



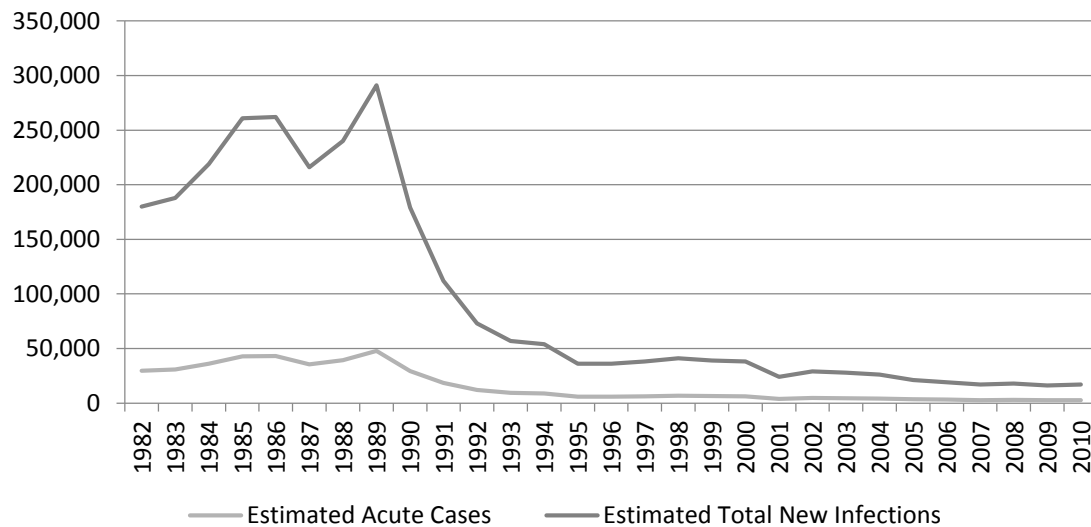
EMERGENCE OF ACUTE HEPATITIS C IN YOUNG INDIANA RESIDENTS WHO INJECT DRUGS

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Introduction

Hepatitis C virus (HCV) is the most common chronic bloodborne infection in the United States with an estimated 4.2 million infected individuals (1, 2). The infection takes two forms – acute and chronic. The acute infection occurs within the first 6 months and is typically asymptomatic. Despite being widespread, symptomatic acute HCV is a relatively rare presentation of the infection (3). The acute inflammatory phase of HCV occurs in approximately 15-30% of those infected (2, 4). Once infected with HCV, a chronic infection is likely. Of every 100 people infected 75-85 people will develop a chronic infection. Among those chronically infected, 60-80% will develop chronic liver disease, 6-26% will develop cirrhosis over a 20-30 year period, and 1-6% will die from cirrhosis or liver cancer (49). Surveillance barriers, such as under reporting and asymptomatic infections, make estimating prevalence and incidence of HCV arduous and often inaccurate. While only 810 acute cases are reported annually in the United States, the estimated incidence of acute HCV infections is approximately 18,000 with 2,900 clinically acute cases (5). HCV is believed to be responsible for approximately 20% of acute hepatitis in the United States and chronic HCV is the leading cause of liver transplantation (6). The incidence of HCV increased in the United States from 0-44 cases per 100,000 before 1965 to 100-200 cases per 100,000 in the 1980s (7). HCV incidence has decreased steadily from its peak of approximately total cases 240,000 cases in 1988, to 15,000 infections in 2010 (Figure 1). Likewise, the number of acute HCV cases peaked in 1989 and has since decreased (8). It estimated 76% of those living with HCV were born between 1945 and 1965 (5, 9). Although incidence of both acute and chronic infections had been decreasing, several reports suggest incidence has increased among 18-34 year old people who inject drugs (PWID) (5, 10-12).

Figure 1. Temporal Trends Hepatitis C Virus in the United States (1982-2010).



Note: Table created from data provided by the Centers for Disease Control and Prevention (2)

In 2010, Massachusetts discovered an emerging trend in HCV cases. Surveillance revealed that from 2002 to 2009, HCV incidence increased in individuals aged 15-29. These young people were primarily white, lived in rural or suburban settings, injected drugs, and were equally male and female (11). Following the Massachusetts publication, other areas in the country began to discover similar trends (13, 14). It is estimated nearly 265,000 (approximately 45%) of young PWID are currently infected with HCV (15, 16). Responding to the emerging epidemic of HCV in this population has proven to be difficult because acute HCV is often asymptomatic, most PWID do not receive adequate medical care, and young nonurban PWID have been shown to be a difficult group to engage in prevention and care activities (16). Similar to Massachusetts, New York, and Wisconsin; Indiana has experienced an increase in acute HCV among young PWID.

Routes of HCV Transmission

Blood transmission

The primary transmission routes of HCV have changed over time. Prior to 1992, the leading cause of transmission was the transfusion of donated blood, blood products such as clotting factors, and donated organs (2). The development and implementation of blood screening tests for HCV in 1992 dramatically decreased the number of transfusion related infections in the United States. Today, the risk of transfusion related infection in the United States is less than one per two million units transfused (17).

Injection Drug Use (IDU)

Parenteral exposure to objects or substances contaminated with HCV is the most efficient method of transmission. It is estimated that there is a 5% chance of transmission per parenteral exposure event (18). Engagement in unsafe practices in which blood-to-blood contact is likely such as splitting drugs by sharing needles¹, syringes², cookers³, cotton⁴, and rinse water⁵ increases the chances of contracting HCV among PWID (19-24). The primary reason HCV transmission has decreased in the United States is blood screening procedures. Transmission of HCV in the United States by IDU has decreased in concordance with the number of PWID (7). Decrease in transmission is largely attributed to a decrease in people choosing to inject drugs, interventions and policies that focus on syringe exchanges, counseling PWID for protection from infection, and altering PWID injection habits (21, 25). Despite these efforts, IDU is the largest risk factor for acquisition of acute HCV and accounts for the majority of newly acquired HCV infections (26, 27). Incident HCV infections have been shown to occur soon after initiation of

¹Hollow barrel hypodermic needle used to inject drugs into the vein, and drugs are shared using the same needle

³A cylindrical metal container used to apply heat to solubilize drugs

⁴Once in the syringe, drugs are filtered through cotton to remove any remaining precipitate

⁵Used to remove remaining fluid after injection

IDU (26, 28). The high degree of infectivity of HCV may explain why incidence of HCV among young, new PWID is increasing (19, 26).

Sexual transmission

Sexual transmission of HCV occurs but with less efficiency than hepatitis B virus or HIV (7). It is estimated that the chance of transmission of HCV is 5% for each year of high risk sexual exposure (unprotected coitus with multiple partners) and 1.2% for each year of monogamous sexual exposure with an HCV-positive partner (29). National surveillance data revealed that 15-20% of acute HCV cases reported a history of sexual exposure in the absence of other risk factors, suggesting that sexual transmission was probable (30). The likelihood of sexual transmission of HCV increases with the number of lifetime sexual partners, existence of other sexually transmitted infections (including HIV), and traumatic sexual events (fisting and use of toys) where blood contact is more likely (30, 31). The observed increased risk with multiple sex partners may be confounded by an increased likelihood of IDU with multiple partners (32). Individuals who are in monogamous long-term relationships with HCV-positive patients have a higher prevalence of HCV than the general population, but this is confounded by the possible sharing of items which may contain blood such as razors and toothbrushes, or undisclosed IDU (33, 34). Still, the risk of sexual transmission between monogamous heterosexual couples is low (1/10 million sex contacts) and the CDC does not currently recommend the use of barriers for these couples to prevent HCV transmission (7, 34). The majority of sexually transmitted outbreaks of acute HCV have been associated with HIV-positive men who have sex with men (MSM) (35-43). The acute HCV cases in this group may exhibit multiple risk factors for blood-blood contact including unprotected anal sex, traumatic sexual practices, and illicit drug use (44).

The estimated risk of sexual transmission in MSM is 0.5-1.0 per 100 person years of HIV infection (32, 45).

Tattoos and Piercings

The risk for transmission of HCV through cosmetic procedures has been controversial. The number of tattoos and piercings, particularly among youth, has been increasing over the last decade (46-48). If an increase risk in HCV transmission from cosmetic procedures existed, one would expect HCV incidence to increase in low-risk populations who obtained tattoos or piercings. However, it was determined that non-injection drug users with a history of tattoos and piercings did not exhibit an increased HCV prevalence (49). Further, no outbreaks of HCV have ever been detected at professional parlors, likely due to the sterilization of equipment. In cases where equipment is not sterilized, or used on multiple people, transmission may be possible. This is often the case when tattoos and piercings are performed in detention facilities or private residences (50). HCV has been shown to survive on inanimate objects for up to 72 hours and nearly a month in the anesthetic propofol (51-54). The greatest risk of HCV transmission from cosmetic procedures occurs in unregulated settings where high risk individuals (e.g. incarcerated PWID) are sharing equipment (OR 2.0-3.6) (55-58). There is no definitive reason to believe that HCV is transmitted by tattoos and piercings when properly sterilized equipment is utilized (50).

Perinatal transmission

The most common cause of HCV infection in children is vertical transmission *in utero* (59). An active HCV infection is estimated to be present in 1% of pregnant women of which 4-7% will transmit HCV to their infant (59, 60). Factors that increase the likelihood of perinatal HCV

transmission from an infected mother include membrane rupture prior to delivery, procedures that expose the infant to maternal blood, increased HCV viremia during pregnancy, maternal co-infection with HCV and HIV, female gender of the infant, and maternal history of IDU (61).

Healthcare associated transmission

In the United States, outbreaks of acute HCV have been primarily limited to hospitals and ambulatory procedure sites. Propagation of HCV has been traced to the contamination of medication vials by reuse of syringes, incomplete disinfection of hemodialysis equipment, and less frequently, drug diversion by providers or healthcare professionals. From 2008 to 2012, there were seven outbreaks with 42 confirmed cases in general outpatient settings (ambulatory procedures such as colonoscopy), two outbreaks with 67 confirmed cases in hospital settings, and six outbreaks with 50 total confirmed cases in hemodialysis clinics (62). Nosocomial HCV infections represent a particularly serious risk to the chronically ill and immunocompromised, who may frequently receive infusions, injections, and hemodialysis.

Occupational transmission

The risk of HCV infection, like other blood-borne infections, represents an occupational hazard to healthcare workers. However, HCV is not efficiently transmitted by means of occupational exposures such as needle sticks. The likelihood of transmission after each HCV-contaminated needle stick injury is approximately 1.8% (63-66). This risk may increase with deep injuries, after procedures utilizing hollow-bore needles, and source patient HIV co-infection (65). Transmission is unlikely to occur from mucous membrane exposure to blood, and no HCV transmission has been reported from intact or non-intact skin exposure to blood (67-69).

Methods

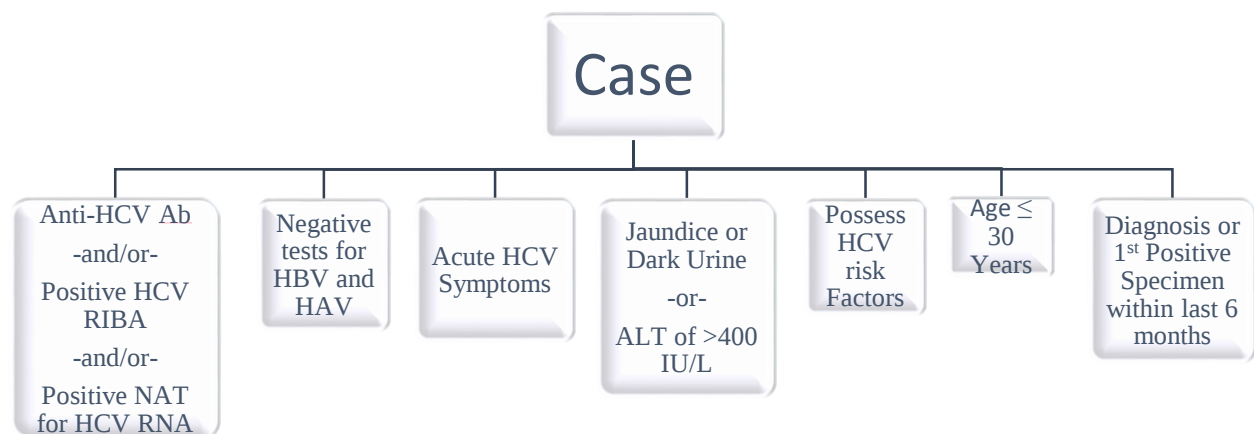
Reported acute HCV cases in Indiana increased significantly in the first five weeks of 2011 (n=10). Based on previous surveillance, it typically took 20-25 weeks before 10 acute cases were reported. Further, commonalities between cases were present: recent incarcerations, 21-30 years of age, IDU, and contact with known HCV cases. The Epidemiology Resource Center, HIV/STD program, and Laboratories of the Indiana State Department of Health developed a retrospective case series study to investigate the clusters. Additionally, the Centers for Disease Control and Prevention (CDC) was notified of the increase in acute HCV cases and was invited to participate in the investigation. With the aid of the CDC, a survey was developed to investigate the cluster. The survey was administered in person by ASPIRE Indiana. ASPIRE Indiana is a mental health and substance abuse program located in the heart of the region in which the cluster was observed who routinely tested and cared for patients with HCV. The willingness and ability for ASPIRE Indiana to conduct in depth interviews with the cases was instrumental in uncovering the details of this cluster.

Case Definition

Soon after the cluster was identified, the CDC was consulted and a case definition was established (Figure 2). To be considered a confirmed acute HCV case in this cluster the patient must have had an acute illness with a discrete onset of any signs and symptoms consistent with hepatitis in (e.g. anorexia, abdominal pain, nausea, vomiting), and either jaundice/dark urine or serum alanine aminotransferase (ALT) level of greater than 400 IU/L, test negative for hepatitis A and B, and meet one of the following criteria: positive for antibodies to HCV that meet the CDC signal to cut-off ratio, hepatitis C virus recombinant immunoblot assay (HCV RIBA)

positive, or nucleic acid test (NAT) positive for HCV RNA (including genotype). Additionally, the potential case must have possessed risk factors for HCV, be 30 years of age or less, have a known date of HCV diagnosis, and their first positive HCV test must have occurred within the previous six months. Over 50 potential cases were evaluated. After applying the strict inclusion criteria, 25 cases were identified in this cluster.

Figure 2. Case Definition for 2011 Acute HCV Cluster in Southeastern Indiana.



Note: All the above conditions must be met to be considered a case

Data Collection

The survey was developed to comprehensively capture known and suspected risk factors for HCV. Background information included name, age, gender, county of residence, race/ethnicity, and highest level of education. Each cases clinical description was established by collecting data on symptoms and date of symptom onset, if a provider was sought, if hospitalization occurred, as well as any prior hepatitis and STI testing. The bulk of the instrument assessed risk factors for HCV transmission in the six months prior to acute HCV diagnosis. Injection drug use was

characterized by frequency of use, place of use, place of purchase, who drugs were injected with, what drugs were injected, and if equipment was shared. The primary interest related to sexual risk factors was number of partners, sex with IDU's, and sex with individuals known or suspected of living with HCV. Potential sources of healthcare exposure were developed based on previous outbreaks associated with dialysis, blood products, long term care, injections/infusions, surgical procedures, and ambulatory procedures. The potential for occupational exposure was measured by inquiring if "any past employment in which direct contact with blood or any accidental skin punctures with objects contaminated with blood occurred." Each participant was asked if they had received any tattoos or piercings and if equipment was shared. Finally, each case was asked if any of the applicable aforementioned sources of exposure occurred while incarcerated.

Statistical Analysis

Descriptive statistics were produced to characterize demographics, clinical symptoms and hepatitis testing, as well as contact and risk factor information. Not all questions in the survey were answered by each participant. To determine the percentage of each characteristic among the number who actually responded, the descriptive statistics were weighted by the response rate. Further, many questions allowed for multiple answers leading to proportions that do not add up to one. One-tailed Fisher's exact tests were applied to determine if behaviors and risk factors were greater in males/females, those who share syringes, and those who have come into contact with suspected or confirmed HCV patients. Hypothesis testing was evaluated using a level of significance of $\alpha = 0.05$. Categorical data with more than two choices were collapsed into "ever" and "never" categories to increase the power of two-by-two table tests. Inferential statistics were limited due to the small sample size and homogeneity of behavior in the population. However,

when applicable, effect measures and confidence intervals were generated using the Mantel-Haenszel test. A case-control design was used to calculate increased odds of a behavior in those who exhibited the risk factor or behavior compared to those who did not. In this scenario, the risk of concluding a behavior or circumstance is a risk factor when it truly is not (type-one error) is less severe than falsely defining the same behavior or circumstance as not a risk factor when it truly is (type-two error). More specifically, taking action against a risk factor when it is not a highly significant predictor of true risk would still possess some benefit to individuals participating in the intervention. For this reason, the level of significance was lowered to $\alpha = 0.20$ and the variables were reevaluated. Data management and graph production was handled using Microsoft Excel, and descriptive and inferential statistics were calculated using SAS version 9.2.

Results

Demographics

Twenty-five cases met the case definition for inclusion in the cluster from 11/1/2010 to 09/01/2011. Figure 3 demonstrates the age and gender distribution of those included in the investigation. The youngest case was 19 years, the oldest 29 years, and the mean age was 24 years. Males (56%) accounted for the majority of cases but were not found at a significantly greater proportion than females ($p = 0.2743$). Even gender distribution of acute HCV in young PWID has been observed through surveillance in other states as well (11). All of the cases were White (100%) with one case identifying as Hispanic or Latino ethnicity. High school graduate or equivalent (63%) was the most commonly reported educational achievement (Figure 4). Cases predominantly occurred in the contiguous counties of Wayne, Henry, and Fayette. The majority

claimed residence in the southeast portion of Indiana (Figure 5). This cluster occurred in a rural portion of the state and many cases reported residence in their counties largest town. Cases were asked their living arrangements and most frequently reported they had been living in jail (46%), at their parent's house (33%), and at their own home or apartment (25%) in the six months prior to diagnosis.

Figure 3. Age and Gender Distribution

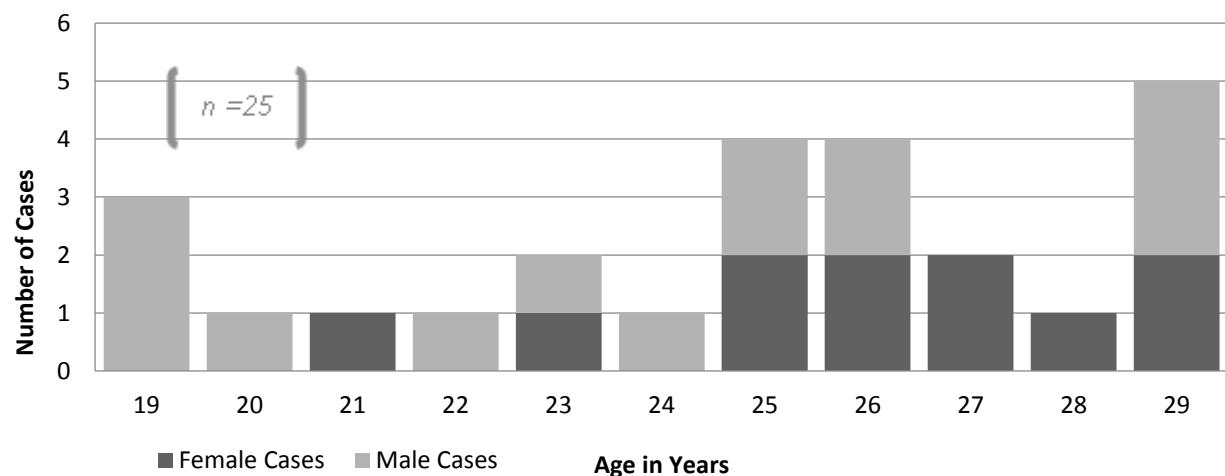


Figure 4. Highest Completed Education

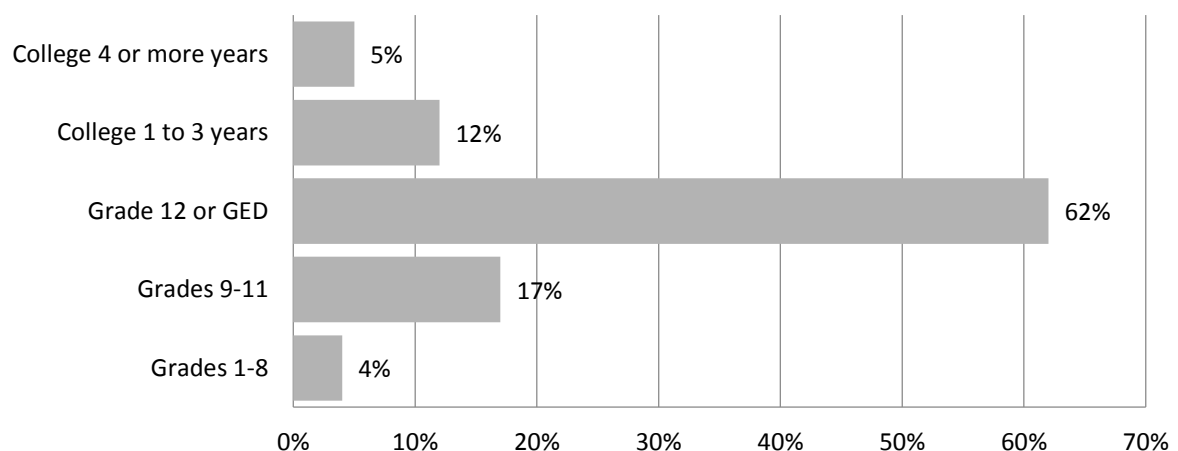
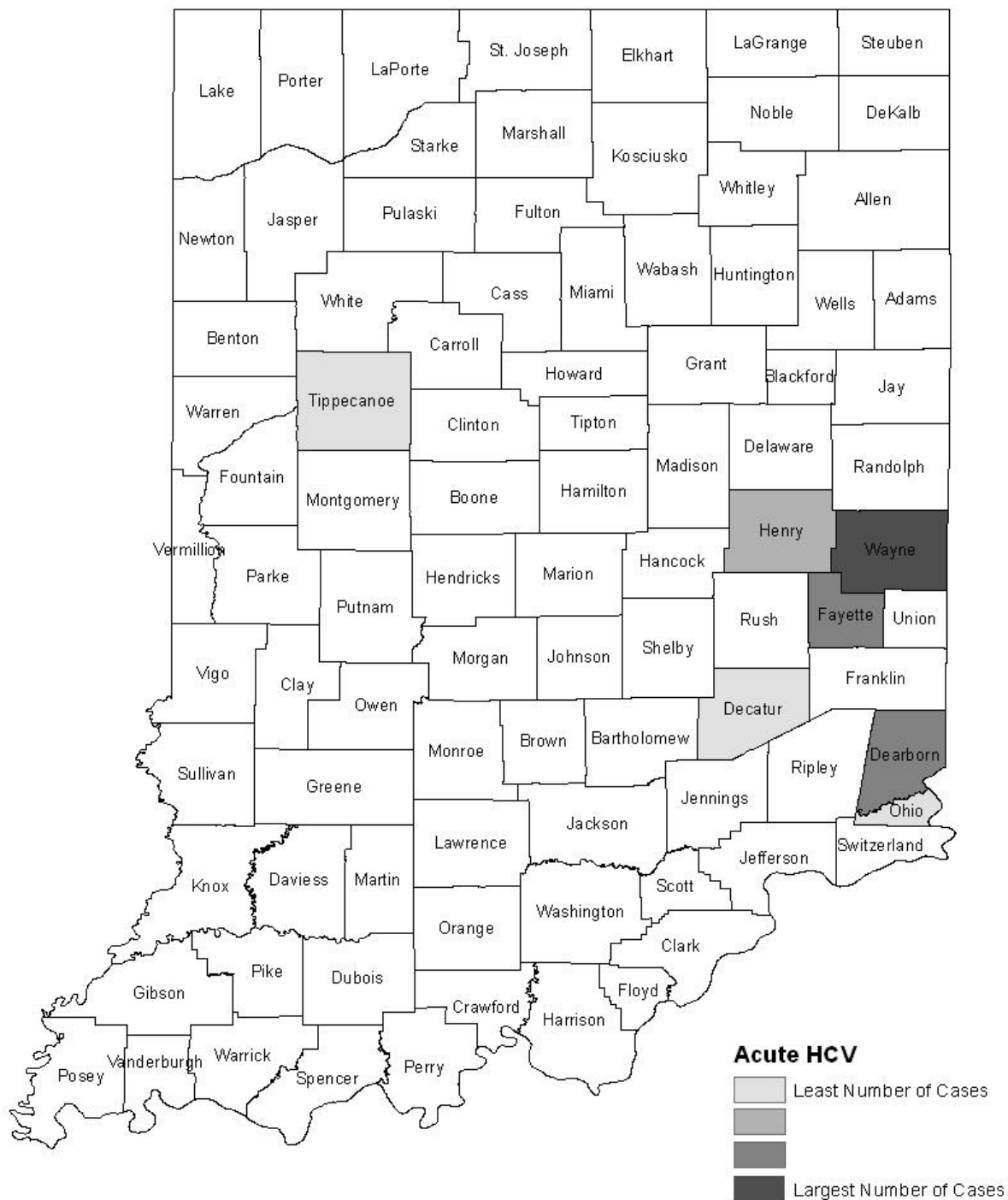


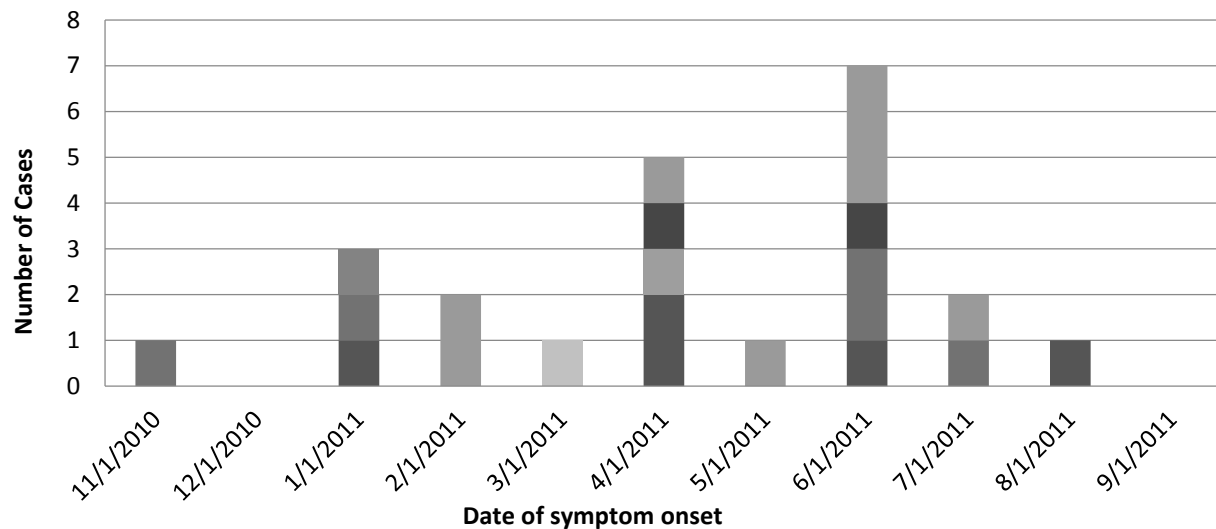
Figure 5. Counties Involved in the Acute Hepatitis C Cluster in Southeastern Indiana



Symptoms

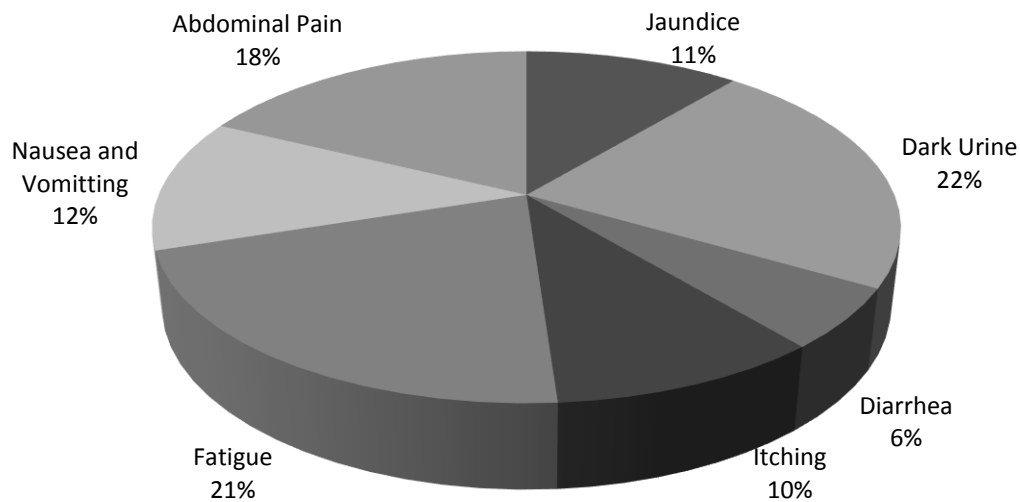
Symptoms were reported to have occurred between 11/01/2010 and 08/01/2011, with the bulk occurring between April and June, 2011 (Figure 6). To be included in the cluster, either jaundice or dark urine must have been reported. As such, dark urine (22%) was the most commonly reported clinical feature. Other symptoms reported (Figure 7) were fatigue (21%), abdominal pain (18%), nausea and vomiting (12%), jaundice (11%), itching (10%), and diarrhea (6%). While only four cases sought medical attention for their acute HCV symptoms, two were hospitalized. Of those who sought medical treatment, jaundice and diarrhea were the most common chief complaint.

Figure 6. Number of Cases by Onset of Symptoms, epidemiologic curve



Note: Each shade represents one county. County names suppressed to maintain confidentiality.

Figure 7. Symptoms Exhibited by Cases the Southeastern Indiana Acute Hepatitis C Cluster



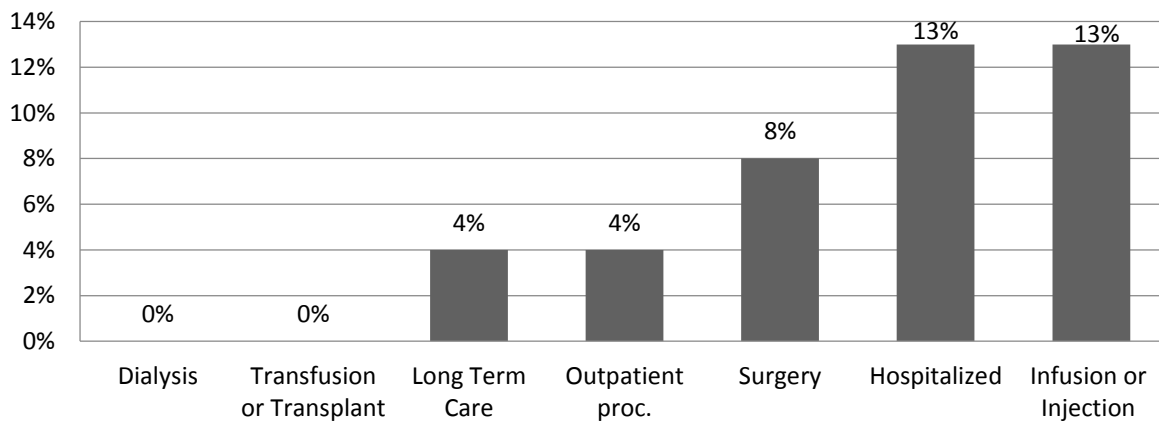
Risk factors

The primary risk factor in this cluster was intravenous drug use. Every case admitted to using intravenous drugs at some point in their lives, and 83% had injected drugs in the six months leading up to their diagnosis. Potential sources of exposure were numerous and shared by most cases. Based on self-report, 91% had injected drugs with others and 84% had lived, shared injection drugs, or had sex with a person known or suspected of having HCV. Other potential sources of exposure explored through the survey included exposure from healthcare procedures, sexual practices, tattoos and piercings, incarceration, and occupation. Brief mention will be given to these items but emphasis will be placed on IDU as it was the most probable source of exposure.

Healthcare risk factors. Healthcare exposure was not a likely source of transmission in this cluster investigation. Most cases did not have any type of procedure in the six months preceding their diagnosis. As Figure 8 demonstrates, only 13% of the cases were hospitalized, and 13% had an infusion or injection. Additionally, 8% reported having a surgical procedure, 4% had an

outpatient procedure, 4% were in long term care, and no cases reported undergoing dialysis or receiving allogeneic blood and organs.

Figure 8. Potential Sources of Exposure to Hepatitis C Virus Related to Healthcare.



Note: Healthcare risk factors are not mutually exclusive

Sexual risk factors. Although sexual transmission was a possible exposure in this cluster, it was not likely a primary source. As previously mentioned, sexual transmission of HCV is less efficient than parenteral exposure. Table 1 summarizes the sexual behaviors assessed within this group. A large proportion (65%) of the cases reported having sex with a PWID in the six months preceding their diagnosis. Less likely contributors included having sex in exchange for drugs (8%) and having anal sex (26%). The mean number of lifetime sexual partners in the group was 21 with three in the preceding 12 months. Three men (23%) reported having sex with another man (MSM).

Table 1. Potential Sources of Exposure to Hepatitis C Through Sexual Activity

Sexual Activity Risk Factors	Response Rate	N	Percent
6 months prior to HCV diagnosis			
Had sex in exchange for drugs	100%	2	8%
Had anal sex	92%	7	26%
Had sex with an IDU	92%	16	65%
Diagnosed with an STI	96%	3	13%
Sexual Encounters		Number of Partners	
Average number of lifetime sexual partners	88%	21	
Average number of sexual partners in the 12 months prior to HCV diagnosis	88%	3	
Number of Men who ever had sex with men	93%	3	23%

Occupational and cosmetic risk factors. Considering 90% of the cases identified as unemployed, occupational transmission was unlikely a significant source of HCV infection in this cluster.

Table 2 demonstrates the proportion of cases that were potentially exposed through occupation, tattoos, and piercings. Ever having direct contact with blood as a component of employment (13%) and ever having been exposed to another person's blood from an accidental needle stick or skin puncture (5%) was rare. The risk of transmission from tattoos and piercings was assessed by asking if these were acquired in the six months preceding their HCV diagnosis. Three cases (13%) were tattooed and one (4%) received a piercing, none of which shared needles in the process.

Table 2. Potential Sources of Exposure to Hepatitis C Virus Related to Occupation, Tattoos, and Piercings

Risk Factors	Response Rate	N	%
Have ever been in direct contact with blood as an occupation	96%	3	13%
Ever had an accidental occupational needle stick contaminated with blood	88%	1	5%
In the 6 months prior to HCV diagnosis			
Got a tattoo	88%	3	14%
Shared needle while getting tattoo	36%		0%
Got a body piercing	92%	1	4%
Shared needle while getting piercing	12%	0	0%

Incarceration. Most cases had been in jail or prison at some point (92%) with 73% having been incarcerated in the six months prior to their diagnosis. Incarceration itself is not generally thought of as a risk factor for HCV. Rather the actions, such as tattooing, IDU, and unprotected sex while detained are of concern. This type of behavior was rare in this cluster (Table 3). Being that only one case reported receiving a tattoo and one case reported IDU, sustained transmission of HCV was unlikely.

Table 3. Potential Sources of Exposure to Hepatitis C Virus Related to Time Spent in Jail or Prison

Risk Factors	Response Rate	N	Percent
Ever been incarcerated	96%	23	92%
Incarcerated 6 months prior to HCV diagnosis	88%	18	73%
While incarcerated			
Injected drugs	84%	1	5%
Received a tattoo	84%	1	5%
Participated in anal sex	84%	0	0%

Injection drug use. IDU was the most commonly observed risk factor in this group (Table 4).

Every case (n=25) disclosed ever injecting drugs. When initially asked, only 21 (84%) claimed to have injected drugs in the six months leading up to their diagnosis. However, follow up questions regarding frequency of injection, injection habits, and drugs of choice revealed that all 25 cases injected in the six months prior to their HCV diagnosis. The majority of IDU's injected drugs with others (91%) and came into contact (through IDU, living quarters, or sex) with individuals who have been confirmed or suspected to be living with HCV (84%). IDU most commonly occurred in vehicles (83%), followed by at the cases' own residence (71%), at a friend or shooting partner's place (46%), at a dealer's place (29%), in public places (25%), and in abandoned buildings (8%) (Figure 9). Sex partners (67%) were the most common individuals with which cases used injection drugs (Figure 10). Thirty-eight percent used drugs with individuals they identified as shooting partners; acquaintances, relatives, and drug dealers were less likely to partake with cases – 14%, 10%, and 5%, respectively. Heavy IDU was common (Figure 11). Drugs were injected two or more times per day every week by 67% of cases and an

additional 21% injected once a day every day. Only three cases claimed to inject with less frequency than once per day in the six months preceding their diagnosis. One case did not reported IDU in the past six-months when frequency was asked, but subsequently answered yes when asked if specific drugs were injected and if they shared equipment during that time frame.

Table 4. . Potential Sources of Exposure to Hepatitis C Virus Related to Injection Drug use

IDU Risk Factors	Response Rate	N	Percent
Ever Injected Drugs	100%	25	100%
Ever injected Drugs with Others	88%	23	91%
Lived, shared injection drugs, or had sex with a known or suspected HCV case	100%	21	84%
Injected Drugs 6 months Prior to HCV Diagnosis	100%	21	84%

Figure 9. Locations of Injection Drug use

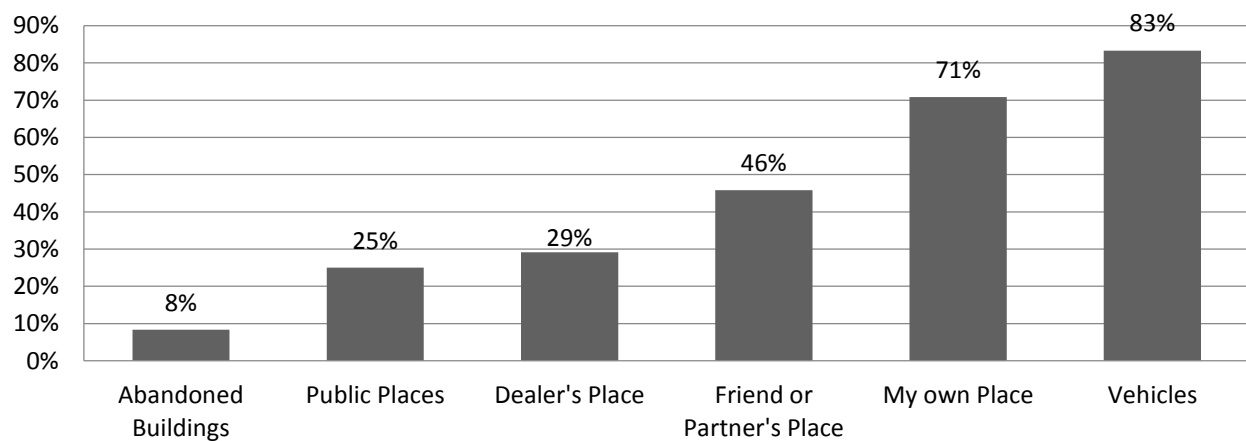


Figure 10. Relationships of Injection Drug use Partners

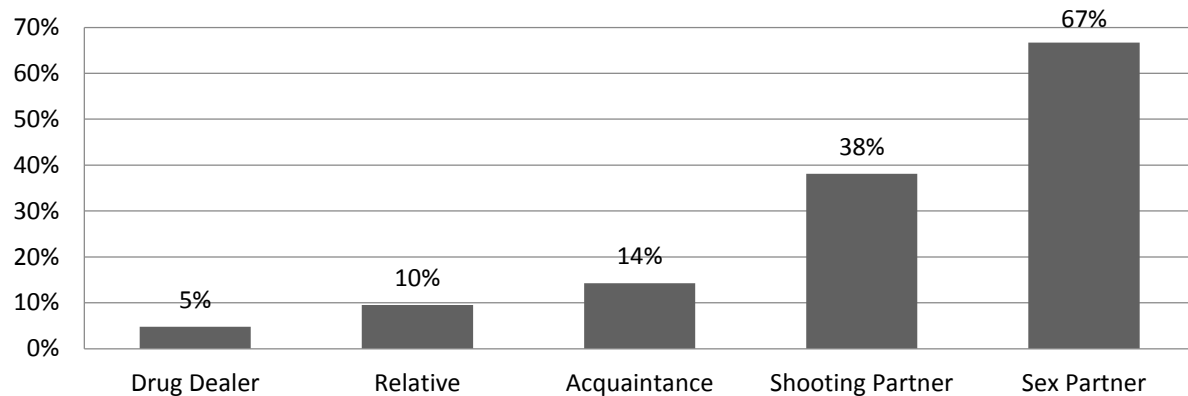
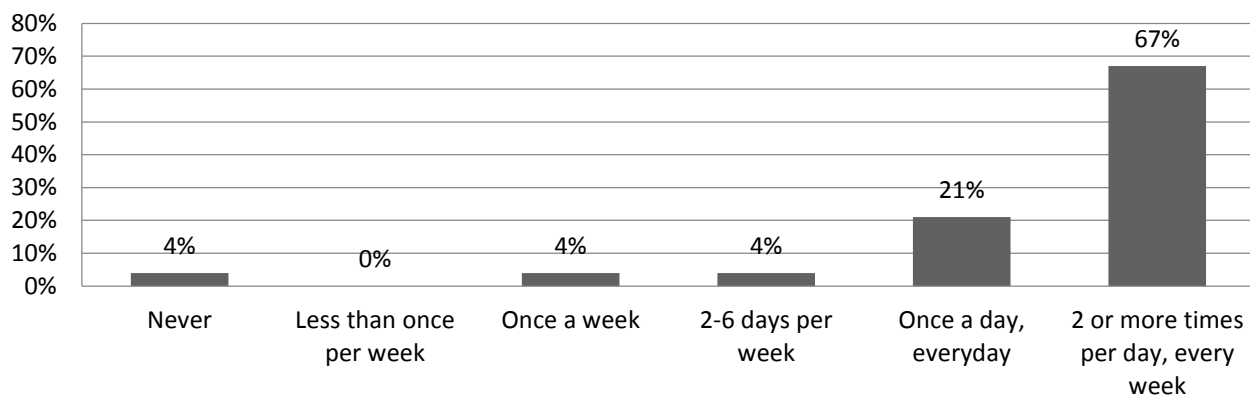


Figure 11. Frequency of Drug use in the 6-Months Leading up to Diagnosis



The majority of cases in this cluster shared drug preparation equipment - 46% always shared a drug cooker, 50% always shared cotton, and 33% always shared rinse water (Figure 12). The proportion who shared needles by splitting drugs was assessed but the polarization of participant responses indicated the question may have been poorly understood (25% always and 21% never). Cases in this cluster had an increased risk of sharing syringes, at a level of significance of $\alpha = 0.05$, if they also shared cookers (OR = 141.0), cotton (OR = 141.0), rinse water (OR = 141.0), or injected heroin (OR = 135.0.) (Table 5). As Table 6 illustrates, cases had increased risk of sharing syringes ($\alpha = 0.20$) if they split drugs with the same needle, used cocaine (injection and non-injection), used non-injection oxycodone, used non-injection methadone, knew where to get

clean needles, and used drugs in vehicles. Conversely, it was found that individuals living with their parents were 85% less likely to share syringes.

Figure 12. Injection Drug Use Practices – Frequency of Sharing Injection Equipment

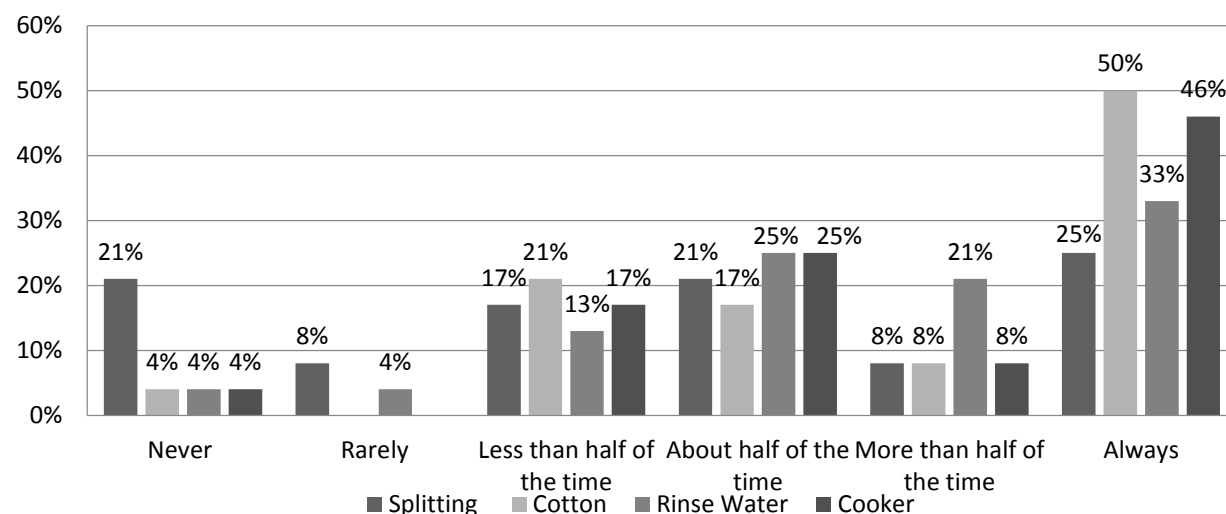


Table 5. Assessing risk factors for sharing syringes with 95% confidence

Variable Associated with Sharing Syringes	Percent Ever	OR	95% CI	One-tailed p-value
Shared Cooker	96%	141	2.01 – 9917.20	0.02085
Shared Cotton	96%	141	2.01 – 9917.20	0.02085
Shared Rinse Water	96%	141	2.01 – 9917.20	0.02085
Injected Heroin	96%	135	1.92 – 9503.31	0.02175

Table 6. Assessing risk factors for sharing syringes with 80% confidence

Variable Associated with Sharing Syringes	Percent Ever	OR	80% CI	One-tailed p-value
Splitting Drugs	79%	13	1.44 - 117.03	0.10415
Cocaine Use (non-injection)	83%	16.71345	1.81 - 154.06	0.08695
Cocaine Injection	64%	5.8	0.67 - 50.83	0.1818
Lived at Parent's House/Apartment	29%	0.1515	0.017 - 1.32	0.16665
Knows where to get clean needles	71%	8.0769	0.92 - 71.02	0.14585
Vehicles	83%	16.143	1.81-154.06	0.08695
Oxycodone use (non-injection)	76%	11.0	1.22 - 99.37	0.11905
Methadone use (non-injection)	75%	10.3333	1.14 - 93.48	0.125

The risk factors for coming into contact (IDU, living quarters, or sexual) with a person living with HCV was investigated (Tables 7,8). At the $\alpha = 0.05$ level of significance, individuals who used non-injection oxycodone were 24 times as likely to come into contact with an HCV-positive individual. When the level of significance was expanded to $\alpha = 0.20$, it was determined that injecting heroin and methadone were independent risk factors for contact, while living at someone else's house and non-injection methamphetamines use was protective.

Table 7. Assessing the Risk of Coming into Contact (Sharing Living Quarters, IDU, or Sexual) With Known or Suspected HCV Patients with 95% Confidence

Variables Associated with Contact	Percent Ever	OR	95% CI	One-tailed p-value
Using Oxycodone (non-injection)	89%	24	1.61 – 356.64	0.01195

Table 8. Assessing the Risk of Coming into Contact (Sharing Living Quarters, IDU, or Sexual) With Known or Suspected HCV Patients with 80% Confidence

Variables Associated with Contact	Percent Ever	OR	80% CI	One-tailed p-value
Living at Someone else's House	10%	0.1111	0.023 - 0.54	0.05745
Heroin Injection	100%	17.5714	1.91 - 161.81	0.08335
Methadone Injection	71%	11.0	1.20 - 100.57	0.08335
Using Methamphetamines (non-injection)	35%	0.0807	0.011 – 0.62	0.03685

Among all illicit drugs, the opiates heroin (96%), oxycontin (85%), oxycodone (77%), morphine (75%), and methadone (56%) were the most commonly injected (Figure 13). The most common non-injection drugs abused were oxycontin (96%), morphine (87%), cocaine (83%), oxycodone (77%), and methadone (76%) (Figure 14). On average, drug use was initiated at age 13 with marijuana use, followed by Adderall/Ritalin (13.7 years), benzodiazepines and hallucinogens (15 years), and then opioids starting at 17.7 years. Non-injection drug use was initiated approximately four years earlier than injection of the same drug (Figure 15).

Figure 13. Injection Drug use in the 6-Months Leading up to Diagnosis

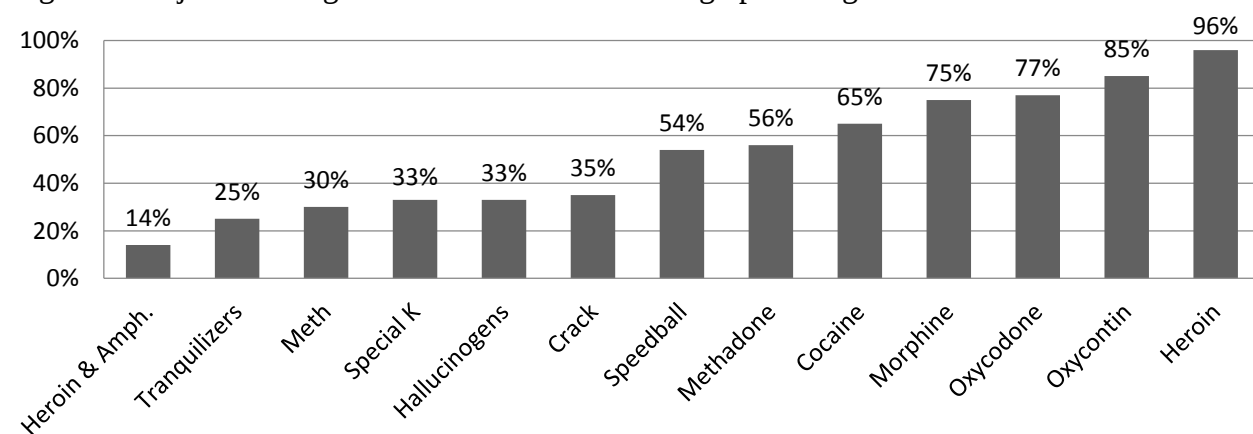


Figure14. Non-Injection Drug use in the 6-Months Leading up to Diagnosis

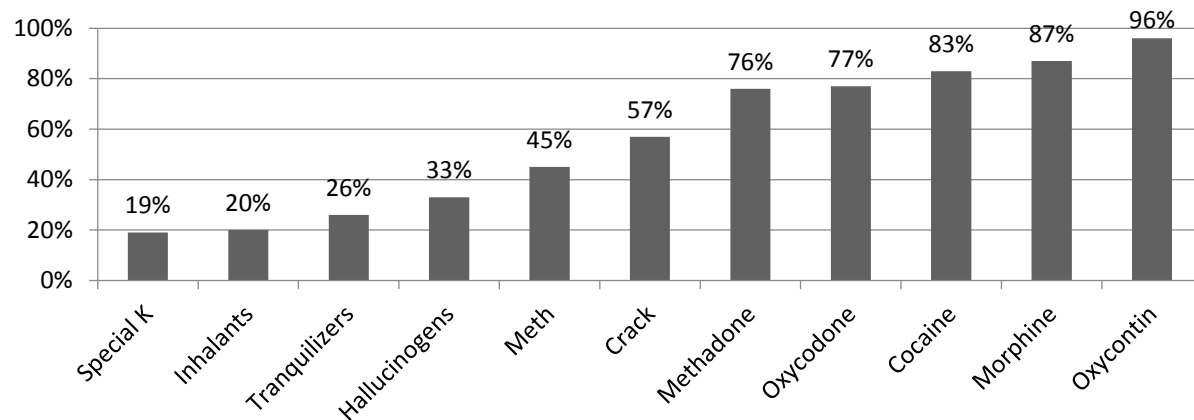
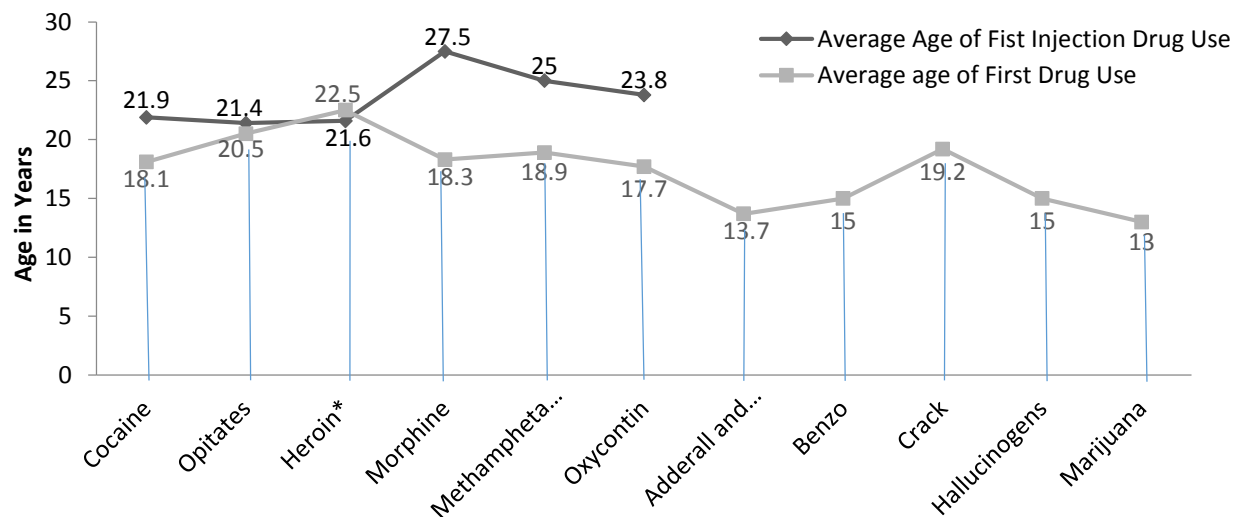


Figure 15. Average age of First Time Drug was Used and First Time Drug was Injection by Drug



Gender was shown to affect several factors related to IDU (Table 9). Specifically, women were shown to be at greater risk than males to use specific drugs or participate in certain risky behavior. Women were highly significantly more likely to use tranquilizers (OR 36.0, $p = 0.0024$) and oxycodone (OR 15.0, $p = 0.0198$) than males. Additionally, women were more likely than males to have been diagnosed with a sexually transmitted infection in the six months

prior to their HCV diagnosis (OR 13.5, $p = 0.02965$). At a level of significance of $\alpha = 0.20$ women were more likely to have sex in exchange for drugs (OR 7.6, $p = 0.09165$) and to inject heroin and methamphetamines together (OR 10.7, $p = 0.0902$).

Table 9. Risk Factors Associated with Gender

Variable	Percent of Females	OR	80% CI	One-tailed p-value
Injecting Heroin and Meth together	30%	10.73	1.41-81.62	0.0902
Using Oxycodone	100%	15.40	2.11-112.62	0.0198
Using Tranquilizers	63%	36.14	4.66-280.27	0.0024
Sex in exchange for drugs	18%	7.63	.98-59.65	0.09165
STD 6 mo before diagnosis	30%	13.53	1.79-102.17	0.02965

Knowledge and behaviors

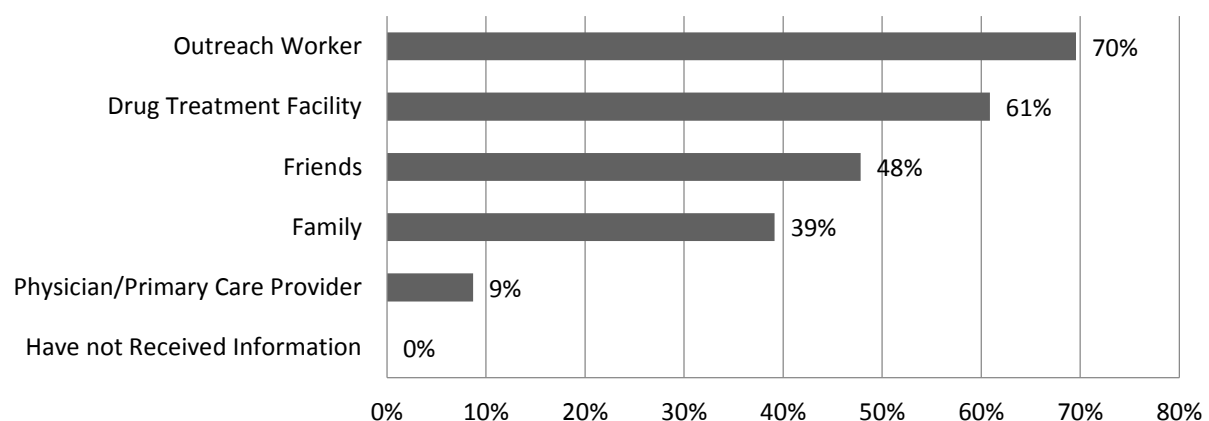
Knowledge of HCV prior to diagnosis, where to obtain clean needles, perceived ability to enroll in a drug treatment program, and healthcare seeking behaviors were assessed (Table 10). All but one (96%) of the respondents had heard of HCV prior to their diagnosis. The majority of individuals (71%) knew where they could obtain clean needles. All cases who responded to the question knew how to gain access to a drug treatment program and 92% had participated in a program at some point. Education regarding HCV was most commonly communicated by outreach workers and drug treatment facilities (Figure 16). Only one case was seeking medical

treatment for their HCV diagnosis which may be influenced by the low rate of health insurance (13%) coverage.

Table 10. Knowledge, Drug Treatment, and Medical Care Among Cases

Question	Response Rate	N	Percent
Knows where to get clean needles	96%	18	71%
Has ever been in a drug treatment program	96%	23	92%
Knows how to get into a drug treatment program	96%	25	100%
Had ever heard about HCV prior to diagnosis	92%	24	96%
Intentional overdose prior to HCV diagnosis	92%	0	0%
Has any form of health insurance	92%	3	13%
Currently seeing a doctor for HCV	88%	1	5%
Vaccinated against HAV	24%	13	50%
Vaccinated against HVB	28%	14	57%

Figure 16. Who Communicated HCV Knowledge to Cases



Discussion

This cluster investigation embodies an emerging epidemic among young white PWID in the Northeast, Southeast, Appalachian Mountains, and Midwest. Similar to recently described acute HCV outbreaks the predominant risk factor for acquisition of HCV in Southeastern Indiana was injection drug use. Also in line with previous findings, cases resided in rural or suburban areas, were under the age of 30, majorly white, drug use began with marijuana at a young age, and prescription opioid use before transitioning to injection heroin use.

Sexual transmission was initially suspected as a possible transmission route in four individuals who reported that they had not injected drugs in the six months prior to their HCV diagnosis, but they subsequently answered several questions which indicated they had injected during that time period. Long term sexual contact with high risk individuals (PWID) and known or suspected HCV-positive individuals was common, generally with a spouse. Sixty-five percent of cases reported sexual contact with potentially infected individuals. Although suspicious, sexual transmission cannot be established because drugs were commonly injected with these sexual partners. Thus, the more efficient route, IDU, is more likely to be the source of transmission. MSM transmission has been increasingly recognized as a significant source of HCV in individuals living with HIV. No cases claimed to have ever been diagnosed with HIV, and although an unlikely contributor in this cluster, monitoring MSM transmission of HCV may be important moving forward.

A particularly concerning aspect of the IDU in this cluster was the proportion of cases who frequently shared injecting equipment with others (Figure 12). The risk of HCV transmission among those who shared drug preparation equipment (drug cookers, cotton, rinse water) has

been shown to be great even in the absence of needle sharing. A cluster investigation in upstate New York found an inverse relationship between sharing needles and sharing preparation equipment. The majority of HCV positive individuals in the New York cluster said they did not share needles but that they commonly shared drug preparation equipment (13). All syringes retain some degree of fluid when the plunger is fully depressed (16). The fluid that remains in the syringe can lead to transmission of HCV by reusing the syringe and by contaminating rinse water. Injectors who engage in sharing of injection equipment or preparation equipment have been shown to be twice as likely to contract HCV than PWID who do not (70). We found that a high rate of sharing drug preparation and injection equipment. Cases in this cluster were at a greater risk for sharing syringes if they also shared preparation equipment. Splitting drugs using the same needle was a less common occurrence. A lower rate of sharing needles may be a testament to education regarding the transmission of HCV. However, the high degree of sharing other equipment highlights future opportunities for educational outreach to address. In this cluster, there was greater risk for sharing syringes among those who injected heroin compared to those who did not. This finding may explain why individuals who inject heroin are more likely to contract HCV than those who inject non-opioid drugs (70).

The development of a tolerance to non-injection prescription opioids (e.g. oxycodone) leads individuals to seek drugs which are cheaper and have a greater bioavailability, such as heroin injection (71). The point at which intervention may be most effective is prior to the onset of IDU, when young illicit drug users are abusing non-injection prescription opiates. In this cluster, there was an average of four years between the first time of prescription opiate use and first time heroin was injected. Reports from other areas of the country indicate time to injection of opiates from onset of non-injection opiate use to be approximately 1-1.5 years (72). HCV education

should be provided prior to onset of IDU because the window for intervention becomes increasingly small once IDU begins.

Educational efforts should tailor messages to attract and captivate young PWID. This may be achieved by involving current and former PWID in the design of intervention and education programs. Based on this cluster, individuals know about HCV and know where they can get clean needles. The majority reported obtaining this knowledge from outreach workers and drug treatment facilities. Because outreach workers and treatment programs have an established rapport with PWID, collaboration between health departments and such healthcare professionals may facilitate intervention efforts. The establishment of structural interventions has been shown to be an effective strategy in rural and suburban areas and may be beneficial to Indiana.

Examples of structural interventions include access to sterile injection equipment, opioid substitution therapy, and secondary syringe exchanges (PWID distribute clean injection supplies to others not attending the exchange). Similar to rural and suburban areas in other states affected by this emerging epidemic, the rural counties represented in this cluster do not have political or public support for sterile syringe access for PWID. The efficacy of exchanges is equivocal. Several syringe exchange programs have shown to be effective (49). Further, harm reduction and syringe/needle exchange has been shown to be a more effective strategy in prevention of HCV in PWID than awareness and education (46, 50). In addition to providing sterile injection supplies, exchange programs support the needs of several social issues such as distribution of condoms; education, counseling, and testing for HIV, HBV, HCV, and HAV; screening for tuberculosis and STI's; vaccination for HBV and HAV; on-site medical care; and referrals for substance abuse programs (46). Community-based coalitions that focus on drug use and promote public awareness, community and provider education, harm reduction, drug diversion control, and

appropriate pain control for patients could help identify current drug abusers and create a more inviting atmosphere in which PWID may seek help.

The primary risk factors related to the acquisition of HCV are well understood and characterized within the IDU population. Moving forward, health departments and drug treatment facilities could work together to enroll HCV-negative PWID for a longitudinal study aimed at assessing how long term PWID maintain HCV-negative serostatus. Such a study may reveal protective factors which can then be reinforced through interventional and educational programs. Among the population of PWID in this cluster, those who live with their parents were less likely to share syringes than those who lived elsewhere. Cases were less likely to come in contact with individuals who are or suspected of being HCV-positive if they “lived at someone else’s house” or used non-injection methamphetamines. The former is likely because many cases identified a spouse or partner as being HCV-positive. Non-injection drug use (e.g. snorting) was found to be protective against HCV infection in young PWID in previous studies (21).

A major barrier to surveillance and timely treatment of acute HCV in PWID is their antipathy towards seeking medical care, which is further complicated by the high frequency of asymptomatic acute infections. When present, acute HCV signs and symptoms vary in presentation and severity. The most commonly reported symptoms are fatigue, right upper quadrant pain, poor appetite, and nausea. Other signs and symptoms include dark urine, jaundice, clay-colored stool, vomiting, joint pain, and rarely fulminant hepatic failure (2, 73). Individuals who develop symptoms typically experience illness for 2-12 weeks. It is imperative that healthcare providers gather potential exposure history when hepatitis is present. If risk factors and symptoms are indicative of acute viral hepatitis, laboratory testing should be performed and results reported to the state department of health. ISDH has developed an

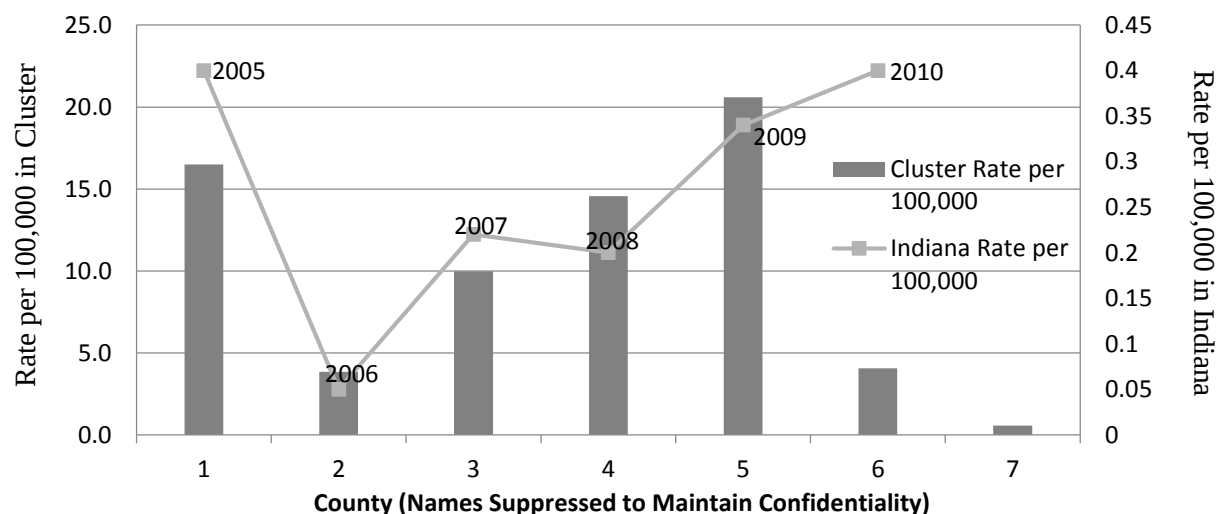
instrument, state form 52588, to assess relevant medical history and risk factors (74). Healthcare providers may also submit information electronically using The Indiana National Electronic Disease Surveillance System (I-NEDSS).

Limitations

The primary limitation of data reported was recall bias. Questions regarding potential exposure history asked participants to recall the six months preceding their diagnosis. The majority of interviews took place a year or more after the beginning of the recall period. For example, one case was interviewed on 10/31/11, diagnosed in 02/1/11, and asked to recall back to 08/01/10. This error was occasionally observed when the same case responded differently to two different questions measuring a similar element. Several questions within the instrument created a source of error as well as excluded potentially important information. Measuring a comparable variable with two different data types created error in the determination of age at first drug use. Cases were asked at what age they started using various drugs, and subsequently, what date they started injecting the drugs. This error became clear in the case of heroin use – the youngest age reported in which the drug was used was 18 years, but the youngest age of injection was (calculated from date provided) 16 years. Additionally, questions that attempted to characterize injection drug use characteristics (purchasing, location of use etc.) were not mutually exclusive leading to several responses by each case, and few differences between cases. It may have been more informative to determine which single behavior or action was done most frequently. Information regarding the date of last injection drug use before their diagnosis may have helped delineate transmission, but was not included on the survey. A concept closely related to sharing syringes that may not be captured by asking the question candidly is if syringes are ever borrowed. Borrowing a syringe may be a source of transmission, but if it is not used at the same sitting it may not be

thought of as sharing. The risk for acquiring HCV from sexual exposure has only been established on a cumulative basis, typically measured by years of exposure. In order to fully assess sexual exposure as a source of transmission, duration of exposure should be collected. Finally, the instrument was too long (90 questions). This was apparent by a sharp decline in response rates to questions toward the end of the interview. Specific question response rates were not homogenous throughout the instrument, and at times very low. No differences were observed between those who answered questions and those who did not, but low response rates compromise the generalizability of our findings. Acute HCV in Indiana may be better described by examining risk factors in all cases reported through traditional surveillance. While the sample size of this cluster is small (n=25), it may represent a significant increase in acute HCV in Indiana, specifically in Southeast Indiana (Figure 17). However, it is important to note that the implementation of I-NEDDS has increased the surveillance capacity for acute HCV. Therefore, the increase in observed acute HCV may be a result of increased surveillance rather than a true increase in the number of cases.

Figure 17. Acute HCV Rate per 100,000 in Indiana (2005-2010) and Acute HCV rate in 2011 Cluster per 100,000.



Conclusion

The population of PWID in Indiana may be experiencing an increase in transmission of acute HCV as a result of IDU. This cluster represents an increase in acute HCV incidence compared to previous years in Indiana, but increased surveillance capacity through I-NEDDS and heightened awareness by ASPIRE Indiana may have led to detection bias. Continued surveillance will be necessary to determine if acute HCV is truly increasing in young rural PWID or if this cluster is an artifact of increased surveillance. Based on the survey administered in this case series, PWID need to be educated on the potential dangers of sharing drug preparation and injection equipment. It was observed that PWID are more likely to share syringes if they also share cotton, rinse water, and cookers; all of which carry an additional risk of transmission. Further, those who injected heroin were more likely to share drug preparation and injection equipment. It was shown that non-injection prescription opioid use may occur up to four years before the transition to injection opioid use. HCV education may be most effective if delivered prior to the onset of IDU as a part of the curriculum in drug treatment programs that focus on non-injection prescription opioid use. This may be achieved by building partnerships between health departments and outreach agencies, such as ASPIRE Indiana. The outreach efforts by ASPIRE Indiana has added an essential resource for PWID to become aware of their HCV infection and set them on a course for long-term treatment. These efforts may be strengthened by the addition of syringe exchange programs in highly affected areas of the state. Finally, detection, prevention and management strategies by physicians may help prevent future HCV infections and alleviate adverse sequelae as a result of current HCV infections.

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