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Genomic epidemiology of resurgent hepatitis A in Florida, 2018–2022

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Abstract

During 2018–2022, a resurgence of hepatitis A occurred in Florida, with 5,491 cases reported. Genotyping was performed on a convenience sample of cases through amplification and sequencing of the HAV VP1-P2B junction region. Virus isolates from 1,190 (22%) cases were genotyped; 69% were subgenotype IB, 30% were subgenotype IA, and 1% were subgenotype IIIA. Subgenotype IB was more common among cases reporting recent drug use or homelessness, whereas IA was more common among those reporting recent international travel and among men who have sex with men. Genotype IB infection was associated with a more than 4-fold greater odds of death compared to IA infection. A network analysis revealed 11 genomic clusters of 10 or more cases, with distinct temporal and spatial distributions. Case reports in 2023 decreased to below pre-2018 numbers, likely due to high population immunity following natural infection and extensive vaccination activities in the highest risk groups.

Article summary:

During 2018–2022, a resurgence of hepatitis A occurred in Florida, with 5,491 cases reported. A network analysis revealed 11 genomic clusters of 10 or more cases, with distinct temporal and spatial distributions.

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Sequence fragment data used in this report are available at the National Center for Biotechnology Information, BioProject ID: PRJNA1229618, <https://www.ncbi.nlm.nih.gov/bioproject/1229618>.

Keywords

hepatitis; hepatitis a; viruses; virus diseases; epidemiology; genotype; Florida

Background

Hepatitis A is an acute liver disease, caused by infection with hepatitis A virus (HAV, *Hepatovirus ahepa*), a non-enveloped RNA *Hepatovirus* of the *Picornaviridae* family [1, 2]. HAV is shed in feces and transmitted primarily through the fecal-oral route. HAV is antigenically stable and replicates slowly, with a much lower mutation rate than other members of the family. The HAV genome is approximately 7.5 kb in length, with a single serotype and three genotypes isolated from humans (I-III), further divided into seven subgenotypes with IA, IB, and IIIA accounting for the vast majority of infections [3, 4]. These classifications are based on HAV viral protein 1-amino terminus of 2A (VP1–2A) genomic region [4–6]. This genomic region is most commonly used to support outbreak investigations [4, 7] and previous reports have utilized unique nucleotide sequence patterns (UNSPs) of this region to draw inferences regarding disease transmission networks and possible sources of infection [8].

Hepatitis A is mostly asymptomatic or subclinical among children under five years old with more clinically apparent illness in older children and adults [9]. The incubation period ranges from 15–50 days and clinical illness usually resolves completely; however, acute liver failure and death may occur [10]. It remains uncertain to what extent illness severity can be explained by specific variations in the HAV genome. Following introduction of a highly effective vaccine in 1996 and incorporation into the routine childhood immunization schedule in the United States [11, 12], hepatitis A has increasingly become a disease of adults, with a corresponding age-related shift toward more severe illness, and epidemiologic risk categories reflective of adult behaviors.

In Florida from 2004 to 2017, the annual number of hepatitis A case reports ranged from 107 to 295 (median 168); annual statewide incidence ranged from 0.58 to 1.69 cases per 100,000 population [13]; international travel to endemic countries was the most common risk factor. Starting in 2016, an increase of hepatitis A occurred in the United States, characterized by person-to-person transmission, primarily among persons reporting injection or non-injection illicit drug use and persons experiencing homelessness [14]. Outbreaks were reported from 37 states, including Florida, resulting in more than 44,900 cases and 420 deaths nationally during 2016–2023 [15]. The outbreak in Florida began in 2018, was declared over in August 2021, and had the highest number of cases and deaths of any state [15].

In 2018, the Florida Department of Health (FDOH), Bureau of Public Health Laboratories (BPHL), with support from the Centers for Disease Control and Prevention (CDC), began implementing HAV sequencing for genotype classification, based on national protocols recommended by CDC [16, 17]. HAV genotyping was utilized by FDOH to monitor the large increase in hepatitis A occurring in Florida during 2018–2019, and to respond to a later outbreak in 2022, primarily among men who have sex with men (MSM) [18].

The objectives of this report are to highlight the changing epidemiology of hepatitis A in Florida by providing a descriptive, cross-sectional, and network analysis of cases over the period 2018–2022, and to assess risk factors and severity of illness by genotype. This is done by combining epidemiologic, clinical, and HAV genomic data for cases reported to FDOH over the five-year period.

Methods

Hepatitis A is a reportable disease in Florida and FDOH utilizes the national surveillance case definition [19]. Reported cases are investigated by FDOH staff to confirm the case definition criteria are met. Case investigations involve patient interviews and medical record review to gather information on the course of clinical illness, history of vaccination, close contacts, employment in settings that may place others at risk of infection, and risk factors for acquiring infection including, recent history (i.e., 2–6 weeks prior to symptom onset) of travel, illicit drug use, sexual activity, housing, and consumption of particular food items. For those reporting recent drug use, a text field is used to note the types of drugs used. Close personal contacts are identified and offered prophylaxis where indicated. Contact type is documented and classified into three categories (e.g., sexual, household non-sexual, other) where the other category consists of shared work, commercial, or non-household living environments, or shared meals.

Blood samples from hepatitis A patients were forwarded from medical providers to BPHL for HAV genotyping, based primarily on specimen availability, resulting in a convenience, non-random sample of all cases. BPHL performed HAV genotyping by amplifying and sequencing the VP1-P2B junction region of the HAV genome [16]. Initial amplification was done with Qiagen's OneStep RT-PCR kit. Next-generation sequencing was conducted on the Illumina MiSeq platform and data were uploaded to the CDC Global Hepatitis Outbreak Surveillance Technology (GHOST) system's online analysis platform [17]. GHOST detects the dominant HAV variant and compares this to a reference set of UNSPs of the HAV VP1/P2B segment. UNSPs with two or more infected persons in the GHOST reference set are assigned names, hereafter referred to as strains.

Descriptive statistical analyses were performed to characterize cases by person, place, and time. All Florida residents, meeting the hepatitis A confirmed case definition and reported to FDOH between January 1, 2018 and December 31, 2022, were included in the analyses. We used population estimates from 2020 to compute disease incidence rates [13]. As some patients could not be contacted for follow-up, the number of cases investigated was used as the denominator to calculate the frequency of risk factors. Cases with and without available genotype results were compared using Chi-squared and Kruskal-Wallis tests for categorical and continuous variables, respectively. For cases with available genotype data, odds ratios (ORs) with 95% confidence intervals (CIs) and P-values were computed to compare demographic, clinical, and risk factor characteristics among HAV subgenotypes. Comparisons were also made between cases that shared the same UNSP with two or more other cases (genomically clustered), versus cases with UNSPs that did not match any other cases in Florida (e.g., singleton UNSPs); genomic pairs with two and only two cases of the same UNSP were excluded from these analyses. Multiple logistic regression was used to

evaluate the association between death and HAV subgenotype. Categorical covariates were dichotomized (yes/no) and included MSM status, non-injection drug use, injection drug use (IDU), current or recent homelessness, and coinfection or a history of acute or chronic infection with hepatitis B virus (HBV, *Orthohepadnavirus hominoides*) or hepatitis C virus (HCV, *Hepacivirus hominis*). Age was included as a continuous variable.

We performed a network analysis using available demographic, risk factor, contact type, and genomic data for all cases. The network analysis utilized the MicrobeTrace software [20] to generate static and dynamic (i.e., time dependent) visualizations of likely HAV transmission networks based on genomic and epidemiologic linkages between cases. For genomic cluster classification, single-nucleotide polymorphism (SNP) differences were set to zero and only clusters with 5 or more cases with either a genomic or epidemiologic linkage were included in network visualizations. Mutually exclusive risk categories were used to classify each case into one and only one of the following categories, with category matches evaluated in the following sequence: MSM, IDU or homelessness, incarceration, international travel, epidemiologic linkage to a confirmed case, and no risk identified. Because many patients reported both IDU and homelessness, these risk factors were combined in a single category for network visualization. Spatial and temporal patterns were further assessed in the largest genomic clusters of 10 or more cases of the same strain.

Statistical analyses were done using R and text fields were analyzed using Text Explorer in SAS JMP [SAS Institute, Cary, NC]. This activity was reviewed by the Ethics and Human Research Protection Program of FDOH and by CDC and was determined to be public health practice and was conducted in a manner consistent with applicable federal law and CDC policy (45 C.F.R. part 46, 21 C.F.R. part 56).

Results

A total of 5,491 acute hepatitis A cases were reported in Florida during 2018–2022 and HAV genotype data were available for 1,190 (22%). Peak incidence occurred during the summer of 2019 (Figure 1), shortly before a public health emergency was declared in Florida on August 1, 2019. There was a predominance of subgenotype IB infections during 2019–2021, with a greater proportion of IA infections in 2022. The annual case incidence rate during the study interval ranged from 0.92 cases per 100,000 in 2021 to 15.95 cases per 100,000 in 2019. Over the entire period, the average annual incidence rate was 5.07 cases per 100,000 statewide; county-specific incidence ranged from zero (four counties) to 19 cases per 100,000 (Citrus and Pasco counties, both north of Tampa Bay) (Figure 2).

Among all patients, the median age was 39 years, and the majority were white (87.3%), non-Hispanic (90.7%), and male (64.6%); 78 deaths were reported (1.4%) (Table 1). Patients with known genotype differed from those with unknown genotype with respect to some demographic, risk factor, and outcome variables. When compared to patients for whom HAV genotype was not determined, patients with known HAV genotype were significantly more likely to have been hospitalized (71.5% versus 67.6%, $P=0.012$) and to have died (2.9% versus 1.0%, $P<0.001$) (Table 1). Among all patients, the most common risk factor for infection was any drug use, followed by IDU, homelessness, incarceration, MSM, and

international travel. There was also substantial overlap in risk categories, e.g., multiple risk categories reported by the same patient (Supplemental Table 1). The greatest overlap occurred between homelessness and IDU, with 63% of patients experiencing homelessness also reporting recent IDU.

Among patients reporting recent drug use, methamphetamines were the most frequently mentioned substance, with text analyses identifying 45% (1,320 of 2,902) of respondents reporting use of ‘meth’, ‘methamphetamines’, or ‘amphetamines’. Other commonly reported substances were marijuana (21%), heroin (13%), cocaine (12%), and other or non-specified opiates (7%). Among patients reporting drug use, 63% reported IDU and approximately 30% of all patients had history of acute or chronic HCV infection.

A total of 1,550 epidemiologic linkages were identified among 1,224 individual cases. Non-sexual household contact accounted for 35% of epidemiologic linkages, followed by sexual contact (20%), and the remainder were classified as other. Among all cases, 238 (4.3%) were food workers, but none were identified as part of onward foodborne transmission or foodborne outbreaks. During the study interval, Florida reported one suspected foodborne outbreak of hepatitis A, in January 2019, involving seven elderly patrons associated with a single restaurant, though no implicated food items or food workers were identified.

Of the 1,190 cases with available data on genotype, 825 (69%) were associated with HAV subgenotype IB infection, 355 (30%) with subgenotype IA, and 10 (1%) with subgenotype IIIA (Table 1). When comparing patient characteristics by the two most common HAV subgenotypes, patients with IB infection were more likely to be white, non-Hispanic, and older compared to patients with IA infection (Table 2). Compared to patients infected with subgenotype IA, patients infected with subgenotype IB were less likely to identify as MSM or report recent international travel, and were more likely to report recent drug use, homelessness, and incarceration. While hospitalization was more common among patients with subgenotype IA infections, the odds of death was more than four-fold higher for patients with subgenotype IB infections [unadjusted OR (95% CI): 4.42 (1.34–14.58)]. In multivariable analysis, the OR for the association between death and subgenotype IB infection increased to 4.75 (95% CI: 1.38–16.34), after controlling for potential confounders. Of the 10 patients with subgenotype IIIA infection, 1 death occurred in a 72-year-old male, with underlying cardiovascular disease and insulin dependent diabetes.

When comparing cases that were genomically clustered to those with unmatched UNSPs (e.g., singletons), clustered cases were more likely to be in patients who were white, non-Hispanic, and reported any drug use or IDU (Table 2). Unclustered cases were more likely to be in patients who were black and reported recent international travel. No other significant differences were noted between genomically clustered and unclustered cases.

The static network visualization shows 18 distinct clusters of 5 or more cases, involving 1,273 cases with a genomic or epidemiologic linkage (Figure 3). An equal number of clusters (7) involved patients infected with subgenotype IA versus IB. One cluster was associated with patients infected with subgenotype IIIA, and 3 clusters involved patients with unknown HAV genotype that were identified by epidemiologic linkage alone. The

network visualization does not fully account for overlapping risk categories, however, most clusters had a substantial proportion of cases among those reporting IDU or experiencing homelessness. Exceptions include 2 subgenotype IA clusters in which MSM was the predominant risk category among cases. Epidemiologic linkages between cases that were part of genomic clusters with differing HAV strains were noted in 6 instances.

The largest cluster observed was subgenotype IB, strain A16 Cluster 1, that consisted of 440 cases with matching UNSP and dozens of other cases with an epidemiologic linkage, but unknown genotype. The predominant risk categories among genomically linked cases in this cluster were IDU (39%) and homelessness (23%), while only 5% identified as MSM. When the temporal evolution of this cluster was observed (dynamic network visualization, data not shown), we noted that the initial cases in this cluster were among MSM and that 10 of 50 (20%) cases in the cluster in 2018 were among MSM.

Additional details of the spatial and temporal distribution of the 10 largest genomic clusters, with 10 or more cases of matching UNSP, are provided in Figures 4 and 5 and consisted of 6 IB and 4 IA clusters. One of these clusters, (subgenotype IA, strain A17 Cluster 21) has been previously described in detail [18]. Each genomic cluster extended across multiple counties, sometimes with a small number of counties predominating. The larger clusters generally had a discrete beginning, peak, and end phase demonstrated by the epidemiologic curves, however, some of the smaller clusters were characterized by sporadic cases occurring over several months. During peak incidence in 2019, with scores of cases occurring each week, there were likely at least 7 distinct outbreak strains circulating in the state at the same time. Among the 10 largest UNSP clusters, 8 included residents of Hillsborough County, 7 included residents of Pasco and Pinellas counties; and 6 included Orange, Polk, and Volusia County residents.

Discussion

This combined epidemiologic and genomic analysis is one of the largest of its kind in the United States to use detailed state-level surveillance data, combined with viral sequence data, and sheds new light on the complexity of transmission networks and spatial-temporal patterns of this recently resurgent disease. Numerous past reports from the United States have described various epidemiologic aspects of the national multistate outbreaks [21–24], and others have described the evolving genomic distribution [17, 25], but few previous reports have combined detailed epidemiologic data with genomic characterization below the genotype level. Some past examples of hepatitis A genomic epidemiology in the U.S. were based on data collected from sentinel sites or during periods of low disease incidence [8, 26]. Our report is derived from population-based surveillance from a large state over a multi-year period of elevated disease incidence. Our findings reveal multiple HAV strains circulating in the same county at the same time; epidemiologic links between persons that were part of differing genomic clusters that highlight the interplay among persons with shared risk behaviors; and cases in a genomic cluster beginning primarily among a particular risk category before spreading or expanding to other risk groups.

We observed a large proportion of cases with multiple risk factors for HAV infection, often making it difficult or impossible to isolate specific activities or practices that resulted in infection. A global synthesis of the literature has found that 24.8% of persons who inject drugs (PWID) experienced recent homelessness and 58.4% of PWID also reported a lifetime history of incarceration [27], highlighting the overlapping and cyclical relation between drug use, homelessness, and incarceration that was also apparent in our data. Among patients who reported recent drug use in our analysis, methamphetamine use was noted in the highest proportion. A previous report described a prolonged hepatitis A outbreak among methamphetamine users in Polk County, Florida in 2001–2002, in which 40% of incarcerated users of methamphetamines showed serologic evidence of past HAV infection [28]. Numerous other reports of hepatitis A outbreaks among persons who use illicit drugs have attempted to shed light on the specific mechanisms of HAV transmission [29–31]. Possibilities include generally poor hygienic conditions in settings where persons use drugs, surface contamination of drug-related material, fecal contamination of specific drug batches, percutaneous transmission, or sexual contact between those who use drugs with one another. HAV particles are highly stable in the environment and high infectious titers can be detected after 60 days of desiccation on surfaces [4] supporting the possibility of surface contamination of drug related material, in settings where drugs are used, or where unhoused persons congregate.

We observed greater odds of death among patients with subgenotype IB infections compared to IA infections. This finding should be interpreted with caution, as the limited number of deaths with genomic data available limited our ability to fully control for all possible confounding factors. Previous reviews have suggested that some genotypes may be associated with a greater likelihood of fulminant hepatitis or more severe disease, however the putative mechanism for increased virulence is unknown and remains speculative [4]. Compared to subgenotype IA, subgenotype IIIA and IB strains show more amino acid replacements in the VP1–2A region, which could relate to higher virulence [4]. However, strain specific virulence could be related to other genomic regions or confounded by other underlying risk factors for severe disease associated with a particular genotype [4]. In a small case control study, Ajmera et al, found higher rates of death or liver transplant in patients with subgenotype IB infection compared to IA, though this was not significant and occurred during a period when subgenotype IB was very rare in the United States [32]. Their findings also suggested that host factors may play an important role in acute liver failure (ALF) following HAV infection. Our study did not fully assess host factors, nor collect the detailed clinical data needed to fully elucidate important factors, such as ALF preceding death. However, the increased mortality associated with subgenotype IB versus IA infections observed in our study is consistent with results from Ajmera and warrants additional research.

Given the large number of cases in Florida in 2019, combined with the onboarding and expansion of HAV sequencing capacity at BPHL, some specimens did not undergo genotype testing for many months following the onset of symptoms in the source patient. Thus, it was not always possible to utilize the results of genotyping for outbreak response in real-time. However, genotype results were used extensively and in a timely manner for response to the 2022 subgenotype IA outbreak among MSM, which helped to characterize the outbreak

and target vaccination efforts [18]. Overall, the proportion of cases in our data set with accompanying genotype data (22%) exceeds the proportion of cases reported nationally from 2016–2019 that had genotype data available (19%) [17].

The public health emergency declaration in August 2019 occurred amid a large statewide response, emphasizing provision of hepatitis A vaccine to case contacts and persons at greatest risk. From January 2019 through June 2021, 409,028 first doses of hepatitis A vaccine were administered statewide [33] and from November 2021–November 2022, 50,451 first doses were provided to adults, partly in response to the outbreak among MSM occurring during that time [18]. Natural immunity from the large number of infections occurring in Florida since 2018, combined with acquired immunity from the large number of vaccine doses provided since then, likely has led to the highest levels of population immunity in Florida since the introduction of vaccine three decades ago. This may have resulted in achieving critical population immunity thresholds that could prevent future outbreaks in some risk groups in the near term [34, 35]. In 2023, the number of hepatitis A case reports among Florida residents was 100, the lowest annual number of cases reported in the state since state-wide electronic disease reporting began in 1992 [13].

Our genomic analysis relied on a 315 nucleotide segment of the 7500 nucleotide HAV genome. This methodology is imperfect for fully distinguishing HAV variants, as short genomic regions can be shared, although infrequently, even by genetically distant HAV strains [36, 37]. Efforts are underway to develop a validated assay for whole-genome sequencing of HAV, which may overcome this limitation [38], however, such an assay is not yet widely available to state public health laboratories. Our study was also limited by genotype data being unavailable for 78% of cases; cases with available genotype data being not fully representative of all cases; investigators not being able to contact and interview all patients; and, incomplete information provided by some patients, particularly related to sensitive topics such as drug use or sexual activity.

In conclusion, these results demonstrate that extending HAV genotyping capability to state public health laboratories holds promise for more detailed characterization of sporadic cases and outbreaks, with the related population health benefits of facilitating more targeted disease control efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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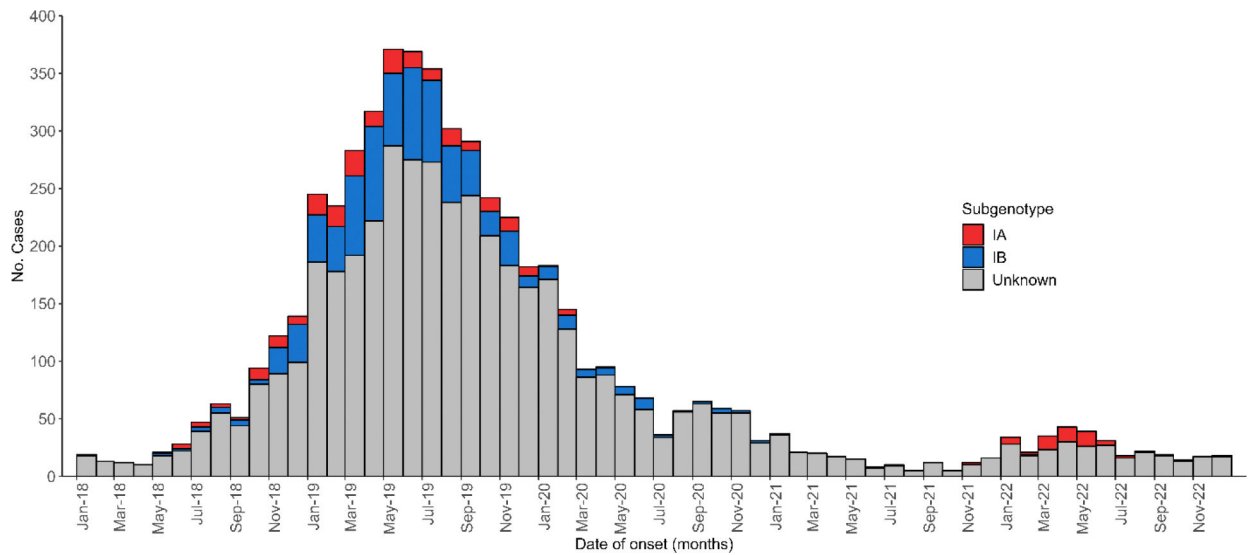


Figure 1. Epidemiologic curve of hepatitis A cases in Florida by month of onset, January 1, 2018–December 31, 2022.

Monthly case counts are distinguished by subgenotype. Ten cases associated with subgenotype IIIA were excluded from the epidemiologic curve due to lack of visibility on the curve. Where data for symptom onset was missing, onset date was imputed based on laboratory report date.

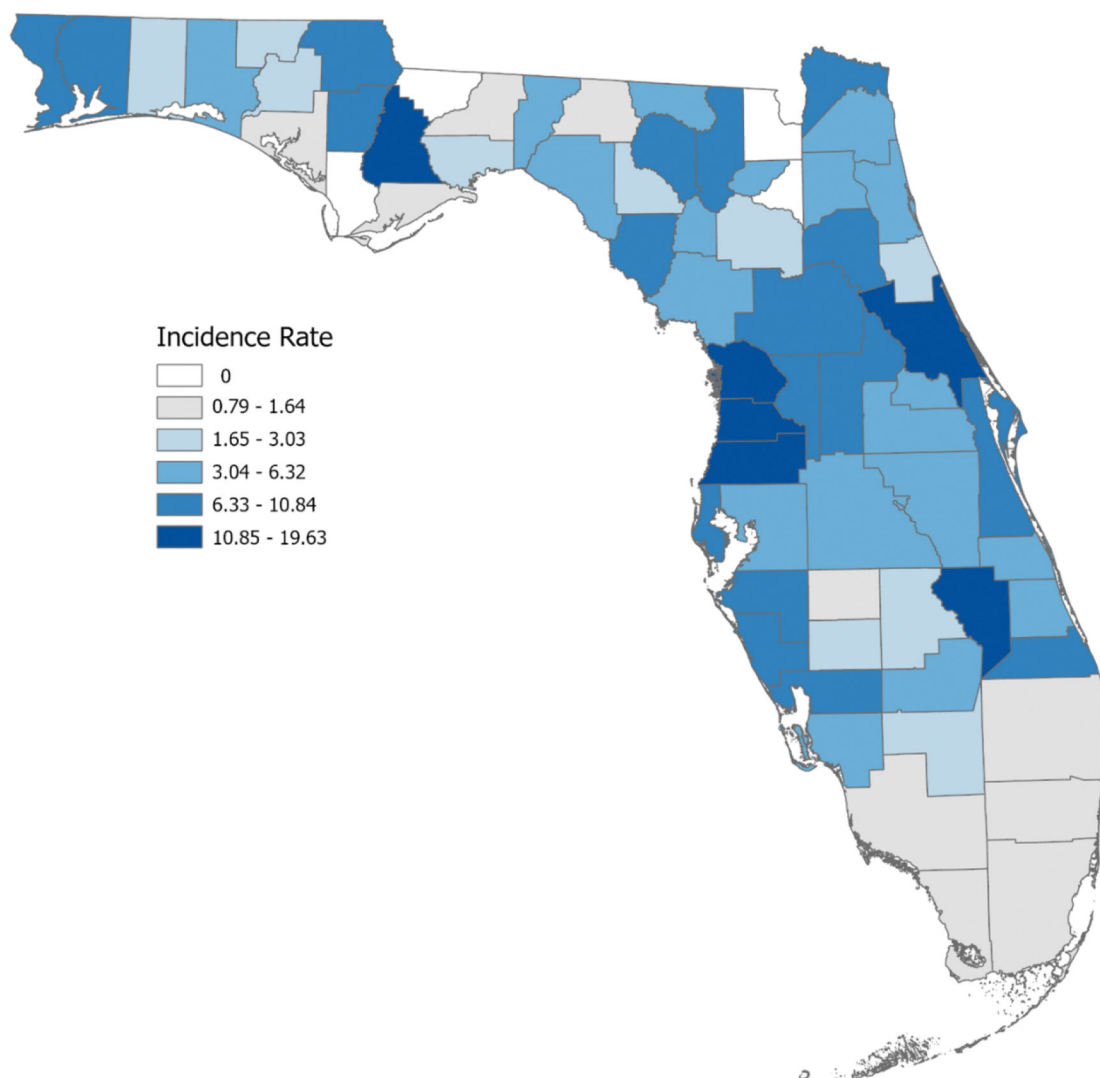


Figure 2. Incidence of Hepatitis A in Florida by county of residence, 2018–2022. Five-year average annual incidence rate per 100,000 population. County population estimates from the 2020 US Census were used for rate denominators.

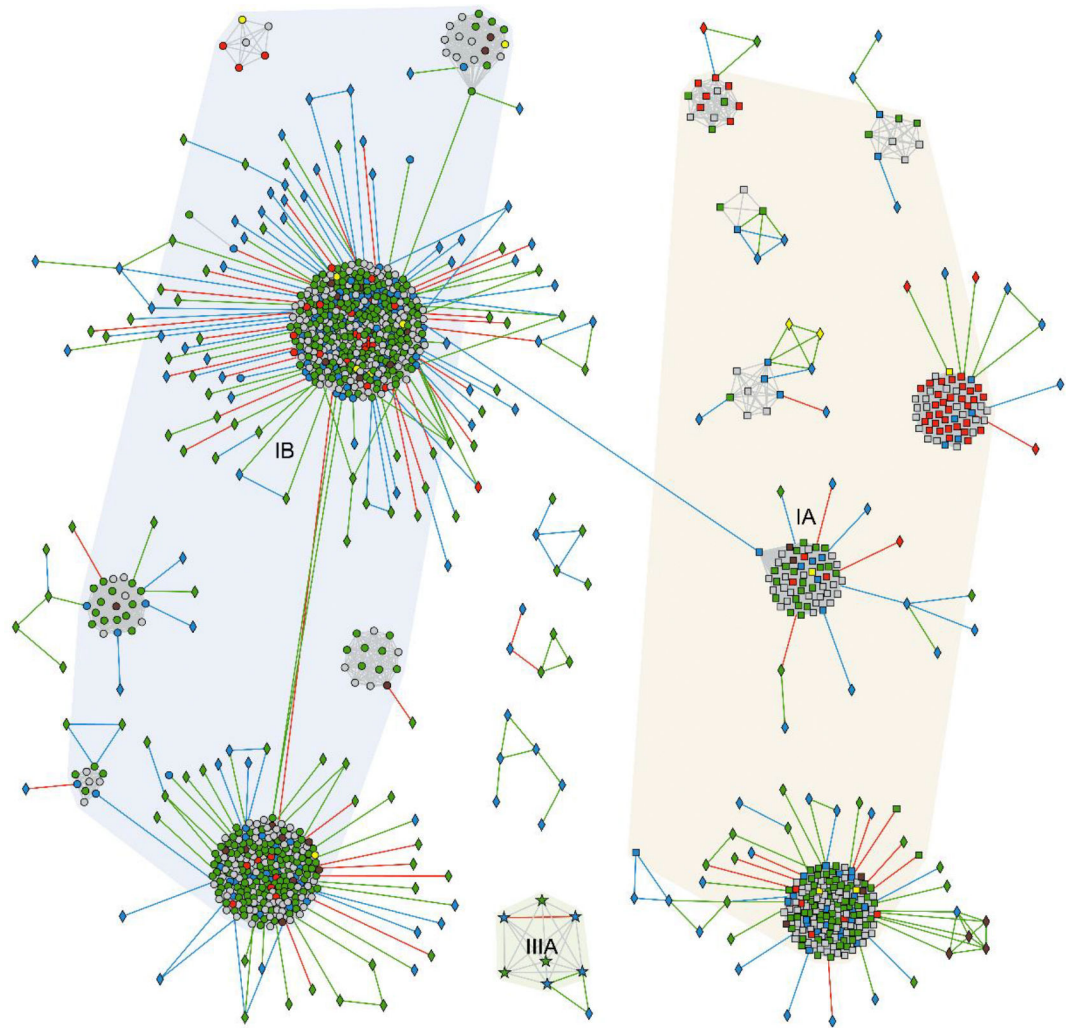


Figure 3. Network visualization of hepatitis A cases in Florida, 2018–2022.

Each point (node) represents a case, and only nodes that are part of clusters of 5 or more cases are displayed. Clusters may consist of genomic linkages, epidemiologic linkages, or both. Node color indicates risk category of the case where (■) = men who have sex with men (n=83); (■) = persons who inject drugs or persons experiencing homelessness (n=539); (■) = persons currently or recently incarcerated (n=29); (■) = persons with recent history of international travel (n=13); (■) = persons epidemiologically linked to a confirmed case (n=241); (■) = persons with no identified risk factor (n=368). Line color between nodes indicates genomic or epidemiologic linkage to another case. Genomic linkage (■) was defined as 0 single nucleotide polymorphism (SNP) differences between sequences. Epidemiologic linkage was categorized as sexual contact (■) (n=59); non-sexual household contact (■) (n=111); other, including shared environment or workplace (■) (n=174). The node shape indicates subgenotype, where (●) = IB (n=754), (■) = IA (n=300), (★) = IIIA (n=7), and (◆) = unknown genotype. Polygon colors indicate clusters of the same subgenotype, where (■) = subgenotype IB, (■) = subgenotype IA, and (■) = subgenotype IIIA.

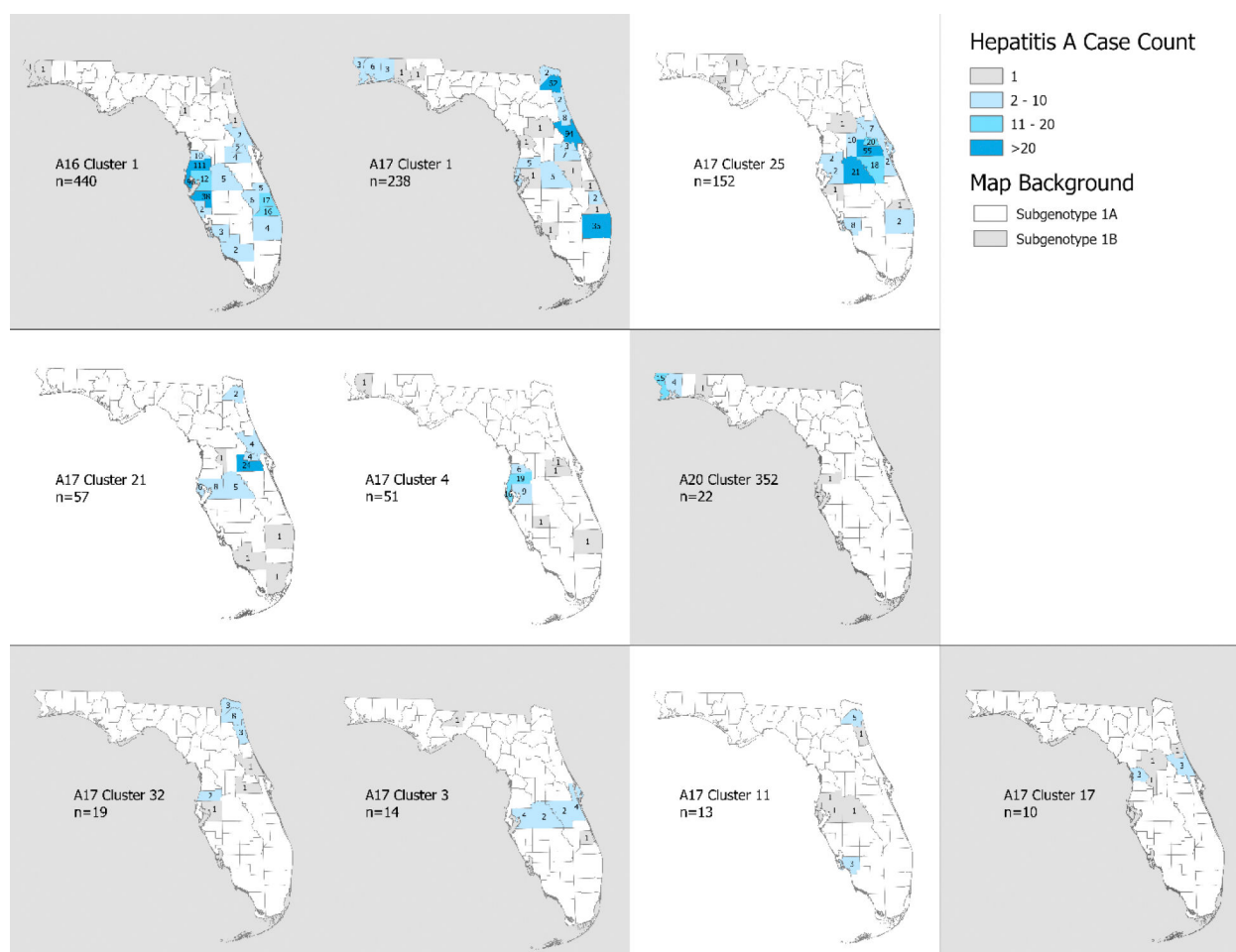


Figure 4. Spatial distribution of hepatitis A cases for major genomic strains identified in Florida, 2018–2022.

Spatial distribution for the 10 largest clusters, with 10 or more cases with matching strain in each cluster. Panels in figure are sorted from largest to smallest cluster.

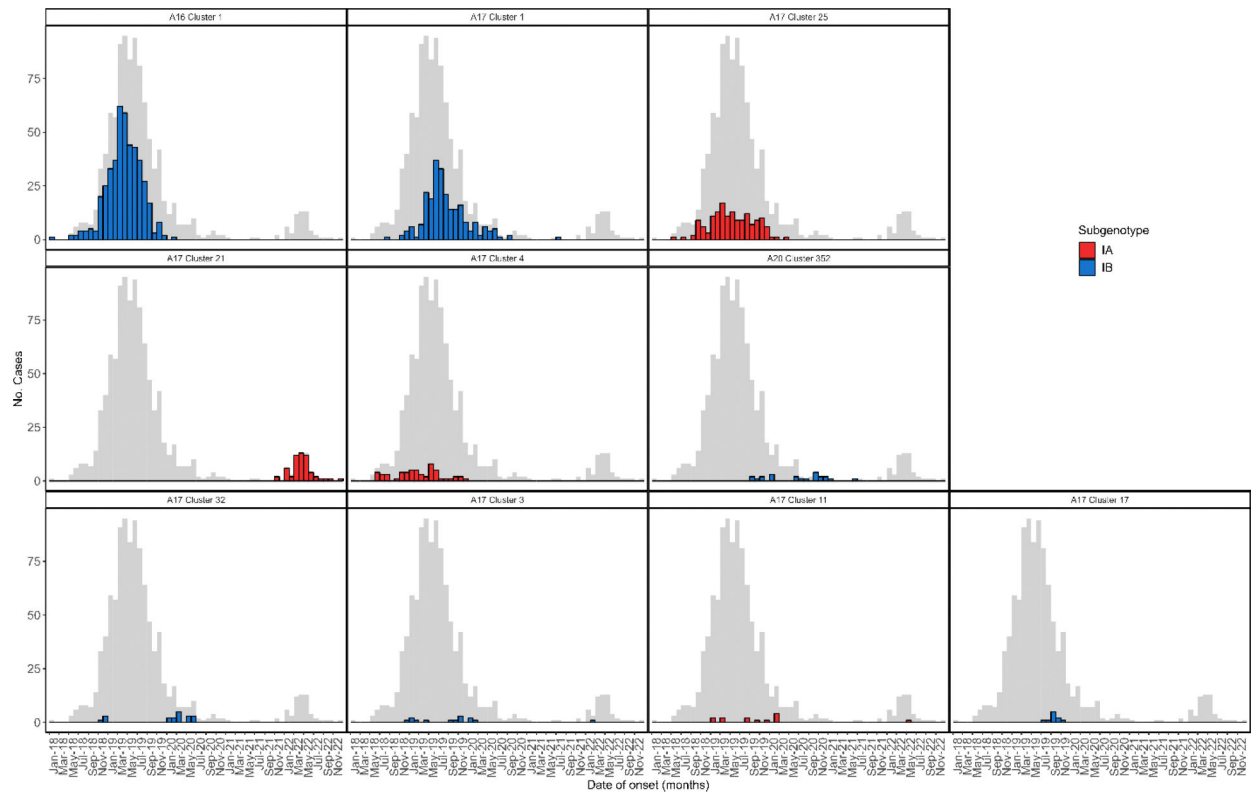


Figure 5. Temporal distribution of hepatitis A cases for major genomic strains identified in Florida, 2018–2022.

Temporal distribution of the 10 largest clusters, with 10 or more cases with matching strain. Cases are plotted by month of onset. Grey bars indicate epidemic curve of all genotyped cases. Panels in figure are sorted from largest to smallest cluster.

Table 1.
Characteristics of Hepatitis A cases in Florida, 2018–2022^a

	All cases	Cases, unknown genotype	Cases, known genotype	P-value
N	5,491	4,301	1,190	
Demographic characteristics				
Median age in years (IQR)	39 (32–50)	39 (32–50)	39 (32–50)	0.337
Male sex (%)	3,544/5,484 (64.6)	2,765/4,297 (64.3)	779/1,187 (65.6)	0.414
White race (%)	4,786/5,481 (87.3)	3,771/4,295 (87.8)	1,015/1,186 (85.6)	0.042
Black race (%)	388/5,481 (7.1)	289/4,295 (6.7)	99/1,186 (8.3)	0.054
Hispanic ethnicity (%)	511/5,478 (9.3)	408/4,293 (9.5)	103/1,185 (8.7)	0.395
Risk category				
Epidemiologic linkage to another case (%)	1,224 (22.3)	948 (22.1)	276 (23.3)	0.377
Recent International Travel (%)	222 (4.1)	193 (4.5)	29 (2.4)	0.002
Men who have sex with men (%)	347 (6.3)	256 (6.0)	91 (7.7)	0.032
Any drug use (%)	2,899 (52.9)	2,259 (52.6)	640 (54.0)	0.397
Injection drug use (%)	1,823 (33.3)	1,417 (33.0)	406 (34.3)	0.417
Current or recent homelessness (%)	1,007 (18.4)	757 (17.6)	250 (21.1)	0.006
Current or recent incarceration (%)	392 (7.2)	322 (7.5)	70 (5.9)	0.060
Comorbidities and health outcomes				
Acute hepatitis B ^b	253 (4.6)	187 (4.4)	66 (5.6)	0.078
Chronic hepatitis B ^b	214 (3.9)	162 (3.8)	52 (4.4)	0.935
Acute hepatitis C ^b	417 (7.6)	315 (7.3)	102 (8.6)	0.144
Chronic hepatitis C ^b	1,262 (23.0)	962 (22.4)	300 (25.3)	0.035
Chronic hepatitis B and C co-infection ^{bc}	118 (2.2)	91 (2.1)	27 (2.3)	0.739
Hospitalized for hepatitis A	3,751 (68.5)	2,904 (67.6)	847 (71.5)	0.012
Died	78 (1.4)	44 (1.0)	34 (2.9)	<0.001
Subgenotype				
IA	NA	NA	355 (29.8)	NA
IB	NA	NA	825 (69.3)	NA
IIIA	NA	NA	10 (0.84)	NA

^aPatients with missing values were excluded from analyses of demographic variables. Patients who were not investigated (n=13) were excluded from analyses of risk categories, comorbidities, and health outcomes. Denominators for risk categories, comorbidities, and health outcomes were: All cases (n=5,478), cases with unknown genotype (n=4,293), and cases with known genotype (n= 1,185).

^bComorbidity with hepatitis B and hepatitis C was ascertained for each patient at the time of hepatitis A case reporting, based on matching patient profile in the Florida Department of Health disease reporting system (Merlin), utilizing national surveillance case definitions for each condition.

Hepatitis B, acute: <https://ndc.services.cdc.gov/case-definitions/hepatitis-b-acute-2012/>

Hepatitis B, chronic: <https://ndc.services.cdc.gov/case-definitions/hepatitis-b-chronic-2012/>

Hepatitis C, acute: <https://ndc.services.cdc.gov/case-definitions/hepatitis-c-acute-2016/>

Hepatitis C, chronic: <https://ndc.services.cdc.gov/case-definitions/hepatitis-c-chronic-2016/>

^cAlso included in chronic hepatitis B and chronic hepatitis C rows above.
IQR = interquartile range; NA = not applicable

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Table 2. Case characteristics by hepatitis A virus subgenotype and clustering of unique nucleotide sequence pattern

Characteristic ^d	Subgenotype ^b				Unique Nucleotide Sequence Pattern (UNSP) ^c			
	IA N (%)	IB N (%)	OR (95% CI) IB vs IA	P-Value	Singleton UNSP N (%)	Clustered UNSP N (%)	OR (95% CI) Clustered vs Singleton	P-Value
Demographic characteristics								
N	355	825			69	1078		
Age in years, median (IQR)	38 (31–48)	40 (33–50)		0.013 ^d	39 (31–54)	39 (32–50)		0.951 ^d
Male sex	246 (69.7)	527 (64.0)	0.77 (0.59–1.01)	0.058	43 (62.3)	711 (66.1)	1.18 (0.71–1.95)	0.517
White race	277 (78.7)	729 (89.0)	2.19 (1.57–3.07)	<0.001	49 (72.1)	928 (86.7)	2.54 (1.45–4.43)	0.001
Black race	35 (9.9)	64 (7.8)	0.77 (0.50–1.18)	0.231	11 (16.2)	86 (8.0)	0.45 (0.23–0.90)	0.023
Hispanic ethnicity	69 (19.8)	34 (4.2)	0.18 (0.11–0.27)	<0.001	12 (17.6)	87 (8.2)	0.42 (0.22–0.81)	0.010
Risk categories and health outcomes								
N	353	822			69	1073		
Epidemiologic linkage to another case	65 (18.4)	207 (25.2)	1.49 (1.09–2.04)	0.012	11 (15.9)	252 (23.5)	1.62 (0.84–3.13)	0.153
Recent international travel	18 (5.1)	9 (1.1)	0.21 (0.09–0.46)	<0.001	12 (17.4)	13 (1.2)	0.06 (0.02–0.15)	<0.001 ^e
Men who have sex with men	55 (15.6)	36 (4.4)	0.25 (0.16–0.39)	<0.001	3 (4.3)	86 (8.0)	1.92 (0.59–6.22)	0.279
Any drug use	158 (44.8)	478 (58.2)	1.72 (1.33–2.21)	<0.001	20 (29.0)	598 (55.7)	3.08 (1.81–5.26)	<0.001
Injection drug use	81 (22.9)	322 (39.2)	2.16 (1.63–2.88)	<0.001	11 (15.9)	382 (35.6)	2.91 (1.51–5.62)	0.001
Current or recent homelessness	47 (13.3)	201 (24.5)	2.11 (1.49–2.98)	<0.001	11 (15.9)	230 (21.4)	1.44 (0.74–2.79)	0.281
Current or recent incarceration	13 (3.7)	57 (6.9)	1.95 (1.05–3.61)	0.034	2 (2.9)	64 (6.0)	2.12 (0.54–18.3)	0.445 ^e
Hospitalized	269 (76.2)	568 (69.1)	0.70 (0.53–0.93)	0.014	53 (76.8)	765 (71.3)	0.75 (0.42–1.33)	0.326
Died	3 (0.8)	30 (3.6)	4.42 (1.34–14.58)	0.015	4 (5.8)	26 (2.4)	0.40 (0.13–1.64)	0.204 ^e

^a Pairwise deletion was used for cases with missing or unknown data for sex, race, and ethnicity. Cases that were not investigated (n=5) were excluded from analyses of risk categories and health outcomes.

^b Ten cases associated with subgenotype IIIA were excluded from analysis.

^c Unique Nucleotide Sequence Pattern (UNSP) over the 315 nucleotide segment of HAV. Cases classified as singleton UNSP did not match any other sequences from Florida cases. Cases classified as clustered UNSPs shared sequence with two or more other cases from Florida. Cases belonging to UNSP pairs of exactly two cases were excluded from this analysis.

^d Kruskal-Wallis test.

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Exact odds ratio and p-value.
OR = odds ratio, CI = confidence interval, IQR = interquartile range