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Abstract

**Background:** Hepatitis C virus (HCV) infection is a serious public health problem. New infections continue to occur, and morbidity and mortality are increasing among an estimated 2.7–3.9 million persons in the United States living with HCV infection. Most persons are unaware of their infection status. Existing CDC guidelines for laboratory testing and reporting of antibody to HCV do not distinguish between past infection that has resolved and current infection that requires care and evaluation for treatment. To identify current infection, a test for HCV RNA is needed.

**Methods:** Surveillance data reported to CDC from eight U.S. sites during 2005–2011 were analyzed to determine the proportion of persons newly reported on the basis of a positive test result for HCV infection. Persons reported with a positive result from an HCV antibody test only were compared with persons reported with a positive result for HCV RNA and examined by birth cohort (1945–1965 compared with all other years), surveillance site, and number of reported deaths. Annual rates of persons newly reported with HCV infection in 2011 also were calculated for each site.

**Results:** Of 217,755 persons newly reported, 107,209 (49.2%) were HCV antibody positive only, and 110,546 (50.8%) were reported with a positive HCV RNA result that confirmed current HCV infection. In both groups, persons were most likely to have been born during 1945–1965 (58.5% of those who were HCV antibody positive only; 67.2% of those who were HCV RNA positive). Among all persons newly reported for whom death data were available, 6,734 (3.4%) were known to have died; deaths were most likely among persons aged 50–59 years. In 2011, across all sites, the annual rate of persons newly reported with HCV infection (positive HCV antibody only and HCV RNA positive) was 84.7 per 100,000 population.

**Conclusions:** Hepatitis C is a commonly reported disease predominantly affecting persons born during 1945–1965, with deaths more frequent among persons of relatively young age. The lack of an HCV RNA test for approximately one half of persons newly reported suggests that testing and reporting must improve to detect all persons with current infection.

**Implications for Public Health:** In an era of continued HCV transmission and expanding options for curative antiviral therapies, surveillance that identifies current HCV infection can help assess the need for services and link persons with infection to appropriate care and treatment.

Introduction

In the United States, hepatitis C virus (HCV) infection is a common bloodborne infection. Based on data from national surveys, an estimated 3.2 (95% confidence interval [CI] = 2.7–3.9) million persons in the United States are living with hepatitis C (1). Once infected, approximately 80% of persons remain infected (i.e., chronically infected) and are at risk for substantial morbidity and mortality in later life (2). Although treatment can be curative, an estimated 45%–85% of infected persons are unaware of their HCV infection (3). HCV infection is a major cause of liver disease, including cirrhosis and liver cancer (4–7), and in the United States, is the leading indication for liver transplantation (8). Moreover, rates of liver cancer and deaths from HCV infection have increased over time; approximately 15,000 HCV-associated deaths were recorded in 2007 (4,9). In addition, considerable costs are associated with HCV infection, both in lost productivity and health-care expenditures (10–11).

CDC guidelines for HCV laboratory testing and reporting, published in 2003, do not focus on identifying persons with current infection (12); therefore, depending on the HCV test used, reports to surveillance programs can include persons with a test result indicating past HCV infection that has resolved and also persons with a test result that identifies current HCV infection. Analysis of state and local surveillance data can be used to assess the proportion of persons who might need additional testing to discriminate previous resolved infection from current infection. Analysis of such data also can estimate the number of persons with current HCV infection requiring clinical assessment for treatment, as well as guide prevention...
strategies. In addition, these surveillance data can serve as a baseline for indirectly evaluating use of the recent HCV testing recommendations to identify HCV infection among persons born during 1945–1965, a group that demonstrates the highest prevalence of infection, compared with those born in other years (3). Finally, examining mortality patterns among persons reported with current HCV infection can improve understanding of the natural history of the disease.

Methods
In 2011, CDC supported surveillance for HCV infection at eight U.S. sites (Colorado, Connecticut, Minnesota, New Mexico, New York City, New York state, Oregon, and San Francisco). CDC began receiving data in 2005 from four sites (Colorado, Minnesota, New York state and Oregon), one site in 2006 (New Mexico), two sites in 2008 (New York City and San Francisco), and one site in 2009 (Connecticut). For all sites, clinical laboratories reported only positive test results of HCV infection (i.e., from HCV antibody testing or from HCV RNA testing); health departments did not require reporting of negative results. Reports were reviewed and de-duplicated to ensure that persons with newly reported positive HCV test results were included only once in the surveillance database.

For this analysis, persons reported to CDC during 2005–2011 were categorized as 1) reported with only a positive test result for HCV antibody (HCV antibody positive only) or 2) reported with a positive HCV RNA result from HCV nucleic acid testing or HCV genotyping (HCV RNA positive). Persons who tested HCV antibody positive only were considered as having had a past HCV infection that had resolved, a false-positive test result, or current HCV infection. Persons who tested HCV RNA positive were considered currently HCV infected. Although no laboratory test exists to distinguish acute from chronic HCV infection, for the purpose of this study all persons determined to be currently infected were considered to have chronic infection.

Each group (HCV antibody positive only and HCV RNA positive) was examined by birth cohort (1945–1965 compared with all other birth years) and surveillance site. Annual rates of all persons newly reported per 100,000 population in 2011 also were calculated for each site using denominators available from U.S. Census population estimates (available at http://www.census.gov/compendia/statab). In addition, seven of the sites reported the frequency of known deaths from any cause among persons newly reported with HCV infection. Sites matched their hepatitis C databases with vital records at the person level. Death status was examined by sex, age group, birth cohort, and type of test result (HCV antibody positive only or HCV RNA positive).

Results
During 2005–2011, among the eight sites, a total of 217,755 persons were newly reported with a positive test result for HCV infection. Of these, 107,209 (49.2%) were HCV antibody positive only and 110,546 (50.8%) were HCV RNA positive. In both groups, persons were more likely born during 1945–1965. Persons born during these years accounted for 58.5% of those who were HCV antibody positive only and 67.2% of those who were HCV RNA positive (Table 1). The distribution of persons reported on the basis of positive HCV antibody only varied by site, ranging from 76% in New Mexico to 23% in Minnesota (Figure). Among sites reporting deaths, 6,734 (3.4%) of 197,844 persons newly reported with HCV infection were known to have died. The highest percentage of these deaths occurred among persons aged 50–59 years (44.8%), and most deaths (71.5%) were among those born during 1945–1965, compared with other years. The percentage of deaths among persons reported with HCV antibody positive only (4.6%) was significantly higher than among those reported as HCV RNA positive (2.4%; p<0.01). In 2011, the annual rate of all persons newly reported with HCV infection (positive HCV antibody only and HCV RNA positive) across all sites was 84.7 per 100,000 population (range: 36.0 in Minnesota to 239.2 in San Francisco) (Table 2).

Conclusions and Comment
These data show that approximately one half of persons newly reported with HCV infection to state or local authorities at eight surveillance sites did not have a report of a positive HCV RNA test; thus, it was not possible to determine whether the reports indicated past resolved HCV infection or current HCV infection. Previous studies have shown similar results. A separate analysis of surveillance data reported for 2006–2007 found that 47.3% of persons reported with

| TABLE 1. Percentage of persons newly reported with positive test results for hepatitis C virus (HCV) infection, by birth cohort and type of test result — eight U.S. sites, 2005–2011 |
|---------------------------------|-----------------|-----------------|-----------------|
| Birth cohort                   | HCV antibody positive only | HCV RNA positive | Total           |
|                                | No.   (%)        | No.   (%)        | No.   (%)        |
| Born during 1945–1965          | 62,728 (58.5)   | 74,270 (67.2)   | 136,998 (62.9)   |
| Born in other years            | 44,481 (41.5)   | 36,276 (32.8)   | 80,757 (37.1)    |
| Total                          | 107,209 (100.0)| 110,546 (100.0)| 217,755 (100.0) |
A multisite cohort study of patients in care for chronic viral hepatitis revealed that 37.7% of 9,086 patients with a positive HCV antibody test during 2006–2008 had no documented follow-up testing for HCV RNA (14). A retrospective study of HCV antibody testing in selected U.S. primary-care settings among persons born during 1945–1965 found that, among patients who were antibody positive, 32% received no follow-up HCV RNA testing (15). In New York City, 33% of persons reported through routine surveillance did not have HCV RNA testing (16).

Given these findings and recent developments in both HCV testing technologies and clinical care for persons with HCV infection, CDC is amending the guidelines for HCV laboratory testing and result reporting that have been in use since 2003 (12). In guidance accompanying this Vital Signs report, CDC recommends following a positive HCV antibody test with HCV RNA testing (17). This guidance is also consistent with that provided in the 2012 HCV testing recommendations for persons born during 1945–1965 (3). The new guidelines will help identify persons with current HCV infection and provide the data necessary to link those who are infected to care, including preventive services, medical management, and evaluation for antiviral treatment.

An unexpected result was the finding of a significantly greater percentage of deaths among persons who were HCV antibody positive only compared with those who were HCV RNA positive. Because persons in the latter group have demonstrated current infection, they would be expected to fare less well than those who were HCV antibody positive only and might or might not be currently infected. The difference between the groups in the percentage of deaths might be explained by health-care access. HCV RNA testing might not be available in sites providing HCV antibody testing and RNA testing requires successful referral to a health-care provider. Thus, this finding could suggest that persons reported on the basis of a positive HCV antibody test only might have had less opportunity to access health care or might have accessed health care less often than those with current infection.

This study also revealed a high rate of reported HCV infection at these U.S. sites, especially among persons born during 1945–1965. These findings reinforce recent CDC recommendations for HCV antibody testing of persons born during 1945–1965, and linkage to care for those with a follow-up positive result after HCV RNA testing (3). These data further showed that deaths were more likely among persons aged 50–59 years and among persons born during 1945–1965 compared...
with those born in other years, illustrating the important impact of HCV infection on years of life lost.

The findings in this report are subject to at least five limitations. First, state and local health departments only report positive HCV test results to CDC. Thus, it was not known whether persons who were reported HCV antibody positive only might actually have been tested for HCV RNA with a negative result. Another possibility is that HCV RNA testing was performed with a positive result, but was not reported. Second, some positive HCV antibody test results might have been false-positives. However, the high specificity of 3rd generation HCV antibody assays used during the period of study would have minimized the number of false positives (18). Third, among sites, there was variation in reporting by health-care providers, laboratories, and health departments, which might affect the consistency of the information reported. For example, the Connecticut hepatitis C surveillance system did not enter HCV RNA results for persons reported with a positive antibody test that previously had been confirmed to be positive for antibody to HCV by another laboratory test. Fourth, some sites began reporting surveillance data to CDC in 2006 or 2008, and in one case, 2009, thereby underestimating the number of cases reported during the entire 2005–2011 study period. In contrast, the number of deaths reported was from all-cause mortality, and therefore was likely an overestimation of HCV-attributable mortality. Finally, HCV surveillance data might not be representative of all persons with HCV infection, and the findings from these eight sites might not be representative of other U.S. cities and states.

Monitoring current HCV infection in states and localities can help gauge what interventions and services are needed to identify persons with HCV infection and effectively link them to appropriate care and treatment. This is of particular importance now in an era of continued HCV transmission and rapidly improving therapeutic options for persons living with HCV infection. To help identify persons with current HCV infection, public health and clinical care providers can offer HCV antibody testing to persons born during 1945–1965, in addition to those with other HCV risk factors, and test for HCV RNA those persons who test positive for HCV antibody. Laboratories can ensure that test results are reported to state and local health authorities, and health departments can develop strategies to monitor and increase the use of HCV RNA testing of persons who are HCV antibody positive.

Reported by

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References


Key Points

• CDC guidelines for laboratory testing and result reporting of antibody to hepatitis C virus (HCV) published in 2003 and developed in the era of limited treatment options fail to identify many persons with current HCV infection. As such, about one half of persons newly reported with hepatitis C lack HCV RNA results, which are necessary to identify current infection.
• In 2011, the overall annual rate of persons newly reported with hepatitis C was 84.7 per 100,000 population; rates varied by site.
• The highest percentage of persons with current HCV infection and the highest percentage of deaths among all persons newly reported with hepatitis C were among those born during 1945–1965, particularly those aged 50–59 years.
• Additional information is available at http://www.cdc.gov/vitalsigns.
12. CDC. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR 2003;52(No. RR–3).
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In the United States, an estimated 4.1 million persons have been infected with hepatitis C virus (HCV), of whom an estimated 3.2 (95% confidence interval [CI] = 2.7–3.9) million are living with the infection (1). New infections continue to be reported particularly among persons who inject drugs and persons exposed to HCV-contaminated blood in health-care settings with inadequate infection control (2).

Since 1998, CDC has recommended HCV testing for persons with risks for HCV infection (3). In 2003, CDC published guidelines for the laboratory testing and result reporting of antibody to HCV (4). In 2012, CDC amended testing recommendations to include one-time HCV testing for all persons born during 1945–1965 regardless of other risk factors (1).

CDC is issuing this update in guidance because of 1) changes in the availability of certain commercial HCV antibody tests, 2) evidence that many persons who are identified as reactive by an HCV antibody test might not subsequently be evaluated to determine if they have current HCV infection (5), and 3) significant advances in the development of antiviral agents with improved efficacy against HCV (6). Although previous guidance has focused on strategies to detect and confirm HCV antibody (3,4), reactive results from HCV antibody testing cannot distinguish between persons whose infection has resolved and those who are currently HCV infected. Persons with current infection who are not identified as currently infected will not receive appropriate preventive services, clinical evaluation, and medical treatment. Testing strategies must ensure the identification of those persons with current HCV infection.

This guidance was written by a workgroup convened by CDC and the Association of Public Health Laboratories (APHL), comprising experts from CDC, APHL, state and local public health departments, and academic and independent diagnostic testing laboratories, in consultation with experts from the Veterans Health Administration and the Food and Drug Administration (FDA). The workgroup reviewed laboratory capacities and practices relating to HCV testing, data presented at the CDC 2011 symposium on identification, screening and surveillance of HCV infection (7), and data from published scientific literature on HCV testing. Unpublished data from the American Red Cross on validation of HCV antibody testing also were reviewed.

Changes in HCV Testing Technologies

Since the 2003 guidance was published (4), there have been two developments with important implications for HCV testing:

1. Availability of a rapid test for HCV antibody. The OraQuick HCV Rapid Antibody Test (OraSure Technologies) is a rapid assay for the presumptive detection of HCV antibody in fingerstick capillary blood and venipuncture whole blood. Its sensitivity and specificity are similar to those of FDA–approved, laboratory-conducted HCV antibody assays (8). In 2011, a Clinical Laboratory Improvements Amendments waiver was granted to the test by FDA. The waiver provides wider testing access to persons at risk for HCV infection, permitting use of the assay in nontraditional settings such as physician offices, hospital emergency departments, health department clinics, and other freestanding counseling and testing sites.

2. Discontinuation of RIBA HCV. The Chiron RIBA HCV 3.0 Strip Immunoblot Assay (Novartis Vaccines and Diagnostics) that was recommended (4) for supplemental testing of blood samples after initial HCV antibody testing is no longer available. As a result, the only other FDA-approved supplemental tests for HCV infection are those that detect HCV viremia.

Identifying Current HCV Infections

In 2011, FDA approved boceprevir (Victrelis, Merck & Co.) and telaprevir (Incivek, Vertex Pharmaceuticals) for treatment of chronic hepatitis C genotype 1 infection, in combination with pegylated interferon and ribavirin, in adult patients with compensated liver disease. Boceprevir and telaprevir interfere directly with HCV replication. Persons who complete treatment using either of these drugs combined with pegylated interferon and ribavirin are more likely to clear virus (i.e., have virologic cure), compared to those given standard therapy based on pegylated interferon and ribavirin (9). Viral clearance, when sustained, stops further spread of HCV and is associated with reduced risk for hepatocellular carcinoma (10) and all-cause mortality (11). Other compounds under study in clinical trials hold promise for even more effective therapies (6).

Because antiviral treatment is intended for persons with current HCV infection, these persons need to be distinguished from persons whose infection has resolved. HCV RNA in blood, by nucleic acid testing (NAT), is a marker for HCV viremia and is detected only in persons who are currently infected. Persons with reactive results after HCV antibody testing should be evaluated for the presence of HCV RNA in their blood.
**Benefits of Testing for Current HCV Infection**

Accurate testing to identify current infection is important to 1) help clinicians and other providers correctly identify persons infected with HCV, so that preventive services, care and treatment can be offered; 2) notify tested persons of their infection status, enabling them to make informed decisions about medical care and options for HCV treatment, take measures to limit HCV-associated disease progression (e.g., avoidance or reduction of alcohol intake, and vaccination against hepatitis A and B), and minimize risk for transmitting HCV to others; and 3) inform persons who are not currently infected of their status and the fact that they are not infectious.

**Recommended Testing Sequence**

The testing sequence in this guidance is intended for use by primary care and public health providers seeking to implement CDC recommendations for HCV testing (1,3,4). In most cases, persons identified with HCV viremia have chronic HCV infection. This testing sequence is not intended for diagnosis of acute hepatitis C or clinical evaluation of persons receiving specialist medical care, for which specific guidance is available (12).

Testing for HCV infection begins with either a rapid or a laboratory-conducted assay for HCV antibody in blood (Figure). A nonreactive HCV antibody result indicates no HCV antibody detected. A reactive result indicates one of the following: 1) current HCV infection, 2) past HCV infection that has resolved, or 3) false positivity. A reactive result should be followed by NAT for HCV RNA. If HCV RNA is detected, that indicates current HCV infection. If HCV RNA is not detected, that indicates either past, resolved HCV infection, or false HCV antibody positivity.

**Initial Testing for HCV Antibody.** An FDA-approved test for HCV antibody should be used. If the OraQuick HCV Rapid Antibody Test is used, the outcome is reported as reactive or nonreactive. If a laboratory-based assay is used, the outcome is reported as reactive or nonreactive without necessarily specifying signal-to-cutoff ratios.

**Testing for HCV RNA.** An FDA-approved NAT assay intended for detection of HCV RNA in serum or plasma from blood of at-risk patients who test reactive for HCV antibody should be used. There are several possible operational steps toward NAT after initial testing for HCV antibody:

1. Blood from a subsequent venipuncture is submitted for HCV NAT if the blood sample collected is reactive for HCV antibody during initial testing.
2. From a single venipuncture, two specimens are collected in separate tubes: one tube for initial HCV antibody testing; and a second tube for HCV NAT if the HCV antibody test is reactive.

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*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
3. The same sample of venipuncture blood used for initial HCV antibody testing, if reactive, is reflexed to HCV NAT without another blood draw for NAT (13).
4. A separate venipuncture blood sample is submitted for HCV NAT if the OraQuick HCV Rapid Antibody Test for initial testing of HCV antibody has used fingerstick blood.

**Supplemental Testing for HCV Antibody**

If testing is desired to distinguish between true positivity and biologic false positivity for HCV antibody, then, testing may be done with a second HCV antibody assay approved by FDA for diagnosis of HCV infection that is different from the assay used for initial antibody testing. HCV antibody assays vary according to their antigens, test platforms, and performance characteristics, so biologic false positivity is unlikely to be exhibited by more than one test when multiple tests are used on a single specimen (14).

**Test Interpretation and Further Action**

See Table.

**Laboratory Reporting**

“Acute hepatitis C” and “hepatitis C (past or present)” are nationally notifiable conditions, and are subject to mandated reporting to health departments by clinicians and laboratorians, as determined by local, state or territorial law and regulation. Surveillance case definitions are developed by the Council of State and Territorial Epidemiologists in collaboration with CDC (15). In all but a few jurisdictions, positive results from HCV antibody and HCV RNA testing that are indicative of acute, or past or present HCV infection, are reportable. Specific policies for laboratory reporting are found at health department websites (16).

**Future Studies**

Research, development, validation, and cost-effectiveness studies are ongoing to inform the best practices for detecting HCV viremia and for distinguishing between resolved HCV infection and biologic false positivity for HCV antibody in persons in whom HCV RNA is not detected. Outcomes of these studies will provide comprehensive guidance on testing, reporting, and clinical management, and will improve case definitions for disease notification and surveillance.

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**TABLE. Interpretation of results of tests for hepatitis C virus (HCV) infection and further actions**

<table>
<thead>
<tr>
<th>Test outcome</th>
<th>Interpretation</th>
<th>Further action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody nonreactive</td>
<td>No HCV antibody detected</td>
<td>Sample can be reported as nonreactive for HCV antibody. No further action required. If recent HCV exposure in person tested is suspected, test for HCV RNA.*</td>
</tr>
<tr>
<td>HCV antibody reactive</td>
<td>Presumptive HCV infection</td>
<td>A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA detected</td>
<td>Current HCV infection</td>
<td>Provide person tested with appropriate counseling and link person tested to medical care and treatment.†</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA not detected</td>
<td>No current HCV infection</td>
<td>No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations§ follow up with HCV RNA testing and appropriate counseling.</td>
</tr>
</tbody>
</table>

* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.
† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.
§ If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
References

4. CDC. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR 2003;52(No. RR–3).
6. CDC. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR 2003;52(No. RR–3).