HCV Epidemiology in the United States

HCV Incidence in the United States

Definitions of HCV Incidence

The incidence of hepatitis C virus (HCV) infection is defined as number of new infections in a specific region in a specific time period. The Centers for Disease Control and Prevention (CDC) defines the incidence of hepatitis C in the United States (or in each state) as the number of new hepatitis C virus infections that occur per year. The incidence rate is the number of cases per total population (typically defined as number of cases per 100,000 persons).

Method of Estimating HCV Incidence

Most patients with acute hepatitis C do not have an acute illness and most do not seek medical care. In addition, many cases of diagnosed acute hepatitis C are not reported. Thus, determining the true incidence of new HCV infections per year based on the number of reported cases requires sophisticated epidemiologic modeling techniques. For each new acute HCV case that is reported in the United States, the CDC estimates there are approximately 13.9 actual new acute HCV cases (reported and unreported) that have occurred.[1] This high ratio (total estimated cases to actual reported cases) is primarily a result of the large proportion of persons with acute HCV who have asymptomatic or minimally symptomatic infection and do not seek medical care or have undiagnosed infection; the passive HCV reporting system likely also contributes to the low number of reported acute HCV cases. The CDC provides several numbers related to the incidence of hepatitis C in the United States, including number of reported acute cases, estimated number of acute clinical cases, estimated number of new infections, and the national rates per 100,000 persons.[1]

HCV Incidence Data

The CDC HCV surveillance data from 1982 to 2016 shows a peak in the number of cases in 1989, a steady decline from 1990 to 2005, a relative leveling off between 2006 and 2010, and then an increase from 2011 to 2016 (Figure 1).[1] In 2016, a total of 2,967 new cases of acute hepatitis C were reported to the CDC from 41 states; based on this number, the CDC estimated a total of 41,200 persons were newly infected with hepatitis C in 2016.[1] From 2005 to 2016, the number of reported new annual acute HCV infections increased approximately 4-fold, with the most steep increases occurring from 2011 to 2016 (Figure 2).[1] This steady and significant increase in new HCV infections from 2011 to 2015 is attributable to the opioid epidemic and associated injection drug use that is ongoing in the United States.[2,3,4] The surge in new HCV cases related to the opioid epidemic has most impacted persons under the age of 30, particularly in states in the central Appalachia region of the United States.[2,4,5]

Importance of HCV Incidence Data
The United States hepatitis C incidence data provide important information for monitoring trends in transmission patterns, developing hepatitis C prevention strategies, monitoring the effectiveness of any implemented plans, and identifying focal outbreaks or regional patterns of infection. The CDC viral hepatitis surveillance regularly reports on HCV outbreaks in the United States.[6] In addition, valuable information emerges when data is categorized by age group, gender, race/ethnicity, and risk factor for acquiring hepatitis C virus.
HCV Prevalence in United States

Definition of HCV Prevalence

The HCV prevalence is defined as the number (or percent) of persons in the total population observed infected with hepatitis C. Most often, the HCV prevalence specifically refers to persons living with active (chronic) hepatitis C infection. The HCV prevalence (chronic active HCV) in the United States is dynamic and is impacted by five factors: (1) the number of new HCV infections, (2) the number of persons who experience spontaneous cure of HCV, (3) the number of treatment cures, (4) the number of deaths, and (5) the number of persons cured who become reinfected (Figure 3). Less frequently, the HCV prevalence data is given for all individuals with anti-HCV (number of persons living who have been infected with hepatitis C), which includes those with active HCV, persons who spontaneously resolved HCV, and those with HCV treatment-related cure. The prevalence rate of chronic hepatitis C is the number of persons living with HCV per population (typically defined as number of persons per 100,000 population).

HCV Prevalence Estimates

In the United States, hepatitis C virus infection is the most common bloodborne infection. The best estimates of HCV prevalence derive from analysis of serum specimens taken from participants in the National Health and Nutrition Examination Survey (NHANES) (Figure 4). The most recent estimate of HCV prevalence in the United States was generated from analysis of 2013 to 2016 NHANES survey data.[11] In this time period, there were an estimated 4.1 million persons living in the United States who were HCV antibody positive and 2.4 million persons who were HCV RNA positive (1% of all adults).[11] When compared with earlier NHANES studies, the number of persons with a positive HCV antibody has remained relatively stable whereas the number of HCV RNA positive persons has decreased significantly from the estimated 3.2 million HCV RNA-positive persons in the 1999 to 2002 time period.[8,11] The declining HCV RNA-positive prevalence likely has resulted from a significant number of persons obtaining cure of chronic HCV infection with direct-acting antiviral therapy. These NHANES surveys, however, did not sample certain populations, including the incarcerated, homeless, nursing home residents, persons on active military duty, and immigrants. Taking this into account, some investigators estimated a higher HCV prevalence than in the NHANES surveys as they included incarcerated, homeless, nursing home residents, hospitalized individuals, and persons on active military duty.[12,13,14]

HCV Prevalence by Year of Birth

The HCV prevalence is highest among persons born during 1945 to 1965 (Figure 5). Indeed, the CDC estimates that approximately three-fourths of all persons living with HCV infection in the United States were born during 1945 to 1965. The relatively high prevalence of HCV infection among persons born during 1945 to 1965 corresponds with the high HCV incidence (new infections) that occurred among young adults in the 1970s and 1980s.[1]

Awareness of HCV Infection Status

An estimated 50% of persons infected with HCV are unaware of their HCV infection status.[15,16] One study reported that among persons 15 to 30 years of age who inject drugs and are living with HCV, 72% were unaware of their HCV infection status.[17] A more recent analysis of NHANES data from 2001 through 2008 found that 50.3% of persons infected with HCV were unaware of their hepatitis C infection.[16] In a study involving persons with access to medical care in four private health care organizations during the years 2006 to 2008, an estimated 43% were unaware of their HCV infection.[18]

HCV Genotype
In the United States, approximately 75% of chronic HCV infections are caused by hepatitis C genotype 1 (subtypes 1a or 1b), 15 to 20% by genotype 2 or 3 and less than 5% genotypes 4, 5, or 6.[19,20,21] Among the genotype 1 infections, genotype 1a is more common than 1b.[21]
Risk Factors for Acquiring HCV

Overview of Risk Factors for HCV Acquisition

Investigators and Public Health Officials have identified multiple risk factors for acquiring HCV in the United States: injection drug use, history of receiving a blood product transfusion prior to July 1992, receipt of a solid organ transplantation, hemophilia with receipt of factor concentrates made before 1987, male-to-male sex, body tattoos, and intranasal cocaine use. Among these, injection drug use is the most common and important risk factor for acquiring HCV in the United States. Several studies have indicated that approximately 45% of persons with HCV infection do not report an exposure. Many of these patients, after undergoing careful questioning, eventually identified injection drug use as a risk factor. In the 1970's and 1980's, receipt of HCV-infected blood products or organs accounted for nearly 50% of new cases of HCV, but after the discovery of HCV as the cause of non-A, non-B hepatitis in 1989 and introduction of blood screening tests in the early 1990's, the proportion of new HCV cases caused by contaminated blood or organs dramatically declined. Persons in different ethnic groups may have relatively different routes of acquiring HCV.

Injection Drug Use

Injection drug use remains the most common risk factor for acquiring HCV in the United States, accounting for more than 60% of all cases of HCV. Approximately 20 to 30% of persons who inject drugs become infected with HCV within the first 2 years of starting to inject drugs and 50% within 5 years. Transmission risk is greatest with “direct sharing” of needles and syringes, but may also occur indirectly via sharing of injection paraphernalia, such as syringes, cookers, and cotton filters. The incidence of HCV in persons who inject drugs markedly declined from the early 1992-2002, likely due to increased availability of needle exchange programs that arose in response to the HIV epidemic. Since about 2002, however, multiple reports have documented a surge in HCV infections in the United States among young persons who inject drugs. This surge in HCV infections in the United States is intricately connected with the ongoing opioid epidemic and its associated injection drug use. These reports identified a new cohort of persons diagnosed with HCV who inject drugs and have the following characteristics: age younger than 30, white race, residence in non-urban areas, and use of oral prescription opiates prior to using heroin. Regions of the United States east of the Mississippi river have been most heavily impacted, with a particularly high intensity of new HCV cases in the central Appalachian region. Other states, including Massachusetts, New York, and Wisconsin, have also reported a rise in HCV cases related to young persons who inject drugs. Throughout the United States, the prototypical new heroin user initiates some type of substance abuse, such as alcohol or marijuana at about age 13, transitions to using oral opiates, most often oxycodone, around age 17, then eventually starts using cheaper and widely available heroin by about age 18.

Noninjection Drug Use

The role of noninjection drug use, such as snorting crack cocaine, powder cocaine, methamphetamine, or heroin, as a risk factor for acquiring hepatitis C remains controversial. The risk of acquiring HCV is plausible with use of pipes that may cause burns in the oral mucosa (with possible open mouth sores) or use of straws or tubing that causes erosion of nasal membranes (with bleeding in the nasal passage). Sharing these blood-contaminated devices could then lead to HCV transmission. The prevalence of HCV in noninjection drug users ranges from 2.3 to 35.3%. It is possible that use of noninjection drugs is a surrogate for other risk behaviors associated with HCV acquisition.

Sexual Exposure
The risk of acquiring HCV through sexual contact with a person who has HCV infection remains highly controversial. Overall, sexual transmission has accounted for up to 15% of cases of HCV in the United States, but with very close interrogation most of these cases of sexual transmission also involved injection drug use as a risk factor. Multiple studies involving monogamous heterosexual couples have shown a rate of HCV transmission less than 1% per year.[36,37,38,39] In a study involving 500 anti-HCV positive, HIV-negative subjects and their long-term monogamous heterosexual partners, investigators reported transmission of HCV by sex at a rate of 0.07% per year among the couples, which translates to approximately 1 per 190,000 sexual contacts.[40] In recent years, multiple reports have identified cases of sexual transmission among men who have sex with men (MSM), particularly among MSM who have HIV infection.[41,42,43,44] Particular risk factors identified with HCV transmission among MSM include coinfection with HIV, use of recreational drugs during sex, and certain sex practices that result in rectal bleeding or damage to the rectal mucosa, including fisting and use of shared sex toys.[41,45]

**Chronic Hemodialysis**

The prevalence of HCV infection in persons receiving hemodialysis is approximately 8%, which is nearly 5-fold higher than the general United States population.[46] Several risk factors have been identified for dialysis patients acquiring HCV, including number of blood transfusions received, number of years on dialysis, mode of dialysis (hemodialysis poses greater risk than peritoneal dialysis), and the prevalence of HCV in the dialysis unit. In the United States, multiple dialysis-associated HCV outbreaks have occurred and with most cases, HCV transmission likely resulted from inadequate infection control practices, particularly in situations when patients received dialysis immediately after a patient with HCV infection received dialysis.[47,48,49,50] The CDC does not recommend using dedicated dialysis machines for patients with HCV, but recommends universal precautions and strict sterilization procedures for all dialysis machines.[51]

**Receipt of Clotting Factor Concentrates**

Two types of clotting factor concentrates are used in clinical practice: plasma factor concentrate and recombinant factor concentrate. Most often, these involve use of factor VIII or factor IX concentrates. In the late 1970s through the mid-1980s, most persons with hemophilia acquired HCV infection via the receipt of contaminated plasma clotting factor concentrates.[52,53,54] In 1985, several companies introduced virus inactivation procedures for hemophilia blood products and by 1987 these procedures were uniformly used, virtually eliminating the risk of transmission of HCV via clotting factor concentrates. Use of recombinant factor concentrate also provides an option for providing factor concentrate with no risk of viral contamination.

**Receipt of Transfusion of Blood Products**

In the 1960’s, the risk of acquiring HCV from a blood transfusion was approximately 33%. The universal screening of blood and organ donors with routine use of second-generation HCV antibody tests in 1992 nearly eliminated subsequent risk of transfusion-associated HCV.[25,31,55] In the mid-1990’s the risk of acquiring HCV from a blood transfusion had declined to less than 0.3%.[25,56] The estimated risk of acquiring HCV from a blood transfusion decreased further following the introduction, in 1999, of the HCV nucleic acid testing (NAT) as a supplement to HCV antibody testing of blood products.[56,57] Blood banks in the United States now use a combination of the third-generation enzyme-linked immunosorbent assay (ELISA) and NAT screening of minipool testing (16 samples). The current estimated risk of acquiring HCV from a transfusion in the United States is approximately 1 in 2 million.

**Receipt of Immune Globulin**

Scattered cases and outbreaks of HCV transmission via gamma globulin have occurred in the United
States and in Europe. In 1993 and 1994, a major outbreak of HCV transmission in the United States occurred following patient receipt of HCV-contaminated lots of intravenous immune globulin; in this outbreak 23 persons became infected with HCV through receipt of contaminated immunoglobulin. Advances in virus inactivation procedures have nearly eliminated any risk of HCV transmission with immune globulin and manufacturers of intravenous immune globulin use vigorous viral inactivation and removal procedures. No cases of HCV transmission have been documented with administration of intramuscular immune globulin. All immune globulin products undergo solvent detergent.

Organ and Tissue Transplantation

Rare cases of inadvertent HCV transmission via organ or tissue transplantation have occurred in the United States. Most cases of transmission have involved HCV-antibody negative, HCV RNA positive donors. Among transplant recipients who receive HCV-infected organs or tissues, the risk of developing chronic HCV infection is high. With the advent of more accurate testing methods for donors, the risk of HCV transmission in this setting has markedly declined. In 2013, the U.S. Public Health Service drafted updated guidelines for prevention of HCV transmission through organ transplantation and these guidelines recommend HCV RNA testing (NAT) of all organ and tissue donors.

Perinatal

In the United States, due to the opioid epidemic, there has been a significant increase in HCV infection in recent years among women of childbearing age; this trend has raised concerns for a potential significant increase in perinatal HCV infections. Among pregnant women with chronic HCV infection, approximately 6% will transmit HCV to their child. Nearly all cases of perinatal HCV transmission have involved mothers who had detectable HCV RNA in plasma during pregnancy. Women coinfecte
CDC Case Definitions and Reporting

CDC Hepatitis C Case Definitions

The CDC has established case definitions and reporting criteria for acute and for past (resolved) or present (chronic) hepatitis C infection.

Acute Hepatitis C—2016 Case Definition

The CDC 2016 Case Definition for Acute Hepatitis C infection includes clinical and laboratory criteria (Figure 6), along with a case classification as probable or confirmed (Figure 7).[73] Of note, a patient can have a confirmed case of acute hepatitis C based on laboratory data alone (a hepatitis test conversion documented by a negative HCV antibody, HCV antigen or NAT laboratory test result followed within 12 months by a positive result of any of these tests). Symptomatic cases often go unreported and for multiple reasons, including many symptomatic patients do not seek medical care, the diagnosis may be missed, and medical providers may fail to report diagnosed cases. It is important not to report cases that have already been reported.

Chronic Hepatitis C Virus Infection—2016 Case Definition

The CDC 2016 Case Definition for Chronic Hepatitis C includes clinical and laboratory criteria (Figure 8), as well as a case definition (Figure 9).[74] These cases pertain to persons with current (active) hepatitis C infection and do not represent persons who spontaneously cleared hepatitis C infection. Also, it is important not to report cases that have already been reported.

Perinatal Infection Hepatitis C Infection—2018 Case Definition

The CDC 2018 Case Definition for Hepatitis C, Perinatal Infection includes clinical criteria, laboratory criteria for diagnosis, criteria to distinguish a new case from an existing case, and a case definition.[75] A confirmed case definition requires the following:

- Infant who has a positive test for HCV RNA nucleic acid amplification test (NAAT), HCV antigen, or detectable HCV genotype at ≥2 months and ≤36 months of age and is not known to have been exposed to HCV via a mechanism other than perinatal.

Reporting Criteria

Persons identified with acute hepatitis C should undergo an interview to determine an identifiable risk factor in the 2-week to 6-month time frame that preceded the onset of their illness. Similarly, the individual with past (resolved) or present (chronic) hepatitis C infection should be interviewed to determine lifetime risk factors for hepatitis C. The Viral Hepatitis Case Report form should be filled out for persons identified with either acute hepatitis C infection or past/present hepatitis C. Cases of hepatitis C should be reported to a health department, which in turn submits reporting data to the CDC via the Nationally Notifiable Diseases Surveillance System (NNDSS).
HCV Disease Burden

Deaths Related to Hepatitis C

From 1999 to 2007, the number of annual deaths related to hepatitis C increased substantially and in 2007, the number of deaths related to hepatitis C had exceeded those related to HIV (Figure 10).[76] A subsequent study that analyzed HCV-related deaths in the United States from 2003 to 2013 concluded the annual HCV-related deaths continued to increase since 2007, with an estimated 19,368 HCV-related deaths in 2013.[77] In this same report, in 2013 the number of hepatitis C-related deaths were approximately 10-fold greater than those related to hepatitis B.[77] Investigators have identified factors associated with an increased risk of death in persons with chronic hepatitis C infection: chronic liver disease, coinfection with hepatitis B virus, alcohol-related conditions, minority status, and coinfection with HIV.[78] More recently, the CDC estimate that during 2011 to 2016, the annual HCV-related deaths in the United States increased steadily until 2016, with annual deaths exceeding 19,000 during 2013 to 2015 year (Figure 11).[1] The CDC reported estimates for HCV-related deaths in the United States are based on death certificat data and are likely significantly underestimate the true number of HCV-related deaths.[1,79]

Projected End Stage Liver Disease Related to Hepatitis C

It is important to consider prior HCV-related disease projections that would occur if treatment for HCV is not widely implemented in the United States. Prior to the availability of direct-acting antiviral therapy for HCV, investigators predicted that 1.76 million persons with chronic HCV infection (if not treated) would develop cirrhosis by 2055, with a peak prevalence of about 1 million persons in the mid-2020s.[80] The projected incidence peak (new cases) of end-stage liver disease was in 2030, with about 38,600 cases per year.[80] The prevalence (number of people living) with end-stage liver disease also was predicted to peak in 2030, with an estimated 131,300 persons living with end-stage liver disease.[80] Transplants would be expected to peak in 2032 to 2033 at a level of 3200 HCV-related transplants per year. Again, the widespread implementation of HCV treatment with directing-acting antiviral agents will dramatically reduce liver-related morbidity, hepatocellular cancer, and the need for liver transplantations in the future.[81,82,83]
Summary Points

The following summarizes the epidemiology of HCV in the United States:

- The number of new acute HCV infections increased significantly from 2005 to 2015; this increase was primarily due to the ongoing opioid epidemic and its associated injection drug use.
- Based on CDC estimates, 3.5 million persons are living with HCV infection; the HCV prevalence is dynamic and impacted by the number of new HCV infections, the number of persons that spontaneously resolve their infection, the number of treatment cures, and the number of deaths.
- An estimated three-fourths of persons living with HCV were born during 1945 to 1965.
- Approximately 50% of persons with HCV infection are unaware of their HCV status.
- Injection drug use is the most common risk factor for HCV acquisition; since 2002, there has been a major increase in HCV among young persons who inject drugs and this is closely tied to the opioid epidemic.
- Sexual transmission of HCV can occur, but this most often involves MSM; the risk among MSM is substantially higher in those with HIV infection.
- The number of annual HCV-related deaths is approximately 19,000 persons and this exceeds the number of annual HIV-related deaths. Without widespread HCV curative treatment, future annual HCV-related deaths could exceed 35,000.
- The CDC has established a clear definition of acute, chronic, and perinatal HCV infection for reporting purposes as well as reporting guidelines.
Citations


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Figures

Figure 1 Hepatitis C Incidence in United States, 1982-2016

This graphic represents the estimated number of new hepatitis C infections per year.

Source: Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance.
Figure 2 Reported Acute (New) Cases of HCV, United States, 2005-2015

Source: Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance.
Figure 3 Dynamics of HCV Prevalence in the United States

This illustration shows the dynamics of HCV prevalence in the United States (persons living with chronic HCV infection) is impacted by multiple factors, including number of new infections, spontaneous resolution of new infections, deaths, and treatment-related HCV cure. Persons cured of HCV can become reinfected. In addition, a small number of persons have spontaneous resolution of chronic HCV infection.

Source: Illustration by David H. Spach, MD
Figure 4 Estimated Number of Persons Infected with HCV in the United States.

This graphic shows data representing seroprevalence (anti-HCV) and chronic infection (HCV RNA) from four distinct NHANES studies. The numbers on the bar graph represent millions of persons.

**Figure 5 Prevalence of HCV Antibody, by Year of Birth.**

The HCV prevalence is highest among persons born from 1945 to 1965. This graphic shows prevalence studies performed during two separate time periods: 1988-1994 (blue line) and 1999-2002 (purple line).

### Acute Hepatitis C: 2016 Case Definition—Clinical and Laboratory Criteria

**Clinical Criteria**

An illness with discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), **AND**

(a) jaundice, **OR**

(b) a peak elevated serum alanine aminotransferase (ALT) level >200 IU/L during the period of acute illness.

**Laboratory Criteria for Diagnosis**

- A positive test for antibodies to hepatitis C virus (anti-HCV)
- Hepatitis C virus detection test:
  - Nucleic acid test (NAT) for HCV RNA positive (including qualitative, quantitative or genotype testing)
  - A positive test indicating presence of hepatitis C viral antigen(s) (HCV antigen)*

* When and if a test for HCV antigen(s) is approved by FDA and available.
Figure 7 Acute Hepatitis C: 2016 Case Definition—Case Classification as Probable or Confirmed

Source: Centers for Disease Control and Prevention (CDC)

### Acute Hepatitis C: 2016 Case Definition

#### Criteria to Distinguish a New Case from an Existing Case

A new acute case is an incident acute hepatitis C case that meets the case criteria for acute hepatitis C and has not previously been reported.

#### Case Classification

**Probable**

- A case that meets clinical criteria and has a positive anti-HCV antibody test, but has no reports of a positive HCV NAT or positive HCV antigen tests,

  **AND**

- Does not have test conversion within 12 months or has no report of test conversion.

**Confirmed**

- A case that meets clinical criteria and has a positive hepatitis C virus detection test (HCV NAT or HCV antigen),

  **OR**

- A documented negative HCV antibody, HCV antigen or NAT laboratory test result followed within 12 months by a positive result of any of these tests (test conversion).
### Chronic Hepatitis C: 2016 Case Definition

#### Clinical Criteria

- No available evidence of clinical and relevant laboratory information indicative of acute infection.
- Most hepatitis C virus (HCV)-infected persons are asymptomatic; however, many have chronic liver disease, which can range from mild to severe.

#### Laboratory Criteria for Diagnosis

- A positive test for antibodies to hepatitis C virus (anti-HCV)
- Hepatitis C virus detection test:
  - Nucleic acid test (NAT) for HCV RNA positive (including qualitative, quantitative or genotype testing)
  - A positive test indicating presence of hepatitis C viral antigen(s) (HCV antigen)*

* When and if a test for HCV antigen(s) is approved by FDA and available.
**Figure 9 Chronic Hepatitis C: 2016 Case Definition—Case Classification as Probable or Confirmed**

Source: Centers for Disease Control and Prevention (CDC)

<table>
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<td><strong>Criteria to Distinguish a New Case from an Existing Case</strong></td>
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<tr>
<td>A new chronic case is an incident chronic hepatitis C case that meets the case criteria for chronic hepatitis C and has not previously been reported.</td>
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**Case Classification**

**Probable**
- A case that does not meet clinical criteria or has no report of clinical criteria,  
  AND  
- Does not have test conversion within 12 months or has no report of test conversion,  
  AND  
- Has a positive anti-HCV antibody test, but no report of a positive HCV NAT or positive HCV antigen test.

**Confirmed**
- A case that does not meet clinical criteria or has no report of clinical criteria,  
  AND  
- Does not have test conversion within 12 months or has no report of test conversion,  
  AND  
- Has a positive HCV NAT or HCV antigen test.
Figure 10 Mortality Rates from HBV, HCV, and HIV in United States, 1999-2007.

This graphic shows that when determining age-adjusted mortality rates, hepatitis C-related deaths surpassed HIV-related deaths in 2006. Abbreviations: PY = person years

Figure 11 Annual Deaths Associated with Chronic Hepatitis C Infection, 2010 to 2016

Source: Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance.

*Current information indicates these data represent a fraction of deaths attributable in whole or in part to chronic HCV*