1.5; 95% CI, 1.3–1.8), nausea (aRR = 1.5; 95% CI, 1.2–1.8), fever (aRR = 1.4; 95% CI, 1.2–1.6), jaundice or icterus (aRR = 1.3; 95% CI, 1.1–1.6), and diarrhea (aRR = 1.3; 95% CI, 1.1–1.5). In addition, the following laboratory indicators were associated with higher relative risk of hospitalization: aspartate aminotransferase (AST) >200 IU/L (aRR = 1.4, 95% CI = 1.1–1.7 for AST 201–1500 IU/L, aRR = 1.6, 95% CI = 1.2–2.0 for AST 1501–3000 IU/L, and aRR = 1.9, 95% CI = 1.5–2.4 for AST >3000 IU/L, compared with AST ≤200) and alanine aminotransferase (ALT) >3000 IU/L (aRR = 1.7, 95% CI = 1.2–2.3, compared with ALT ≤200) (Table 1).

DISCUSSION

During the largest person-to-person hepatitis A outbreaks in the vaccine era, we analyzed a random sample of hepatitis A outbreak-associated cases from 3 states that experienced extensive person-to-person transmission and found that 52% of the study population was hospitalized. This figure substantially exceeded the proportion of hospitalized cases reported in recent major US foodborne hepatitis A outbreaks and in national surveillance data. For example, 42% of cases were hospitalized during a 2013 outbreak involving frozen pomegranate arils, 25% were hospitalized during a 2016 outbreak involving frozen scallops, and 39% were hospitalized during a 2016 outbreak involving frozen strawberries [14–16].

Among hepatitis A cases reported nationally to NNDSS in 2016, 42% were hospitalized [7]. We described the epidemiology of the ongoing person-to-person hepatitis A outbreaks more thoroughly than would be possible using traditional surveillance data, characterized the increased morbidity reported during the outbreaks, and identified factors associated with hospitalization during the outbreaks. We determined that noninjection drug use, being a man who reported sexual contact with men, and homelessness were associated with higher relative risk of hospitalization, whereas incarceration was associated with lower relative risk of hospitalization.

Among hospitalized study participants, the mean length of stay was 5 days, slightly longer than the overall mean hospital length of stay in the United States in 2016 (the most recent year for which data are available) [17]. Approximately 10% of those hospitalized required substantial escalations of care as evidenced by admission to an intensive care unit. A recent study using Healthcare Cost and Utilization Project data estimated that the overall average costs per hepatitis A-related hospitalization in the United States in 2017 was $16 232, suggesting that there was a substantial financial burden that accompanied the hospitalization burden [18].

There were significant geographic differences in the relative risk of hospitalization, with residents of Michigan having 1.8 times the risk of hospitalization compared with residents of Kentucky (aRR = 1.8; 95% CI, 1.5–2.0). Michigan consistently reported one of the highest proportions of hospitalized outbreak-associated hepatitis A cases of any affected state throughout the person-to-person outbreaks [11, 19]. A higher proportion of study participants from Michigan were (1) aged ≥60, (2) African American/non-Hispanic race/ethnicity, (3) men who reported sexual contact with men, or (4) privately insured compared with study participants from Kentucky or West Virginia. In addition, fulminant hepatitis occurred in 3 and 9 times the proportion of Michigan residents compared to Kentucky or West Virginia residents, respectively. It appears that inherent characteristics of outbreak-associated hepatitis A cases in Michigan might have contributed to the high proportion of hospitalized cases in that state; however, future research is necessary to determine the relative contributions of inherent patient characteristics versus provider decision-making or hospital admission policies.

Risk factors for acquiring hepatitis A were also associated with increased relative risk of hospitalization among study participants. Drug use and being a man who has sex with men are recognized risk factors for acquiring hepatitis A and 2 of the longest standing ACIP indications for hepatitis A vaccination [3]. We found that noninjection drug use, but not injection drug use, was associated with statistically significantly higher relative risk of hospitalization among hepatitis A outbreak-associated cases; those participants who reported noninjection drug use had 1.3 times the risk compared with those who denied noninjection drug use (aRR = 1.3; 95% CI, 1.1–1.5). Likewise, among male study participants, we found that the risk of hospitalization among those who reported sexual contact with men was 1.5 times as high as the risk of hospitalization among those who did not report sexual contact with men (aRR = 1.5; 95% CI, 1.2–1.9). Homelessness has been recently recognized as an important risk factor for hepatitis A; accordingly, in 2019, the ACIP recommended hepatitis A vaccination for persons experiencing homelessness [5]. Homelessness, unstable housing,

or transient living was associated with significantly higher relative risk of hospitalization among study participants; those participants who reported homelessness, unstable housing, or transient living had 1.3 times the risk of hospitalization compared with those who did not (aRR = 1.3; 95% CI, 1.1–1.5). Likewise, researchers found that people experiencing homelessness had 2.5 times higher odds of hospitalization than those not experiencing homelessness in the 2016–2018 person-to-person hepatitis A outbreak in San Diego County, California [20]. This association may be driven in part by provider recognition that people experiencing homelessness often have nowhere safe to convalesce and consequently pose a potential risk for continued transmission in the community during their infectious period [21]. We suspect that these results are conservative estimates of the actual associations with hospitalization. We compared hospitalized hepatitis A patients to nonhospitalized hepatitis A patients. Had we used an approach that included healthy patients without hepatitis A as the comparison group, the associations with hepatitis A-related hospitalization might have been even more robust. These findings provide strong support for current ACIP recommendations to vaccinate all persons who use drugs, MSM, and persons experiencing homelessness against hepatitis A.

Previous hepatitis A outbreak studies have not examined the effect of incarceration status on hospitalization. We found that incarcerated participants were less likely to be hospitalized compared with nonincarcerated participants (aRR = 0.7; 95% CI, 0.5–0.9). The reasons for this association are unclear. It is possible that medical services available at correctional facilities were adequate to provide supportive care to patients, thereby reducing the need for hospitalization. Further research is warranted to clarify this finding.

Contrary to prior studies, we did not find coinfection (with HBV or HCV) to be associated with hepatitis A-related hospitalization [4, 10, 22–24]. It is possible that our classification scheme (evidence of past or current HBV or HCV infection) played a role in the lack of evidence of an association between HBV or HCV coinfection and hospitalization in our study; however, we assessed active, current HCV infection via quantifiable HCV ribonucleic acid viral load, and the association with hospitalization was not statistically significant. Based on medical record review, several coinfected individuals were diagnosed with hepatitis B or C for the first time concurrently with their hepatitis A diagnosis. If HBV or HCV infections were recent, the pathologic sequelae of chronic liver disease that place patients with chronic liver disease diagnosed with hepatitis A at higher risk for acute liver failure (and consequently hospitalization) may not have had time to manifest.

Likewise, we did not find age to be associated with hepatitis A-related hospitalization. However, previous studies have found that hepatitis A infection among older adults results in more severe disease; the mean age of hepatitis A-hospitalized cases reported to NNDSS increased from 36.0 years in 1999 to 45.1 years in 2011, whereas the proportion of individuals hospitalized in the United States for hepatitis A aged ≥40 years increased from 2002 to 2011 [4, 10, 22]. Our study population was relatively young; only 19% of participants were aged ≥50 years, and only 2% were aged ≥70 years. The preponderance of young study participants might have negated the historically observed association between older age and hospitalization.

Our study has several limitations. First, we were unable to assess the effect of medical provider decision-making or of hospital admission policies on hospitalization. Second, risk factor data, except for toxicology or drug screen results, were self-reported and subject to recall and social desirability biases. Third, there are missing data for several of the variables assessed in the study. More than 25% of data were missing for 6 of the 8 risk factors and 5 of the 7 comorbidities assessed, which likely led to underestimates of the proportions of participants with those characteristics. In addition, information on race and ethnicity was missing for approximately 55% of study participants, limiting our ability to (1) evaluate potential associations of race and poor outcomes or (2) control for the effect of race in the regression analyses. Furthermore, approximately two thirds of study participants were missing data on hepatitis A vaccination status. However, among those with available information, approximately 90% had not been previously vaccinated against hepatitis A (data not shown). The populations most heavily affected by these outbreaks were often difficult to reach, which complicated the collection of data by public health staff and resulted in relatively high rates of loss to follow-up among cases who could not be reached for interview. Although loss to follow-up rates during the person-to-person hepatitis A outbreaks varied widely by state, the rates for the state participants in this study were similar [19, 25]. Fourth, our models only adjust for age. Fifth, data were abstracted by 5 different authors, so it is possible that there were discrepancies among abstractors. However, the use of a standardized abstraction form, an abstraction guidance document, and a pilot session on the use of the form before the start of record review likely mitigated the potential for differential classification among abstractors. Finally, the representativeness of the study may be limited because it was restricted to 3 states experiencing person-to-person hepatitis A outbreaks. However, at the end of the study period in June 2019, Kentucky, Michigan, and West Virginia accounted for 40% of the publicly reported person-to-person hepatitis A cases nationally.

CONCLUSIONS

In summary, this study provides more comprehensive insight into the epidemiology of the ongoing person-to-person hepatitis A outbreaks than is available through traditional surveillance data. We report that state of residence, noninjection drug use, being a man who has sex with men, and homelessness were associated with higher relative risk of hospitalization, whereas incarceration was associated with lower relative risk of hospitalization. Our findings support current ACIP recommendations to vaccinate all persons who use drugs, MSM, and persons experiencing homelessness against hepatitis A. In addition, they highlight potential missed opportunities for prevention; examining only a single variable (drug use) reveals that more than half of the study participants reported this ACIP indication for vaccination and should already have been protected against hepatitis A. Given the high hospitalization burden during these outbreaks and the persistently low hepatitis A seroprevalence and self-reported hepatitis A vaccination coverage among adults in the United States, clinicians should strive to improve hepatitis A vaccination coverage among at-risk adults recommended for vaccination by the ACIP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1.

Associations With Hospitalization During Person-to-Person Hepatitis A Outbreaks—Kentucky, Michigan, and West Virginia, 2016–2019

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
Demographic					
Age, Years					
≤19	16 (2.0)	4 (0.9)	12 (3.0)	-	-
20–29	168 (20.6)	81 (19.1)	87 (22.1)	-	-
30–39	292 (35.7)	146 (34.5)	146 (37.1)	-	-
40–49	188 (23.0)	99 (23.4)	89 (22.6)	-	-
50–59	100 (12.2)	59 (13.9)	41 (10.4)	-	-
60–69	36 (4.4)	23 (5.4)	13 (3.3)	-	-
≥70	17 (2.1)	11 (2.6)	6 (1.5)	-	-
Sex					
Male	511 (62.5)	270 (63.8)	241 (61.2)	1.0 (0.9–1.2)	.615
Female	306 (37.5)	153 (36.2)	153 (38.8)	REF	-
Race/Ethnicity (n = 368)					
White/NH	337 (91.6)	291 (92.4)	46 (86.8)	REF	-
African American/NH	26 (7.1)	21 (6.7)	5 (9.4)	0.9 (0.8–1.1)	.339
Other[c]	5 (1.4)	3 (1.0)	2 (3.8)	0.7 (0.3–1.4)	.334
State					
Kentucky	472 (57.8)	218 (51.5)	254 (64.5)	REF	-
Michigan	92 (11.3)	78 (18.4)	14 (3.6)	**1.8 (1.5–2.0)**	**<.001**

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
West Virginia	253 (31.0)	127 (30.0)	126 (32.0)	1.1 (0.9–1.3)	.337
Risk Factor					
Drug Use (n = 627)					
Yes	459 (73.2)	280 (73.5)	179 (72.8)	1.1 (0.9–1.2)	.495
No	168 (26.8)	101 (26.5)	67 (27.2)	REF	-
Injection Drug Use (n = 557)[d]					
Yes	329 (59.1)	211 (59.9)	118 (57.6)	1.1 (0.9–1.2)	.411
No	228 (40.9)	141 (40.1)	87 (42.4)	REF	-
Noninjection Drug Use (n = 450)[d]					
Yes	267 (59.3)	192 (64.2)	75 (49.7)	**1.3 (1.1–1.5)**	**.002**
No	183 (40.7)	107 (35.8)	76 (50.3)	REF	-
Homelessness, Unstable Housing, or Transient Living (n = 656)					
Yes	92 (14.0)	61 (17.7)	31 (10.0)	**1.3 (1.1–1.5)**	**.001**
No	564 (86.0)	284 (82.3)	280 (90.0)	REF	-
MSM (n = 149)[e]					
Yes	15 (10.1)	14 (14.6)	1 (1.9)	**1.5 (1.2–1.9)**	**.003**
No	134 (89.9)	82 (85.4)	52 (98.1)	REF	-
Incarcerated (n = 317)					
Yes	94 (29.7)	41 (21.8)	53 (41.1)	**0.7 (0.5–0.9)**	**.002**
No	223 (70.3)	147 (78.2)	76 (58.9)	REF	-

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
International Travel (n = 446)					
Yes	1 (0.2)	1 (0.4)	0 (0.0)	N/A	N/A
No	445 (99.8)	270 (99.6)	175 (100.0)	REF	-
Epidemiologically Linked (n = 229)					
Yes	141 (61.6)	83 (57.2)	58 (69.0)	0.8 (0.7–1.0)	.070
No	88 (38.4)	62 (42.8)	26 (31.0)	REF	-
Clinical					
History of Hepatitis B (n = 662)					
Yes	83 (12.5)	52 (12.6)	31 (12.4)	1.0 (0.8–1.2)	.939
No	579 (87.5)	360 (87.4)	219 (87.6)	REF	-
History of Hepatitis C (n = 723)					
Yes	370 (51.2)	203 (48.4)	167 (54.9)	0.9 (0.8–1.1)	.284
No	353 (48.8)	216 (51.6)	137 (45.1)	REF	-
Other Pre-existing Liver Disease (n = 186)					
Yes	83 (44.6)	80 (46.0)	3 (25.0)	1.0 (1.0–1.2)	.375
No	103 (55.4)	94 (54.0)	9 (75.0)	REF	-
Diabetes (n = 448)					
Yes	61 (13.6)	54 (13.8)	7 (12.1)	1.0 (0.9–1.1)	.969
No	387 (86.4)	336 (86.2)	51 (87.9)	REF	-
Pregnancy (n = 140)[f]					

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
Yes	11 (7.9)	9 (8.0)	2 (7.1)	1.0 (0.8–1.4)	.906
No	129 (92.1)	103 (92.0)	26 (92.9)	REF	-
Immunosuppression (n = 374)					
Yes	8 (2.1)	8 (2.4)	0 (0.0)	N/A	N/A
No	366 (97.9)	326 (97.6)	40 (100.0)	REF	-
Cardiovascular Disease (n = 425)					
Yes	138 (32.5)	133 (34.9)	5 (11.4)	1.1 (1.0–1.2)	.194
No	287 (67.5)	248 (65.1)	39 (88.6)	REF	-
Signs or Symptoms					
Fever (n = 767)					
Yes	269 (35.1)	176 (43.9)	93 (25.4)	**1.4 (1.2–1.6)**	**<.001**
No	498 (64.9)	225 (56.1)	273 (74.6)	REF	-
Headache (n = 677)					
Yes	121 (17.9)	69 (20.8)	52 (15.1)	1.2 (1.0–1.4)	.071
No	556 (82.1)	263 (79.2)	293 (84.9)	REF	-
Malaise (n = 738)					
Yes	334 (45.3)	213 (56.6)	121 (33.4)	**1.5 (1.3–1.8)**	**<.001**
No	404 (54.7)	163 (43.4)	241 (66.6)	REF	-
Anorexia (n = 725)					
Yes	266 (36.7)	183 (49.2)	83 (23.5)	**1.6 (1.4–1.9)**	**<.001**

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
No	459 (63.3)	189 (50.8)	270 (76.5)	REF	-
Nausea (n = 791)					
Yes	646 (81.7)	358 (86.7)	288 (76.2)	**1.5 (1.2–1.8)**	**<.001**
No	145 (18.3)	55 (13.3)	90 (23.8)	REF	-
Vomiting (n = 780)					
Yes	368 (47.2)	265 (65.3)	103 (27.5)	**2.1 (1.8–2.4)**	**<.001**
No	412 (52.8)	141 (34.7)	271 (72.5)	REF	-
Diarrhea (n = 689)					
Yes	201 (29.2)	131 (35.0)	70 (22.2)	**1.3 (1.1–1.5)**	**<.001**
No	488 (70.8)	243 (65.0)	245 (77.8)	REF	-
Abdominal Pain (n = 797)					
Yes	561 (70.4)	338 (81.3)	223 (58.5)	**1.8 (1.5–2.2)**	**<.001**
No	236 (29.6)	78 (18.8)	158 (41.5)	REF	-
Dark Urine (n = 736)					
Yes	382 (51.9)	235 (63.3)	147 (40.3)	**1.6 (1.4–1.8)**	**<.001**
No	354 (48.1)	136 (36.7)	218 (59.7)	REF	-
Acholic stool (n = 263)					
Yes	122 (46.4)	79 (47.9)	43 (43.9)	1.0 (0.9–1.3)	.574
No	141 (53.6)	86 (52.1)	55 (56.1)	REF	-
Jaundice/Icterus (n = 769)					

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
Yes	602 (78.3)	340 (82.9)	262 (73.0)	**1.3 (1.1–1.6)**	**.003**
No	167 (21.7)	70 (17.1)	97 (27.0)	REF	-
Date of symptom onset (range)	7/30/2016–6/4/2019	7/30/2016–5/13/2019	1/10/2017–6/4/2019	N/A	N/A
Laboratory Results					
ALT (IU/L) (n = 801)					
≤200	71 (8.9)	29 (6.9)	42 (11.1)	REF	-
201–1500	362 (45.2)	172 (40.7)	190 (50.3)	1.2 (0.9–1.6)	.301
1501–3000	232 (29.0)	128 (30.3)	104 (27.5)	1.3 (1.0–1.8)	.056
>3000	136 (17.0)	94 (22.2)	42 (11.1)	**1.7 (1.2–2.3)**	**.001**
AST (IU/L) (n = 794)					
≤200	139 (17.5)	53 (12.5)	86 (23.2)	REF	-
201–1500	382 (48.1)	195 (46.1)	187 (50.4)	**1.4 (1.1—1.7)**	**.012**
1501–3000	187 (23.6)	112 (26.5)	75 (20.2)	**1.6 (1.2–2.0)**	**<.001**
>3000	86 (10.8)	63 (14.9)	23 (6.2)	**1.9 (1.5–2.4)**	**<.001**
AST/ALT ratio (n = 794)					
<1	600 (75.6)	310 (73.3)	290 (78.2)	REF	-
≥1	194 (24.4)	113 (26.7)	81 (21.8)	1.1 (1.0–1.3)	.194
Total bilirubin (mg/dL) (n = 531)					
<3	97 (18.3)	75 (17.7)	22 (20.4)	REF	-
3–6	157 (29.6)	122 (28.8)	35 (32.4)	1.0 (0.9–1.1)	.920

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
>6 - 9	149 (28.1)	114 (27.0)	35 (32.4)	1.0 (0.9–1.1)	.848
>9	128 (24.1)	112 (26.5)	16 (14.8)	1.1 (1.0–1.2)	.269
Platelet count (K/μL (n = 470)					
<150	101 (21.5)	96 (23.0)	5 (9.6)	1.1 (1.0–1.1)	.110
≥150	369 (78.5)	322 (77.0)	47 (90.4)	REF	-
HBsAg (n = 627)					
Positive/reactive	45 (7.2)	30 (7.2)	15 (7.1)	1.0 (0.8–1.2)	.942
Negative/nonreactive	582 (92.8)	385 (92.8)	197 (92.9)	REF	-
IgM Anti-HBc (n = 618)					
Positive/reactive	35 (5.7)	25 (6.1)	10 (4.8)	1.1 (0.9–1.4)	.330
Negative/nonreactive	576 (93.2)	377 (92.4)	199 (94.8)	REF	-
Indeterminate/ borderline	7 (1.1)	6 (1.5)	1 (0.5)	1.4 (1.0–1.8)	.056
Anti-HCV (n = 659)					
Positive/reactive	327 (49.6)	197 (47.2)	130 (53.7)	1.0 (0.8–1.1)	.357
Negative/nonreactive	331 (50.2)	219 (52.5)	112 (46.3)	REF	-
Indeterminate	1 (0.2)	1 (0.2)	0 (0.0)	N/A	N/A
HCV RNA Viral Load (n = 141)					
Undetectable	74 (52.5)	63 (50.8)	11 (64.7)	REF	-
Detected but not quantifiable	19 (13.5)	16 (12.9)	3 (17.6)	1.0 (0.8–1.2)	1.000

Characteristic	Overall, n (%) (n = 817)[a]	Hospitalized, n (%) (n = 423)[a]	Nonhospitalized, n (%) (n = 394)[a]	Age-Adjusted RR (95% CI)[b]	*P* Value
Detected and quantifiable	48 (34.0)	45 (36.3)	3 (17.6)	1.1 (0.9–1.2)	.389

Abbreviations: ALT, alanine aminotransferase; anti-HCV, hepatitis C antibody; AST, aspartate aminotransferase; CI, confidence interval; HBsAg, hepatitis B surface antigen; IgM anti-HBc, immunoglobulin M hepatitis B core antibody; MSM, men who have sex with men; N/A, not applicable; NH, non-Hispanic; REF, reference category; RR, risk ratio.

NOTE: Statistically significant associations are highlighted in bold.

[a]Percentages are calculated based on participants with available information and may not sum to 100.0% due to rounding.

[b]Log-binomial regression analyses, adjusted by age (continuous).

[c]Other: Hispanic ethnicity or white and American Indian/Alaska Native.

[d]Restricted to those with available information on reported drug use (n = 627).

[e]Restricted to male study participants (n = 511).

[f]Restricted to female study participants (n = 306).