

# Hepatitis C

## Investigative Guidelines

### January 2020

## 1. DISEASE REPORTING

### 1.1 Purpose of Reporting and Surveillance

1. To identify common source outbreaks (e.g., from contaminated reuse of multi-dose vials in the healthcare setting).
2. To provide counseling as necessary to cases and contacts of cases.
3. To identify whether the case may be a source of infection for other persons, and if so, to prevent future transmission.

### 1.2 Laboratory and Physician Reporting Requirements

1. All diagnoses of acute hepatitis C are reportable by physicians to the Local Health Department (LHD) within one working day of diagnosis.
2. All positive laboratory tests for hepatitis C (HCV) must be reported by licensed laboratories to the LHD within one working day.

### 1.3 Local Health Department Reporting and Follow-Up Responsibilities

#### 1. Acute cases

Report all confirmed and presumptive (but not suspect) cases (see definitions below) to the Public Health Division (PHD) by the end of the calendar week. Begin follow-up investigation within one week. Submit all case data electronically.

#### 2. Chronic cases

Report all chronic cases to the PHD within 7 days of initial report. Because there is currently no test (like an IgM) that is specific for recent infection, it is impossible to distinguish between recently and distantly acquired infections based on laboratory results, and our case definition for acute infections relies on clinical criteria. Since physicians are required to report acute cases of HCV to the LHD, LHDs should investigate all reports from clinicians to ascertain whether the patient meets the case definition for acute illness.

If the LHD receives a positive report for HCV from a laboratory only, the LHD is not required to conduct any further investigation but should simply electronically transmit all of the patient information on the laboratory report (typically name, address, telephone number, age, sex, location of test and ordering physician) to PHD.

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### 3. Perinatal cases

Report all confirmed cases to PHD by the end of the calendar week. Submit case data electronically.

## 2. THE DISEASE AND ITS EPIDEMIOLOGY

### 2.1 Etiologic Agent

The etiologic agent of hepatitis C is a flavivirus (same family as the yellow fever virus) — unrelated to the viruses that cause hepatitis A or B. Specific tests for HCV first became available in 1990, although the existence of the virus was inferred for many years. The overall prevalence of antibody to HCV in the U.S. population is estimated to be 1.3%, corresponding to an estimated 3.6 million Americans.<sup>1</sup> Of these, 75% (estimated 2.7 million Americans) are chronic carriers. Peak prevalence is observed among individuals born between 1945 and 1965. In 2012, CDC recommended that all Americans born in this period be tested once for HCV infection. CDC estimates that this age group comprises 75% of hepatitis C cases in the United States; among Oregon cases 64% belong to this age group. There are 6 HCV genotypes; genotype 1 accounts for 70% to 75% of all HCV infections in the United States and is associated with a lower rate of response to treatment.

### 2.2 Description of Illness

Hepatitis C cannot be clinically distinguished from other viral hepatitises with any reliability. Onset of symptoms is usually insidious, with fever, malaise, anorexia, nausea, and abdominal discomfort, followed by jaundice (for most patients). Urine may become unusually dark, and stools quite pale. Infections vary from completely asymptomatic (~80% of infections) to a disabling illness lasting several months. Fulminant hepatitis is rare, but can be fatal. Liver enzyme levels are elevated (between 5 and 20x upper limit of normal in a large number of cases; usually >7x the upper limit of normal).

Between 75% and 85% of infected individuals develop chronic infection, and 50%–60% of these develop chronic liver disease, as evidenced by persistently elevated liver enzyme levels, regardless of whether they became ill at the time of infection. Long-term carriage is associated with the same long-term sequelae linked to hepatitis B carriage — chronic active hepatitis, cirrhosis, and hepatocellular carcinoma, and the risk of these sequelae increases for patients chronically infected with both HBV and HCV. Patients with signs of chronic liver disease due to HCV are also at an increased risk of fulminant hepatic failure should they acquire hepatitis A.

Antibodies develop after infection, but are not protective.

### 2.3 Reservoirs

Human beings.

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### 2.4 Modes of Transmission

HCV is transmitted through contact with contaminated blood such as via needle sharing, drug paraphernalia sharing, and blood transfusion. Although HCV is transmitted by needle-stick injury, the prevalence of HCV antibodies among health care workers is only 1.4%, similar to the overall prevalence in the U.S. population. Household contact with infected blood (e.g., via toothbrush and razor sharing) can result in infection, but the efficiency of transmission by such sources is unclear. Sexual transmission can occur, but the efficiency of transmission is much lower than with most sexually-transmitted diseases (STDs). For a person with chronic HCV infection, the estimated risk of sexual transmission to an uninfected partner is 0% to 0.6% per year for those in monogamous relationships, and 0.4% to 1.8% per year for persons with multiple sexual partners or those at risk for sexually transmitted diseases. The presence of other STDs or sexual practices that traumatize the mucosa (i.e., receptive anal sex) increase risk.

Mother-to-infant transmission at birth occurs in <5% of births, unless the mother is simultaneously HIV-infected, in which case the probability of vertical transmission increases 4–5 fold.

### 2.5 Incubation Period

HCV RNA appears in the blood within 1-2 weeks of infection in a majority of patients. For the ~30% of patients who develop symptoms of acute HCV infection, the onset is 3-12 weeks after infection, with an average of 7 weeks. HCV antibodies generally develop during the same time period, typically 7-8 weeks after infection. Antibody development may be delayed in immunosuppressed patients — up to 24 weeks (or not at all, making PCR the only way to diagnose some of these patients).

### 2.6 Period of Communicability

The period of communicability following initial infection has not been determined, but is likely lifelong. It is not clear if communicability waxes and wanes, and if so, under what circumstances. HCV viremia is probably low relative to hepatitis B and high relative to HIV.

### 2.7 Treatment

Previous treatments with pegylated interferon (PEG-IFN) and ribavirin for hepatitis C virus (HCV) infection resulted in significant adverse events and low cure rates, even with the addition of first-generation protease inhibitors. The standard of care for chronic HCV infection changed dramatically in 2013 with the approval of second-generation direct-acting antivirals, which led the way for IFN-free combination regimens.

All-oral combinations of direct-acting antivirals, with or without ribavirin, have shown high efficacy (over 90% achieve a sustained virologic response, defined as no detectable virus detectable 12 weeks after completion of treatment) and are well tolerated in patients with the predominant genotypes, advanced fibrosis

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stages, and HIV co-infection.<sup>2</sup> New fixed-dose co-formulations of direct-acting antivirals have allowed simpler regimens with shorter treatment durations (as low as 6-12 weeks) and low rates of discontinuation, but are associated with substantial costs.

### 3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

#### 3.1 Confirmed Acute Case Definition

An individual (> 36 months of age) with:

1. A documented negative HCV antibody followed within 12 months by a positive HCV antibody test (anti-HCV test conversion) in the absence of a more likely diagnosis; **OR**
2. A documented negative HCV antibody or negative HCV detection test (in someone without a prior diagnosis of HCV infection) followed within 12 months by a positive HCV detection test (HCV RNA conversion) in the absence of a more likely diagnosis; **OR**
3. A positive nucleic acid test (NAT) for HCV RNA (including qualitative, quantitative or genotype testing) or a positive HCV core antigen test

#### **AND**

Jaundice or a peak elevated serum alanine aminotransferase (ALT) level >200 IU/L or peak elevated total bilirubin levels  $\geq$  3.0 mg/dL.

#### 3.2 Presumptive Acute Case Definition

An individual (> 36 months of age) with:

1. Jaundice or a peak elevated serum alanine aminotransferase (ALT) level >200 IU/L or peak elevated total bilirubin levels  $\geq$  3.0 mg/dL; **AND**
2. A positive anti-HCV antibody result; **AND**
3. No evidence of anti-HCV or HCV RNA test conversion.

(\*a new presumptive acute case may be reclassified as a confirmed acute case is a positive HCV viral detection test is reported in the same reporting year)

#### 3.3 Confirmed Chronic Case Definition

1. A positive nucleic acid test (NAT) for HCV RNA (including qualitative, quantitative or genotype testing); **AND**
2. No evidence of anti-HCV or RNA test conversion within 12 months; **AND**
3. No report of jaundice, elevated bilirubin or elevated ALT levels.

#### 3.4 Presumptive Chronic Case definition

1. A positive anti-HCV antibody test (includes rapid tests) but no report of a positive HCV NAT test; **AND**
2. No evidence of anti-HCV or RNA test conversion within 12 months; a **AND**
3. No report of jaundice, elevated bilirubin or elevated ALT levels.

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### 3.5 No Cases

Cases with a positive anti-HCV result followed by a negative HCV NAT test are not considered chronic carriers and should be marked as no cases.

### 3.6 Perinatal HCV Case definition

Any infant  $\geq 2$  months and  $\leq 36$  months of age with a positive HCV NAT test or detectable HCV genotype and is not known to have been exposed to HCV via a mechanism other than perinatal.

**Table 1. Quick reference table for case classification**

Test Result	Discrete onset of symptoms <sup>¶</sup> AND either jaundice or ALT >200 IU/L	
	YES	NO or UNKNOWN
HCV antibody (anti-HCV) Positive ONLY**	Acute, presumptive	Chronic, presumptive
Any HCV Nucleic Acid Test Positive <sup>§</sup>	Acute, confirmed	Chronic, confirmed

\*\*Any antibody result, regardless of signal-to-cutoff ratio; includes rapid tests.

§ Nucleic acid tests for HCV include: quantitative HCV RNA tests, qualitative HCV RNA tests and HCV genotype tests.

¶ If a case has 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, symptoms are *not* required. Classify these as acute, confirmed cases.

You can also refer to Appendix 1. Hepatitis C Case Definition FAQs for further clarification.

### 3.7 Confirm that the Case Requires Investigation

Positive reports received from laboratories only do not require further investigation (except for perinatal cases; see §3.8) although the patient information on the laboratory slip should be transmitted to PHD. Reports from clinicians' offices or emergency departments do require some follow-up to determine if the case is acute or chronic. Only unambiguously new HCV infections reported by a clinician or emergency department require a full investigation in Oregon. Typically, contacting the clinician or reviewing the emergency department note will allow you to answer the following questions. If the answer to all of the following three questions is yes, you need to interview the patient and complete a case investigation form.

1. Does the patient have acute hepatitis?

If so, the patient should have either jaundice, elevated bilirubin levels or ALT levels over 200 IU/L. If liver enzymes were not checked or not found to be high, refer case for confirmatory testing with their primary care provider if possible.

2. Can other causes of acute hepatitis be ruled out?

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Because of overlapping symptom manifestation for hepatitis A, B, and C (and alcohol-related hepatitis), it is important to rule out hepatitis A and hepatitis B.

### 3. Is it reasonable to conclude that HCV is the cause of the acute hepatitis?

This means evidence of HCV infection, either through positive EIA test or the presence of viral RNA. Note that false-positive EIA tests are common (up to 50% in low-risk populations). Antibody-negative patients can be retested in 6-9 months if there is concern about delayed seroconversion.

Only acute cases of hepatitis C require a full investigation and completion of the acute hepatitis C case report form. There is no test to determine acute infection. However, a positive HCV test result in a person  $\leq 30$  years of age may be more likely to represent an acute infection. In this case, PHD recommends further follow-up if time and resources permit. LHD should request liver function tests (LFTs) on any anti-HCV positive individual  $\leq 30$  years of age from the reporting laboratory. If the ALT levels are  $>200$  IU/L, LHD should contact the provider and determine the reason for testing in order to rule out acute infection. If the client experienced any signs and symptoms of acute viral hepatitis, the LHD should conduct the usual investigation for an acute case of HCV. Although not required, further investigation of cases for whom a positive laboratory report has been received is encouraged. When possible, such cases should be contacted and referred for confirmatory testing by their primary care physician and counseled about modes of transmission, means of reducing spread to others, alcohol cessation, and the need for hepatitis A and B vaccination.

### 3.8 Perinatal HCV follow up

When possible, in order to verify the infection source for an infant that has been reported as having evidence of HCV infection status, the HCV status of the mother should be determined.

### 3.9 Services Available at the Oregon State Public Health Laboratories

OSPHL uses a screening EIA test to assay sera for HCV antibodies. Sera are screened on request or when possibly infected samples test negative for HAV and HBV markers.

When the screening test result is reactive, follow-up testing is recommended for confirmation. Beginning February 1, 2020, the OSPHL will begin providing confirmatory testing by sending serum to the Florida Bureau of Public Health Laboratories for Hepatitis C NAAT viral load testing. Clinicians will no longer need to order this testing independent of the screening order. There is no fee for the confirmatory testing. At this time, this confirmatory service is grant funded and is conditional upon ongoing funding.

### 4. ROUTINE CASE INVESTIGATION

#### 4.1 Identify the Source of Infection

For acute HCV cases, ask about the 6 months prior to onset (although rarely, the incubation may be shorter or longer). Risk factors include:

- Parenteral drug use;
- Occupational or other needlestick injuries;
- Blood transfusion or receipt of immunoglobulins or other blood products;
- Other parenteral exposures including tattooing, ear piercing, organ or tissue transplant, dialysis, recent surgery or receipt of an injection at a doctor's office or clinic (notify the Acute and Communicable Disease [ACDP] on-call epidemiologist if you suspect the infection may be health care associated); or
- High-risk sexual contact (e.g., multiple partners, history of other STDs, etc.)

#### 4.2 Identify Potentially Exposed Persons

1. Determine if the case has donated blood or plasma in the three months prior to onset or any time thereafter. If so, notify the relevant blood bank or plasma center with particulars (date, etc.).
2. Identify persons who shared needles with the case or might have otherwise had contact with blood. Inform these contacts about the signs and symptoms of hepatitis C and the need for testing regardless of symptoms (since the majority of those acutely infected are asymptomatic).
3. Sexual and household contacts should be queried about recent signs and symptoms of hepatitis those with such a history should be referred for medical follow-up. Since the risk of transmission in these settings is low, testing is not automatically performed.

#### 4.3 Environmental Evaluation

None.

### 5. CONTROLLING FURTHER SPREAD

#### 5.1 Education

Cases should be counseled about the natural history of disease, modes of transmission and means of preventing further spread (e.g., if still injecting, they should not share needles or works; keep wounds and skin lesions covered; do not share razors or toothbrushes with anyone). HCV-positive persons with one long-term steady sex partner do not need to change their sexual practices, although they should discuss the risk of transmission with their partner. HCV-positive persons engaged in high-risk sexual activities should be counseled to use latex condoms correctly every time they have sex. Active injection drug users should be encouraged to stop injecting and referred drug rehabilitation services, including medication-assisted treatment. Since the risk of progression to cirrhosis is increased among heavy drinkers, cases should be advised to abstain from alcohol (or at least significantly reduce their intake). They should

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also be cautioned to ask their provider about use of over-the-counter drugs (e.g., acetaminophen) that could be hepatotoxic and advised of the need for hepatitis A and B vaccine (if negative for hepatitis A and B). If possible, they should be referred to a primary care provider for further follow-up.

### 5.2 Isolation and Work or Day Care Restrictions

Blood should be assumed infectious; standard precautions suffice for hospitalized patients. No occupational, school, or day-care restrictions are necessary for HCV-infected individuals.

### 5.3 Case Follow-up

None required. The majority (75-85%) of HCV-infected individuals become chronic carriers, and they should understand their elevated risk of long-term sequelae (chronic or recurrent hepatitis, cirrhosis, hepatocellular carcinoma).

### 5.4 Protection of Contacts

Not applicable.

### 5.5 Environmental Measures

Ensure that surfaces and objects contaminated with blood are properly disinfected using gloves and appropriate disinfectant solutions.

## 6. MANAGING SPECIAL SITUATIONS <sup>4</sup>

### 6.1 Needlesticks and Similar Exposures

The risk of HCV transmission to a health care worker or similar stick is approximately 2%. Current CDC guidelines recommend an HCV antibody test and ALT level at baseline and at 6 months to capture the full seroconversion time-window. Infection can be usually detected within 2 weeks by PCR. Risk for HIV and hepatitis B virus should also be assessed using current CDC guidelines.

### 6.2 Possible Healthcare-Associated Infections.

Particularly in patients without the usual behavioral risk factors associated with the acquisition of HCV, further questioning into possible healthcare exposures should be pursued. Contact the on-call epidemiologist at 971.673.1111 if you suspect a healthcare-associated infection.

### 6.3 Common Source Outbreak Suspected

On-the-job, scene of an accident, or in-home blood-to-blood transfers place a person at risk. In the case of any other unusual possible infection occurrences, consult with ACDP epidemiologists.

## 7. GLOSSARY OF TERMS

**ALT/AST:** these are both liver enzymes classified as serum aminotransferases or transaminases and are useful indicators of liver damage. Alanine

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aminotransferase is usually abbreviated as ALT (or SGOT) and is particularly sensitive for assessing liver damage secondary to HCV. Aspartate aminotransferase is referred to as AST (or SGPT).

**Anti-HCV EIA:** enzyme immunoassay to measure HCV antibody. Indicates presence of antibody only and cannot be used to distinguish between recent and past infection. Additional testing is required to determine if the individual is chronically infected.

**HBsAg:** hepatitis B surface antigen, a marker of replicating virus. It occurs as part of acute infection and persists in chronic infection. Its presence indicates that the patient is considered to be infectious.

**HBeAg:** hepatitis B e antigen, a core protein exported from infected liver cells and a marker of high levels of infectivity. Similar to HBsAg, it occurs (albeit transiently) as part of acute infection and may persist in the chronic carrier state.

**HBeAb:** hepatitis B e antibody is produced by the immune system temporarily during acute HBV infection and may persist in chronic infections. Spontaneous conversion from e antigen to e antibody (a change known as seroconversion) is a predictor of long-term clearance of HBV in patients undergoing antiviral therapy and indicates lower levels of HBV. Chronic hepatitis B surface antigen carriers can be positive for either HBeAg or anti-HBe, but are less infectious when anti-HBe is present.

**HBV DNA:** signifies active replication of the virus and indicates that the patient is infectious. It is usually measured to test for chronic infection, and the viral load may be used to decide whether treatment is warranted.

**HCV genotype:** HCV can be divided into at least 6 different genotypes. Genotype 1 is the most common in the US, accounting for 70%-75% of infections.

**IgM anti-HAV:** IgM antibody to HAV. Indicates acute infection with HAV.

**IgM Anti-HBc:** IgM antibody to hepatitis B core antigen, indicative of recent infection with HBV. Antibody to core antigen only occurs following infection, not immunization.

**RIBA:** recombinant immunoblot assay, a more specific test for anti-HCV antibody (in other words, it's good for ruling out false positives). It is not as sensitive as the anti-HCV EIA and should not be used as an initial screening test, but it is useful for ruling out false-positive EIA tests. **This test is no longer available.**

**PCR (i.e., Nucleic Acid Test [NAT]):** polymerase chain reaction, used to measure HCV RNA and indicates active replication of the virus (e.g., the chronic carrier state). The qualitative PCR is more sensitive than the quantitative assay and is preferred for the initial test. The quantitative PCR is often used to guide initial treatment decisions and to follow the progress of individuals undergoing treatment.

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**Signal-cutoff ratio:** can be used to help determine the likelihood that a positive anti-HCV EIA represents a true positive. Each assay has a cut-off value that is considered a “positive” result; the signal-cutoff ratio can be calculated by dividing the optical density (OD) value of the sample being tested (e.g., the client’s test result) by that particular assay’s cut-off value. Due to the increase in hepatitis C assays available on the market, CDC is unable to validate each test to determine the s/co ratio predictive of a true positive. **As of January 1, 2016, the s/co ratio will no longer be used in the acute or chronic hepatitis C case definitions.**

### CASE DEFINITION FAQs

1. What do I do with a chronic case that has a +anti-HCV and a subsequent negative RNA test?
  - a. If a case has a +anti-HCV and the subsequent negative RNA is within 12 months – change to a no case
  - b. If the negative RNA is >12 months, leave the case “as is,” which is a presumptive case.
2. What do I do with chronic cases that only have a +anti-HCV test but with a low signal to cutoff (s/co) ratio?
  - a. The signal to cutoff ratio is no longer being considered in any case definition for hepatitis C. These cases should be classified as “presumptive”.
3. What do I do when I get a new +anti-HCV lab for an existing chronic case? Case already had a +anti-HCV lab with no s/co ratio and so had previously been given status “suspect” under the old case definition?
  - a. Change classification to “presumptive”.
4. What do I do when I get a new +anti-HCV lab for an existing chronic case? Case already had a +anti-HCV lab with a predictive s/co ratio and so had previously been given status “confirmed”?
  - a. Leave case as is.
5. What do I do when I get a new HCV RNA lab for an existing chronic case? Case already had a +anti-HCV lab with no s/co ratio and so had previously been given status “suspect”?
  - a. Change to “confirmed”.
6. What do I do when I have an acute case (either confirmed or presumptive) and receive a subsequent positive RNA or antigen test?
  - a. If the result is within 12 months – simply add to the acute case and reclassify as confirmed acute if previously presumptive.
  - b. If the result is >12 months after the onset of symptoms– create a new chronic case.
7. What do I do when I have an acute case (either confirmed or presumptive) and receive a subsequent negative RNA or antigen test?
  - a. Nothing.

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### REFERENCES

1. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Int Medicine* 2014;160:293-300.
2. Nyalakonda H and Utay NS. A new era of therapy for hepatitis C virus infection. *Curr Opin Infect Dis* 2015;28:471-8.

### UPDATE LOG

- January 2020 – Updated case definition. Removed the requirement for the presence of a discrete onset of symptoms for acute cases; added use of bilirubin test results for case classification. Added new NAAT confirmatory testing available at the OSPHL as of February 1, 2020. (Tasha Poissant).
- January 2018 – Added perinatal case definition. (Tasha Poissant)
- April 2016 – Added case definition FAQs. (Tasha Poissant)
- January 2016 – Updated case definition. Removed criteria for s/co ratio; removed Table 1. Seroconversion time frame now goes back 12 months. Updated treatment section. (Tasha Poissant)
- July 2014 – Updated Table 1. Added Kaiser/OHSU to list of labs that do not report s/co value but all positive reports are above s/co ratio predictive of a true positive. Added new lab - CDD.
- December 2013 – Removed RIBA confirmatory test from guidelines as it is no longer available. Removed statement that OHA will request LFTs on positive persons <30 years of age. Recommended that LHDs perform this follow-up. (Poissant)
- January 2013 – Updated Table 1, s/co ratio. Moved Samaritan Lebanon Community Hospital from the “Abbott Assym” to Abbot Architect. (Cunningham)
- October 2012 – Inserted reference to CDC screening guidelines for 1945-1965 birth cohort and updated Table 1 (s/co ratio). (Cunningham)
- March 2012 – Removed “3.3 4. previously reported as acute HCV (or presumptive chronic HCV) with a subsequent positive RIBA, PCR or genotype result >6 months later.” from confirmed chronic case definition in order to follow CDC/CSTE guidelines. (Poissant)
- January 2012 – Updated case classifications per CDC/CSTE guidelines. Asymptomatic seroconverters may now be classified as confirmed acute cases. Presumptive chronic cases must have elevated ALTs to meet the case definition. Added suspect case definition. Updated assay and s/co ratio for Interpath Laboratory and Legacy. Updated labs that may not report the s/co ratio. (Poissant)

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September 2011 – Updated anti-HCV assay and s/co ratio for Salem Hospital laboratory. Updated new treatment therapies. Updated acute case classification for clarity. (Poissant)

November 2010 – Updated age guidelines for anti-HCV testing for infants born to HCV-positive women per CDC, the American Association for the Study of Liver Disease and the American Academy of Pediatrics. (Van Ness)

April 2010 – Added guidelines for anti-HCV testing for infants born to HCV-positive women, per CDC guidelines.

October 2008 – Updated Table 1 “Signal cut off ration of HCV screen tests used by Oregon laboratories. November 2008. Added details on OPHD requesting LFTs for for anti-HCV+ people <30. Updated case definition: acute cases with positive PCR/genotype results >6 months later should be reported as chronic.

May 2007 – Updated case definition to reflect CSTE changes. Added Glossary of Terms for hepatitis serologies.