Hepatitis

Conditions that Cause Hepatitis in Humans

Hepatitis Viruses

Nonviral Infectious Agents

Hepatitis A virus

Pneumococcal pneumonia

Hepatitis B virus

Leptospirosis

Hepatitis C virus

Syphilis

Hepatitis D virus

Coxiella burnetti

Hepatitis E virus

Toxoplasmosis

Other Viruses

Noninfections

Epstein-Barr virus

Alcohol

Human immunodeficiency virus

Medications

Lassa fever virus

Dilantin

Yellow fever virus

Isoniazid

Adenovirus

Ritonavir

Herpes simplex virus

Chlorpromazine

Human herpes-6 virus

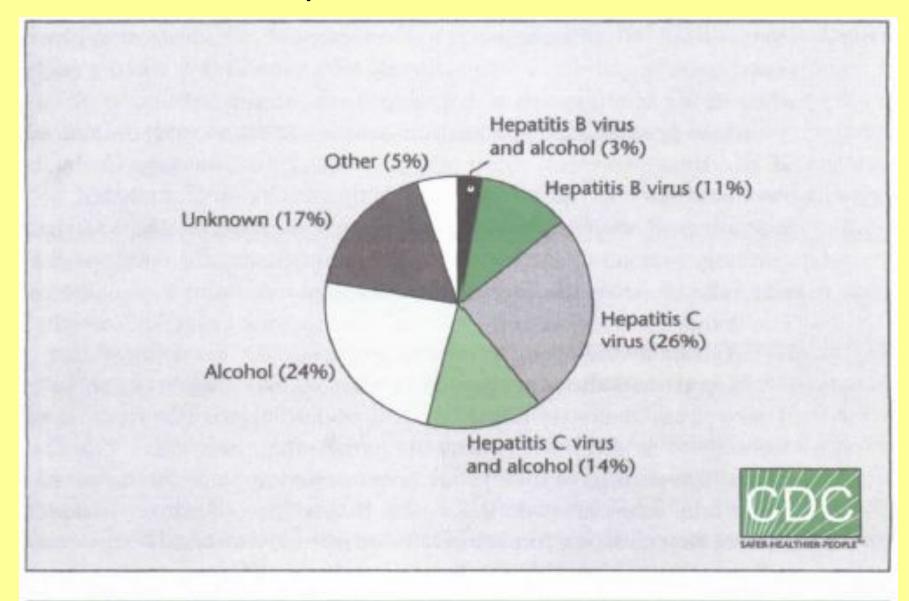
Rifampin, etc.

Ebola virus

Anesthesia (halothane)

Nelson KE, Thomas DL. Viral hepatitis. In *Infectious Disease Epidemiology*, 2nd ed., Nelson KE, Williams CM (eds). Jones & Bartlett, Sudbury MA, 2007; p. 896.

Primary causes of chronic liver disease



Note: Based on data for Jefferson County, Alabama.

Source: CDC/NCID.

Hepatitis (Liver-Attacking) Viruses

<u>Hepatitis A</u> – fecal/oral, contaminated food, vaccine available

<u>Hepatitis B</u> – blood, semen, vertical (mother-child), vaccine available

<u>Hepatitis C</u> – blood (IV drug use, transfusion, organ donation, unsterile injecting equipment, sexual intercourse)

<u>Hepatitis D</u> – survives only in cells co-infected with hepatitis B

<u>Hepatitis E</u>* – contaminated food or water, fecal/oral

*causes short-term disease and is not a chronic carrier state

Characteristics of Hepatitis Viruses

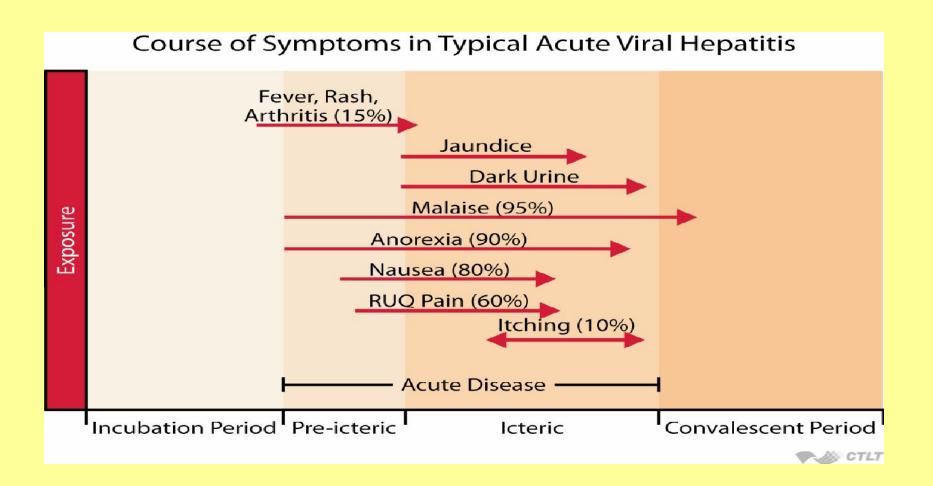
<u>Virus</u>	Nucleic Acid	Routes of Transmission	Mortality	Risk of Chronic Illness
HAV	Unenveloped single- stranded RNA	Fecal-oral	Low	None
HBV	Enveloped double- stranded DNA	Parenteral (sex, perinatal)	Moderate-high	High
HCV	Enveloped single- stranded RNA	Parenteral (sex, perinatal)	Moderate-high	High
HDV	Enveloped single- stranded RNA	Parenteral (sex)	High	High
HEV	Unenveloped single- stranded RNA	Fecal-oral	Low-moderate	None

Nelson KE, Thomas DL. Viral hepatitis. In *Infectious Disease Epidemiology*, 2nd ed., Nelson KE, Williams CM (eds). Jones & Bartlett, Sudbury MA, 2007; p. 898.

Viral Hepatitis

- When they occur, the signs and symptoms of viral hepatitis can include:
 - Fever
 - Fatigue
 - Loss of appetite
 - Nausea
 - Vomiting
 - Abdominal pain
 - Jaundice
 - Dark urine
 - Clay-colored stool
 - Joint pain

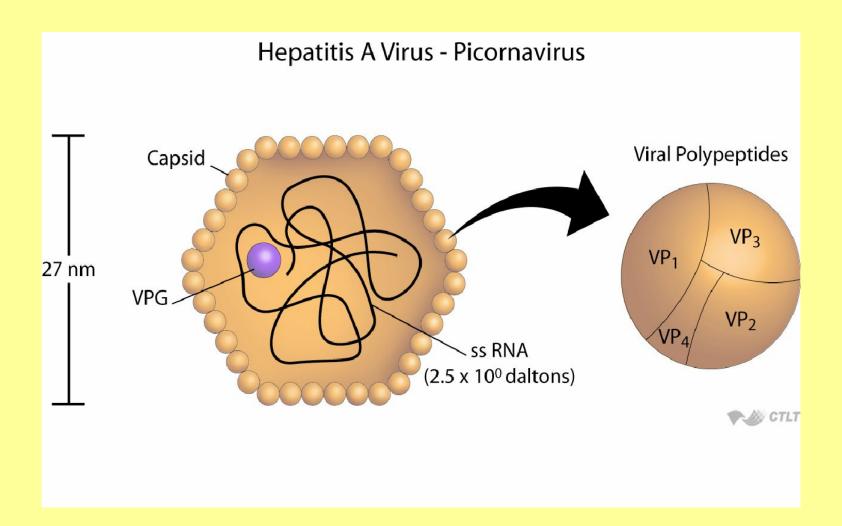
Viral Hepatitis



Viral Hepatitis

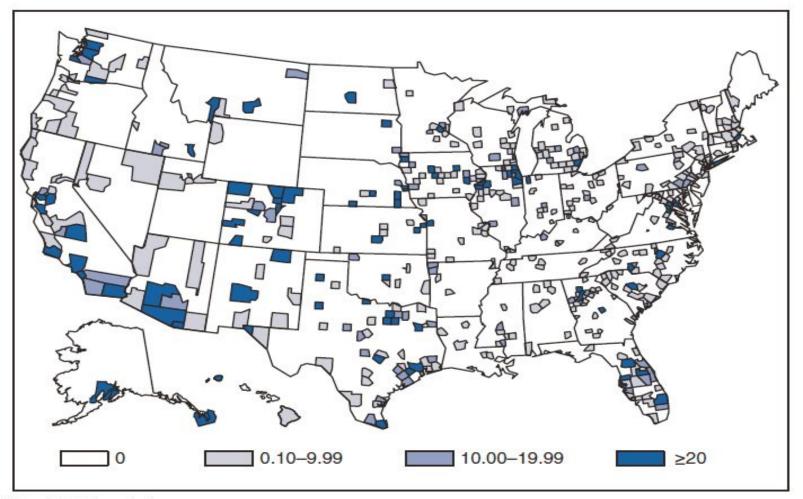
- Viral hepatitis is the leading cause of liver cancer and the most common reason for liver transplantation
- In the United States, an estimated 1.2 million Americans are living with chronic Hepatitis B and 3.2 are living with chronic Hepatitis C
 - Many do not know they are infected
- Each year an estimated 21,000 persons become infected with Hepatitis A; 35,000 with Hepatitis B, and 17,000 with Hepatitis C

Hepatitis A



Hepatitis A Epidemiology

Hepatitis A. Incidence,* by county --- United States, 2009



^{*} Per 100,000 population.

Hepatitis A Epidemiology



Prevalence of antibody to hepatitis A virus, 2010

Source: CDC YellowBook

Hepatitis A

- Hepatitis A has an incubation period of approximately 28 days (range: 15–50 days)
- HAV replicates in the liver and is shed in high concentrations in feces from 2 weeks before to 1 week after the onset of clinical illness
- HAV infection produces a self-limited disease that does not result in chronic infection or chronic liver disease
- Humans are the only natural host

Hepatitis A Features

Incubation period: 28-30 days

Symptoms: None (especially children <5 years old)

Fever

Malaise

Anorexia

Nausea

Jaundice

Fulminant → death (acute)

Likelihood of clinical disease increases with age

Duration: 25-30 days

Hepatitis A Acute Illness

- In children aged <6 years, 70% of infections are asymptomatic; if illness does occur, it is typically not accompanied by jaundice.
- Among older children and adults, infection is typically symptomatic, with jaundice occurring in >70% of patients.
- Symptoms usually last less than 2 months, although 10%–15% of symptomatic persons have prolonged or relapsing disease for up to 6 months.

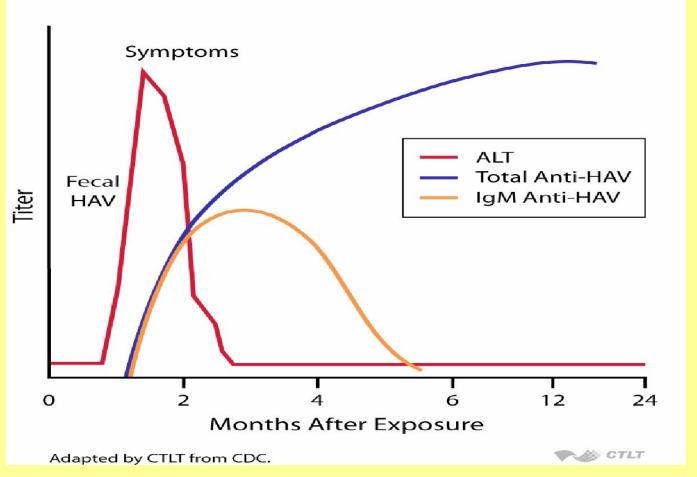
Diagnosis, Treatment & Reservoir of Hepatitis A

<u>Diagnosis</u>: Anti-IgM detectable 5-10 days before symptoms; disappears by six months
Anti-IgG – convalescent, life-long, confers protection

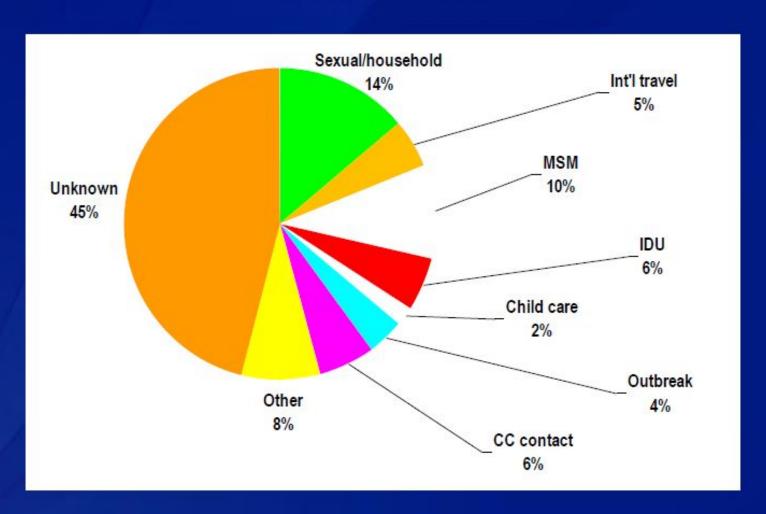
Treatment: Supportive

Hepatitis A Diagnosis

Hepatitis A Virus Infection; Typical Serologic Course



Hepatitis A—United States, 1990-2000 Risk Factors



Transmission & Risk Groups for Hepatitis A

Transmission: fecal-oral, contaminated food, water, sexual

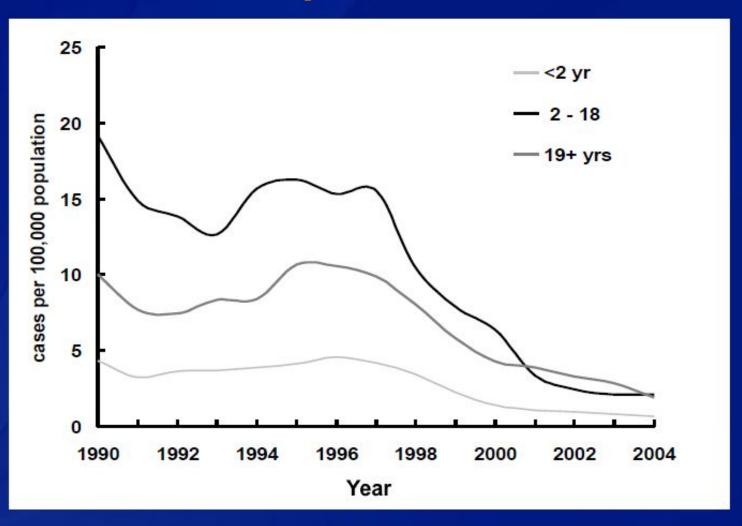
Risk groups: international travellers, MSM, child care-givers, persons with chronic liver disease, injection drug users

<u>Period of communicability</u>: 1-2 weeks before symptoms, to one week after onset of jaundice

Endemic areas: Central & South America, Middle East, Asia, and western Pacific

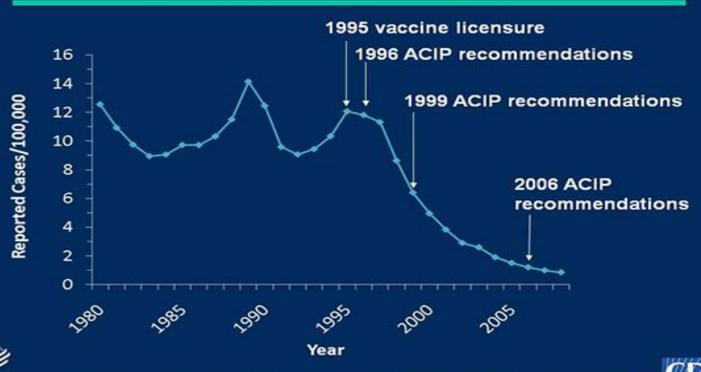
Reservoir: Humans

Hepatitis A Incidence By Age Group, 1990-2004



Hepatitis A Epidemiology









Hepatitis A Vaccines

- Inactivated whole virus vaccines
- Pediatric and adult formulations
 - pediatric formulations approved for persons 12 months through 18 years
 - adult formulations approved for persons 19 years and older

Hepatitis A Vaccine Immunogenicity

Adults

- >95% seropositive after one dose
- 100% seropositive after two doses
- Children (>12 months) and Adolescents
 - >97% seropositive after one
 - 100% seropositive after 2 doses

ACIP Recommendation for Routine Hepatitis A Vaccination of Children

- All children should receive hepatitis A vaccine at 12-23 months of age
- Vaccination should be integrated into the routine childhood vaccination schedule
- Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits

Hepatitis A Vaccine Recommendations

- International travelers
- Close contact with an international adoptee from a country of high or intermediate endemicity
- Men who have sex with men
- Persons who use illegal drugs
- Persons who have a clotting factor disorder
- Persons with occupational risk
- Persons with chronic liver disease

Hepatitis A Postexposure Prophylaxis

- For healthy persons 12 months through 40 years of age:
 - single-antigen hepatitis A vaccine should be administered as soon as possible after exposure
- For persons older than 40 years:
 - immune globulin is preferred
 - vaccine can be used if IG cannot be obtained

Hepatitis A Prevention

- Hepatitis A vaccine is the best protection.
- Good sanitation measures are essential for preventing environmental contamination.
- Good personal hygiene is also essential for prevention and control including:
 - Hand washing with soap:
 - After using the bathroom
 - After changing a diaper
 - Before preparing and eating food

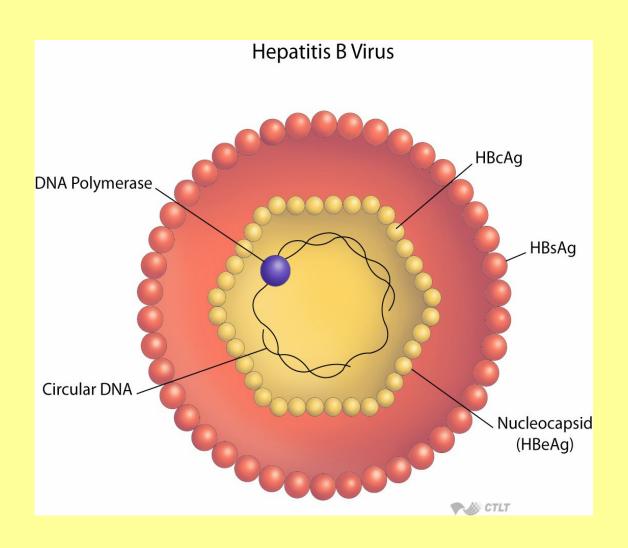
Hepatitis B

- Hepatitis B is caused by infection with the Hepatitis B virus (HBV), the prototype member of the hepadnavirus family
 - HBV is the only human representative of this family.
 - It has a circular DNA genome of 3.2 kb
- Currently, eight genotypes (A-H) are identified by a divergence of >8% in the entire genome

Hepatitis B Characteristics

- A Hepadnaviridae partially double-stranded DNA virus
- HBsAg stimulates protective antibodies, a marker for current infection
- HBcAg localized within liver cells, identifies acute infection, anti-HBcAg persists for life and is a marker of past infection
- HBeAG a marker of active replication and infectivity

Hepatitis B



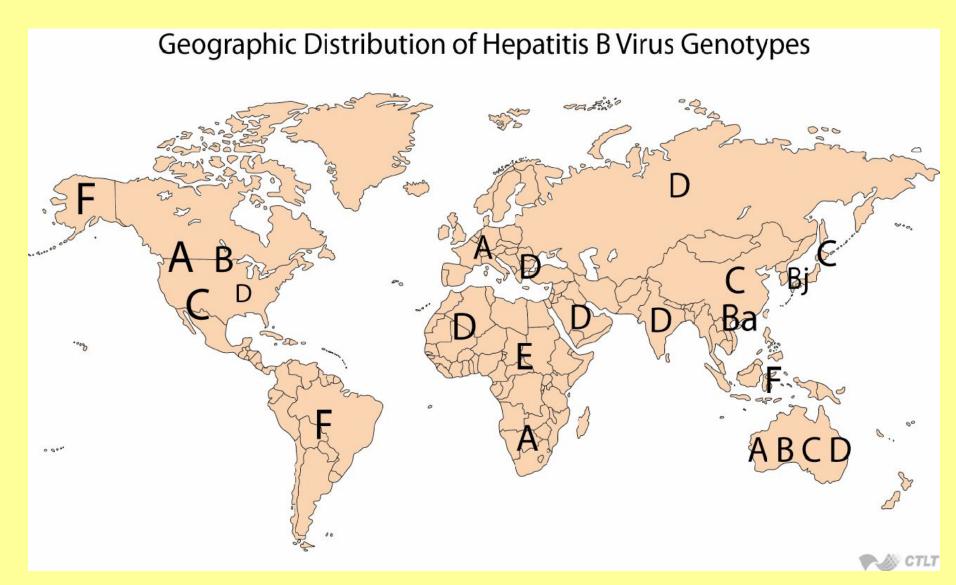
Hepatitis B Virus

- Hepadnaviridae family (DNA)
- Numerous antigenic components
- Humans are only known host
- May retain infectivity for more than 7 days at room temperature

Hepatitis B Virus Infection

- More than 350 million chronically infected worldwide
- Established cause of chronic hepatitis and cirrhosis
- Human carcinogen—cause of up to 80% of hepatocellular carcinomas
- More than 600,000 deaths worldwide in 2002

Hepatitis B



Source: J Viral Hepat. 2010 Apr;17(4):229-35. Hepatitis B virus: origin and evolution.

Hepatitis B Epidemiology

- Worldwide, HBV is the primary cause of liver cancer
 - For males, it is the third leading cause of cancer mortality
 - For females, it is the sixth leading cause of cancer mortality

Hepatitis B Epidemiology

- An estimated 800,000–1.4 million persons in the United States have chronic HBV infection.
- Chronic infection is an even greater problem globally, affecting approximately 350 million persons.
- An estimated 620,000 persons worldwide die from HBV-related liver disease each year.

Hepatitis B Epidemiology

- The incubation period from the time of exposure to onset of symptoms is 6 weeks to 6 months.
- HBV is found in highest concentrations in blood and in lower concentrations in other body fluids (e.g., semen, vaginal secretions, and wound exudates).
- HBV infection can be self-limited or chronic.

Hepatitis B

In adults, only approximately half of newly acquired HBV infections are symptomatic, and approximately 1% of reported cases result in acute liver failure and death.

- Hepatitis B is detected by looking for a number of different antigens and antibodies:
 - Hepatitis B surface antigen (HBsAg):
 - A protein on the surface of HBV; it can be detected in high levels in serum during acute or chronic HBV infection.
 - The presence of HBsAg indicates that the person is infectious.
 - The body normally produces antibodies to HBsAg as part of the normal immune response to infection.
 - HBsAg is the antigen used to make Hepatitis B vaccine.

- Hepatitis B is detected by looking for a number of different antigens and antibodies:
 - Hepatitis B surface antibody (anti-HBs):
 - The presence of anti-HBs is generally interpreted as indicating recovery and immunity from HBV infection.
 - Anti-HBs also develops in a person who has been successfully vaccinated against Hepatitis B.
 - Total Hepatitis B core antibody (anti-HBc):
 - Appears at the onset of symptoms in acute Hepatitis B and persists for life.
 - The presence of anti-HBc indicates previous or ongoing infection with HBV in an undefined time frame.

- Hepatitis B is detected by looking for a number of different antigens and antibodies:
 - IgM antibody to Hepatitis B core antigen (IgM anti-HBc):
 - Positivity indicates recent infection with HBV (≤6 months).
 - Its presence indicates acute infection.
 - Hepatitis B e antigen (HBeAg):
 - A secreted product of the nucleocapsid gene of HBV that is found in serum during acute and chronic Hepatitis B.
 - Its presence indicates that the virus is replicating and the infected person has high levels of HBV.

- Hepatitis B is detected by looking for a number of different antigens and antibodies:
 - Hepatitis B e antibody (HBeAb or anti-HBe):
 - Produced by the immune system temporarily during acute HBV infection or consistently during or after a burst in viral replication.
 - 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.

Hepatitis B

Typical interpretation of serologic test results for hepatitis B virus infection

Serologic Marker				Interpretation
HBs Ag ¹	Total anti-HBc ²	IgM ³ anti-HBc	Anti-Hbs ⁴	
_5	-	-	_	Never infected
₊ 6,7	-	-	_	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	_	Acute infection
1000 E	+	+	+ or —	Acute resolving infection
<u></u>	+	_	+	Recovered from past infection and immune
+	+	-	_	Chronic infection
_	+	_	_	False-positive (i.e., susceptible); past infection; "low-level" chronic infection; 8 or passive transfer of anti-HBc to infant born to HBsAgpositive mother
_	_	2	+	Immune if concentration is ≥10 mIU/mL after vaccine series completion; ⁹ passive transfer after hepatitis B immune globulin administration

Source: MMWR Recomm Rep. 2006; 55(RR-16):1-25.

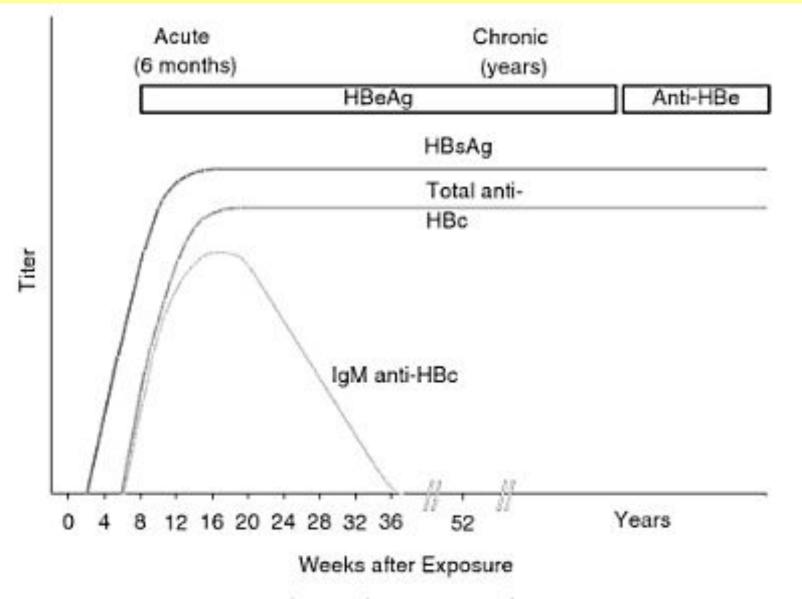


FIGURE 22-8 Progression to chronic hepatitis B infection.

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

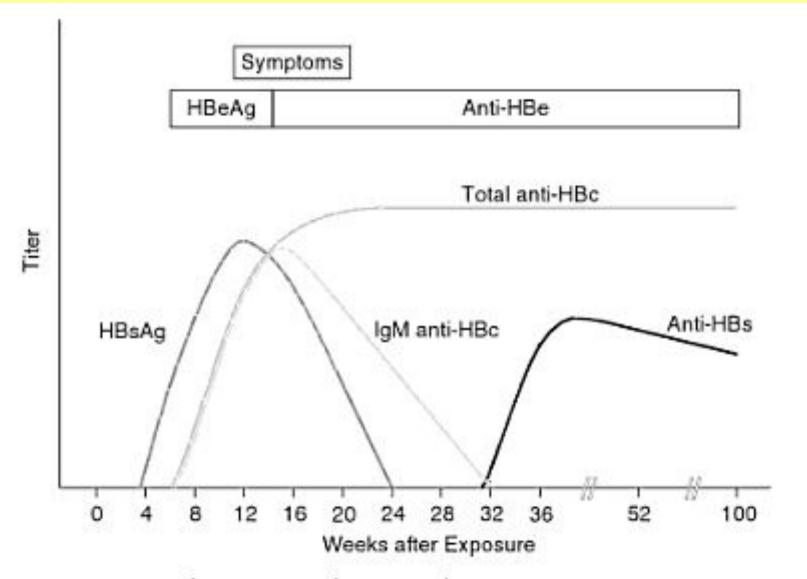
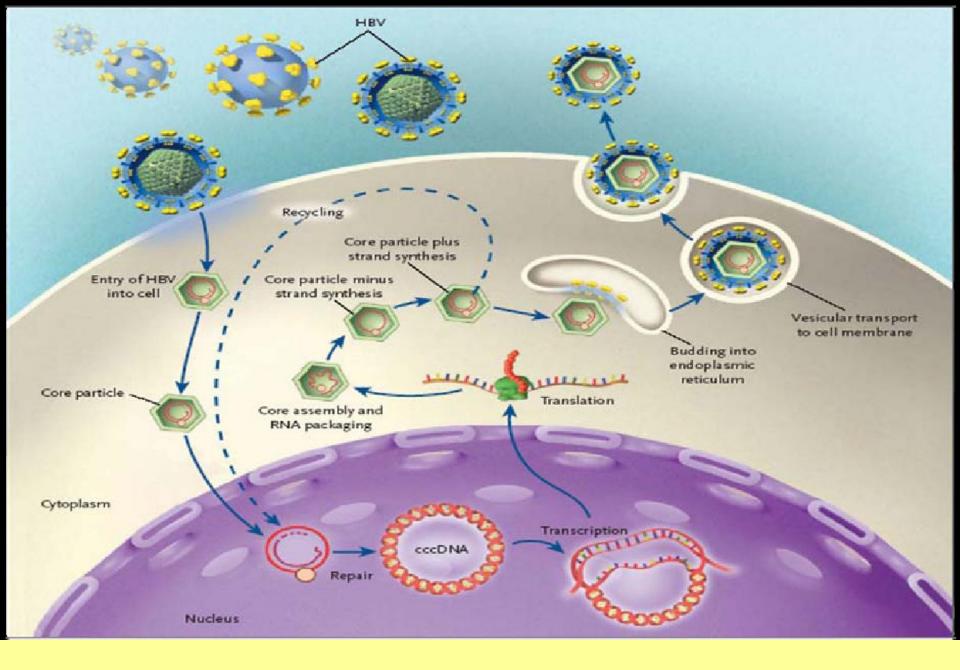


FIGURE 22-9 Acute hepatitis B infection with recovery.

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



Source: Ganem, D., et al. (2004). N Engl J Med.

Hepatitis B Clinical Features

- Incubation period 45-160 days (average 120 days)
- Nonspecific prodrome of malaise, fever, headache, myalgia
- Illness not specific for hepatitis B
- At least 50% of infections asymptomatic

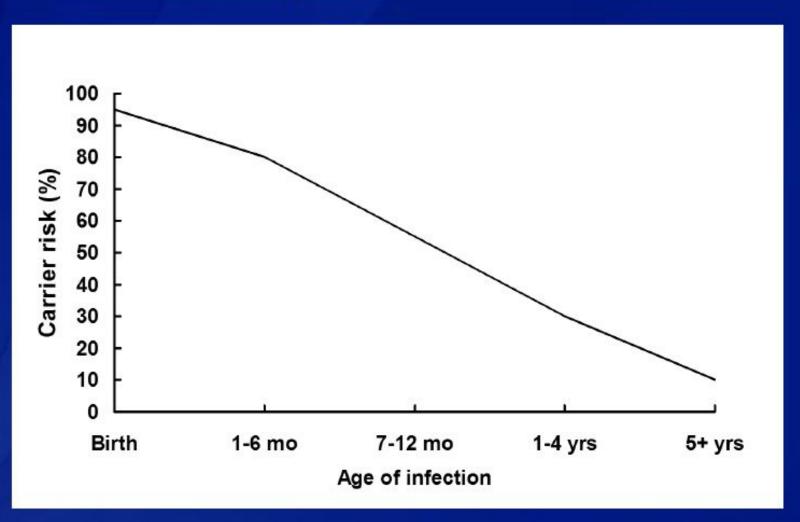
Hepatitis B Complications

- Fulminant hepatitis
- Hospitalization
- Cirrhosis
- Hepatocellular carcinoma
- Death

Chronic Hepatitis B Virus Infection

- Chronic viremia
- Responsible for most mortality
- Overall risk 5%
- Higher risk with early infection

Risk of Chronic HBV Carriage by Age of Infection



Hepatitis B Epidemiology

Reservoir Human

Transmission Bloodborne Asymptomatic

infections transmit

Communicability 1-2 months before

and after onset of

symptoms

Chronic infection

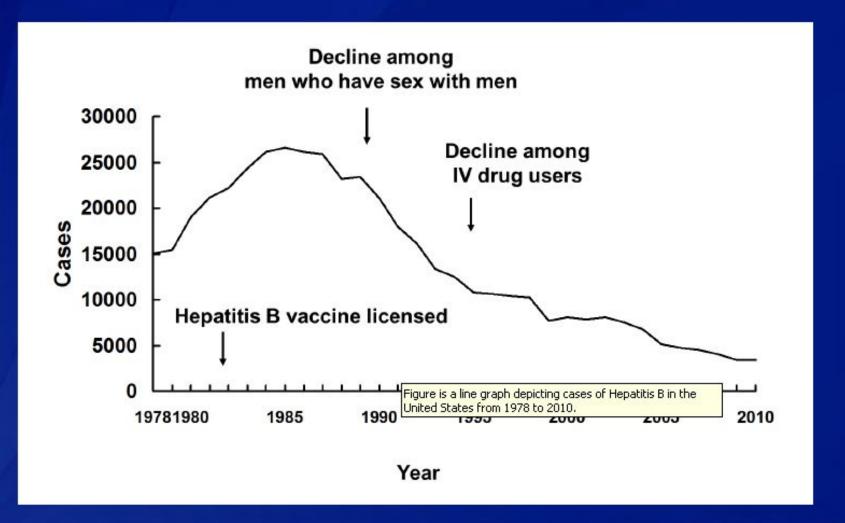
Hepatitis B Perinatal Transmission*

- If mother positive for HBsAg and HBeAg
 - 70%-90% of infants infected
 - 90% of infected infants become chronically infected
- If positive for HBsAg only
 - 5%-20% of infants infected
 - 90% of infected infants become chronically infected

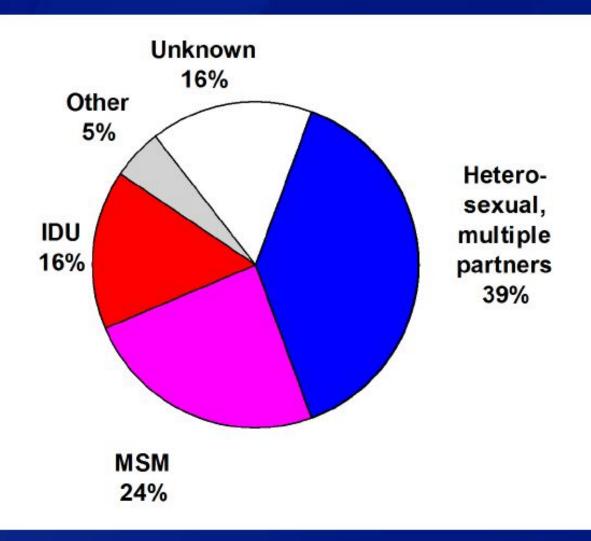
Global Patterns of Chronic HBV Infection

- High (>8%): 45% of global population
 - lifetime risk of infection >60%
 - early childhood infections common
- Intermediate (2%-7%): 43% of global population
 - lifetime risk of infection 20%-60%
 - infections occur in all age groups
- Low (<2%): 12% of global population</p>
 - lifetime risk of infection <20%</p>
 - most infections occur in adult risk groups

Hepatitis B—United States, 1978-2010



Risk Factors for Hepatitis B



Adults at Risk for HBV Infection

Sexual exposure

- sex partners of HBsAg-positive persons
- sexually active persons not in a long-term, mutually monogamous relationship*
- persons seeking evaluation or treatment for a sexually transmitted disease
- men who have sex with men

^{*} persons with more than one sex partner during the previous 6 months

Adults at Risk for HBV Infection

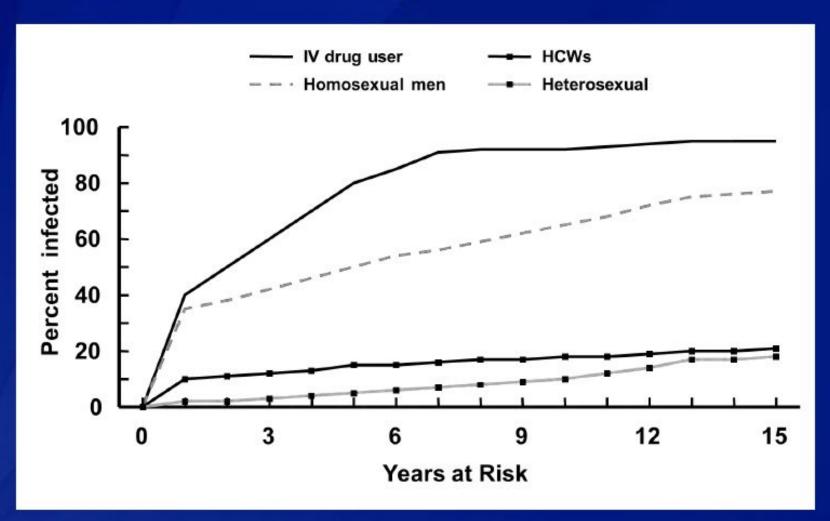
- Percutaneous or mucosal exposure to blood
 - current or recent IDU
 - household contacts of HBsAg-positive persons
 - residents and staff of facilities for developmentally disabled persons
 - healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids
 - persons with end-stage renal disease
 - persons with diabetes mellitus

Adults at Risk for HBV Infection

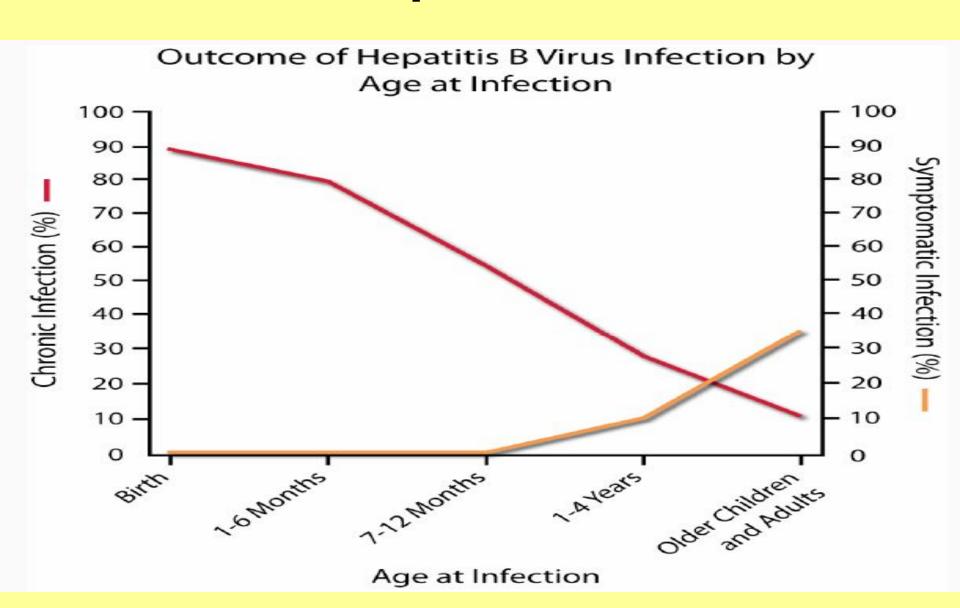
Others groups

- international travelers to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection
- persons with HIV infection

Hepatitis B Virus Infection by Duration of High-Risk Behavior



Hepatitis B



Hepatitis B Treatment

- For acute infection, no medication is available; treatment is supportive.
- For chronic infection, several antiviral drugs (adefovir dipivoxil, interferon alfa-2b, pegylated interferon alfa-2a, lamivudine, entecavir, and telbivudine) are available.
 - Persons with chronic HBV infection require medical evaluation and regular monitoring to determine whether disease is progressing and to identify liver damage or hepatocellular carcinoma.

Hepatitis B Elimination

- CDC's national strategy to eliminate transmission of HBV infection includes:
 - Prevention of perinatal infection through routine screening of all pregnant women for HBsAg and immunoprophylaxis of infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status
 - Routine infant vaccination
 - Vaccination of previously unvaccinated children and adolescents through age 18 years
 - Vaccination of previously unvaccinated adults at increased risk for infection

Hepatitis B Vaccine

Composition Recombinant HBsAg

Efficacy 95% (Range, 80%-100%)

Duration of Immunity

20 years or more

Schedule 3 Doses

Booster doses not routinely recommended

Protection* by Age Group and Dose

Dose	Infants**	Teen and Adults***	
1	16% - 40%	20%-30%	
2	80%-95%	75%-80%	
3	98%-100%	90%-95%	

- * Anti-HBs antibody titer of 10 mIU/mL or higher
- ** Preterm infants less than 2 kg have been shown to respond to vaccination less often
- *** Factors that may lower vaccine response rates are age older than 40 years, male gender, smoking, obesity, and immune deficiency

Hepatitis B Vaccine Long-term Efficacy

- Immunologic memory established following vaccination
- Exposure to HBV results in anamnestic anti-HBs response
- Chronic infection rarely documented among vaccine responders

Hepatitis B Vaccine Routine Infant Schedule

Dose+	Usual Age	Minimum Interval	
Primary 1	Birth		
Primary 2	1-2 months	4 weeks	
Primary 3	6-18 months*	8 weeks**	

+an additional dose at 4 months is acceptable if the clinician prefers to use a combination vaccine that contains hepatitis B vaccine

^{*} infants who mothers are HBsAg+ or whose HBsAg status is unknown should receive the third dose at 6 months of age

^{**} at least 16 weeks after the first dose

Hepatitis C

- Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States; approximately 3.2 million persons are chronically infected
- By contrast to Chronic HBV, patients with chronic hepatitis C almost always develop HCC in the presence of established cirrhosis
- The annual risk of HCC development in HCV patients with cirrhosis is in the range of 1–4%, and an estimated 1–3% of patients chronically infected with HCV will develop HCC after 30 years

Hepatitis C Characterisitcs

- Flavivirus small, enveloped, single-stranded RNA virus, six genotypes
- Replicates in liver cells, lymphocytes and monocytes
- Replicates >1 trillion progeny per day
- Mutates rapidly (error-prone RNA polymerase)
- Down-regulates stimulatory receptors on NK cells
- Increases inhibitory receptors on NK and CD8+ killer cells
- Produces TGF-beta, which blocks activation of T cells and inhibits production of IFN-gamma

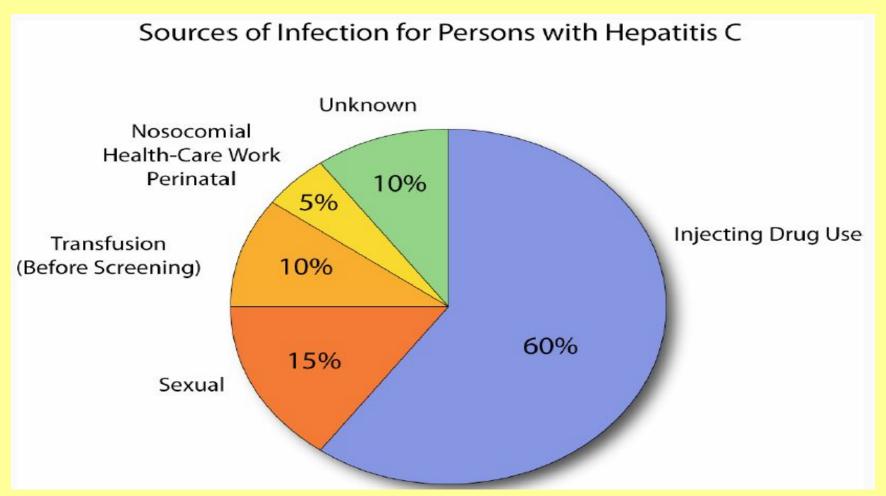
Hepatitis C Epidemiology

- Transmission of HCV occurs through:
 - Percutaneous
 - Injecting drug use
 - Clotting factors before viral inactivation
 - Transfusion, transplant from infected donor
 - Therapeutic (contaminated equipment, unsafe injection practices)
 - Occupational (needlestick)
 - Permucosal
 - Perinatal
 - Sexual

Hepatitis C Epidemiology

- The following persons are at known to be at increased risk for HCV infection:
 - Current or former injection drug users, including those who injected only once many years ago
 - Recipients of clotting factor concentrates made before 1987, when more advanced methods for manufacturing those products were developed
 - Recipients of blood transfusions or solid organ transplants before July 1992, when better testing of blood donors became available
 - Chronic hemodialysis patients
 - Persons with HIV infection
 - Children born to HCV-positive mothers

Hepatitis C Epidemiology

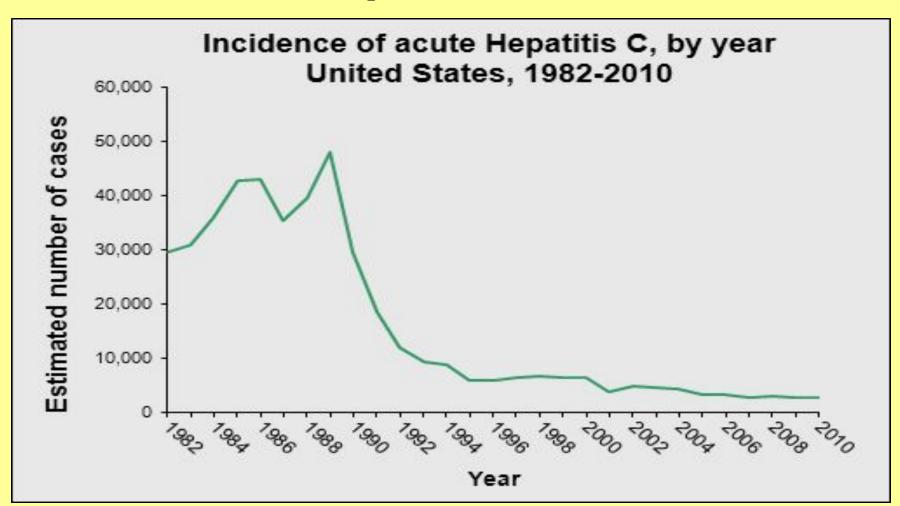


Source: CDC DVH

Hepatitis C

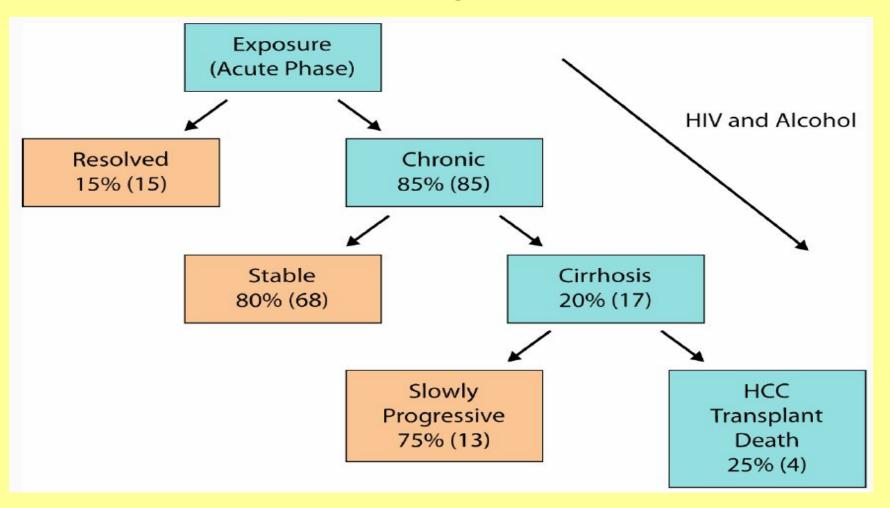
- Although only 850 cases of confirmed acute
 Hepatitis C were reported in the United States
 in 2010, CDC estimates that approximately
 16,000 new HCV infections occurred that
 year, after adjusting for asymptomatic
 infection and underreporting.
- Persons newly infected with HCV are usually asymptomatic, so acute Hepatitis C is rarely identified or reported.

Hepatitis C



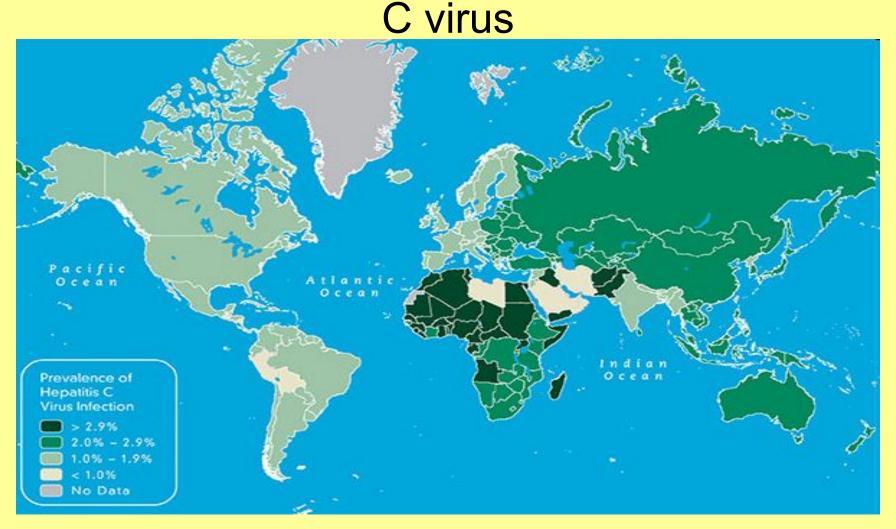
Source: CDC DVH

Hepatitis C Natural History of Infection



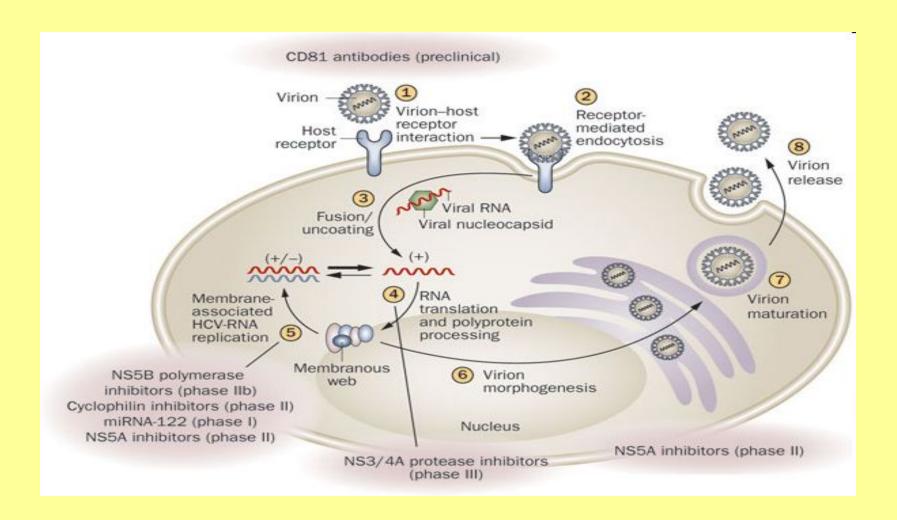
Hepatitis C

Prevalence of chronic infection with hepatitis



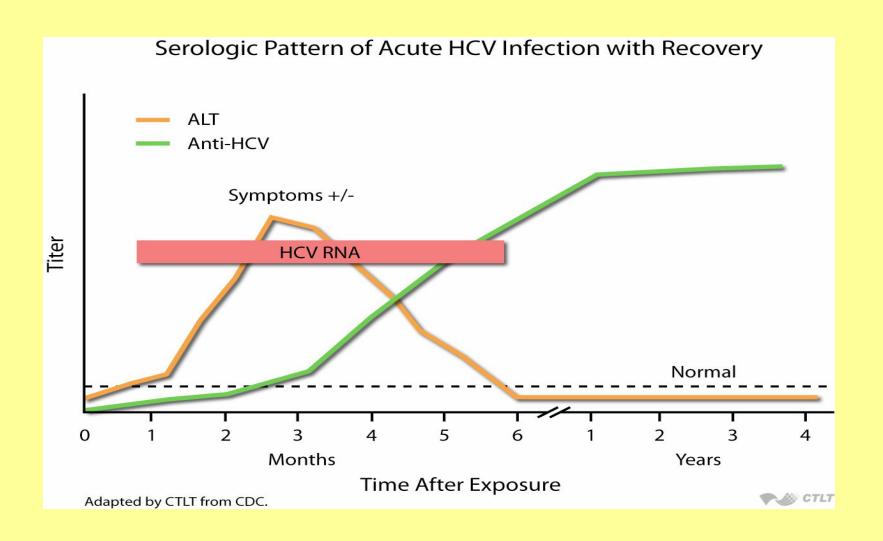
Source: CDC YellowBook 2012

Hepatitis C

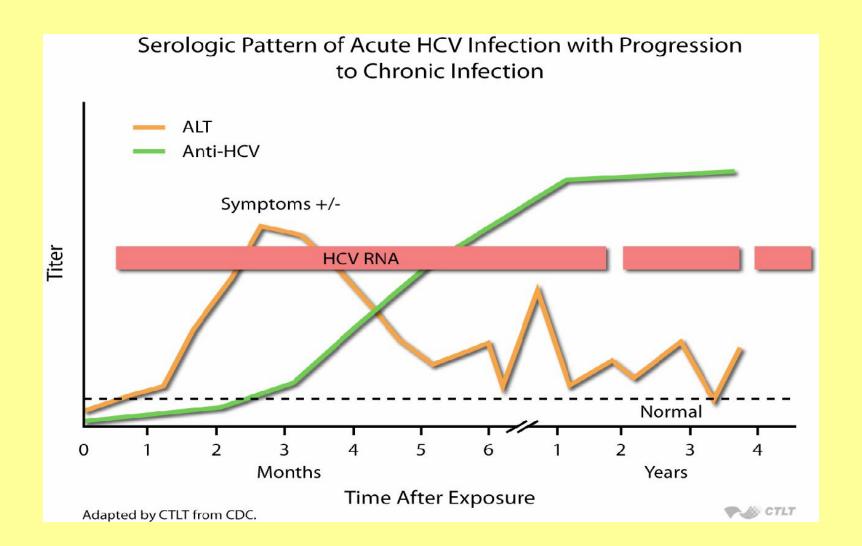


Source: Nature Reviews Gastroenterology & Hepatology 8, 69-71 (February 2011)

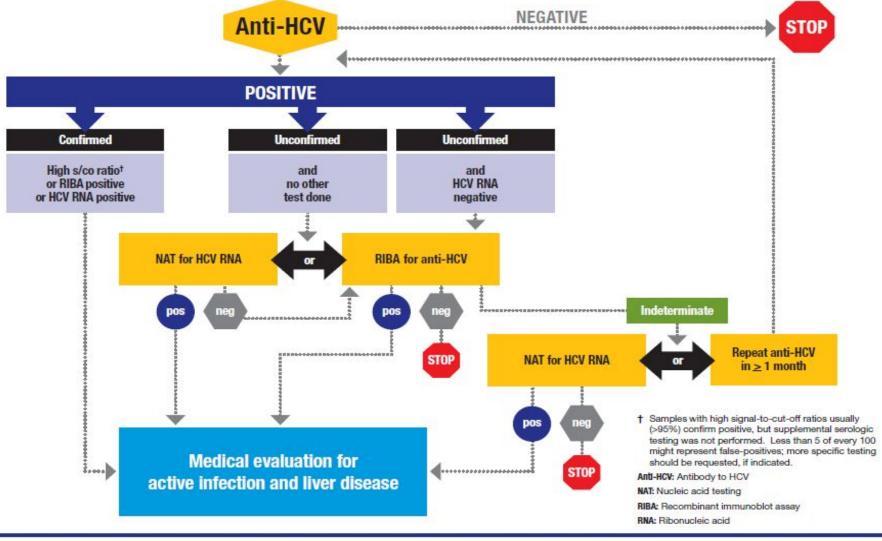
Hepatitis C Diagnosis



Hepatitis C Diagnosis



Hepatitis C Virus (HCV) Infection Testing for Diagnosis





DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention

Division of Viral Hepatitis



Hepatitis C Diagnosis

- Sixty to 70% of persons newly infected with HCV typically are usually asymptomatic or have a mild clinical illness.
- HCV RNA can be detected in blood within 1–3 weeks after exposure.
- The average time from exposure to antibody to HCV (anti-HCV) seroconversion is 8–9 weeks, and anti-HCV can be detected in >97% of persons by 6 months after exposure.

Hepatitis C Chronic Illness

- 75-85% of those infected with HCV will develop chronic infection.
- 60-70% of those infected with HCV will develop chronic liver disease.
- 5-20% of those infected will develop cirrhosis over a period of 20-30 years
- 1-5% will die from the consequences of chronic infection (liver cancer or cirrhosis)

Hepatitis C Treatment

- Interferon-based therapy is currently the standard of care for patients with chronic HCV, and has been proven to be effective in eliminating HCV.
- Both conventional and pegylated interferon (IFN) therapy have been used widely, with the aim of achieving a sustained virological response (SVR).

Hepatitis C Prevention

- Unlike HBV, there is currently no vaccine for HCV.
- However, with the screening of HCV in blood transfusion services, transfusion-related HCV infection has been lowered to almost zero.

Hepatitis C Prevention

- It may be possible to develop a preventive vaccine for HCV:
 - 30% of persons clear the virus spontaneously
 - The genome of HCV is not integrated into the host genome
 - After HCV infection, CD-8 CTL responses and antibodies appear, but the "protective immune response" or critical epitopes are not known
 - Persons who clear HCV and become re-infected have low viral loads and are more likely to clear HCV

Hepatitis D

- Hepatitis D (HDV), also known as "delta hepatitis," is a single-stranded circular RNA virus structurally unrelated to the Hepatitis A, B, or C viruses
- Hepatitis D, which can be acute or chronic, is uncommon in the United States

Hepatitis D

- HDV is an incomplete virus that requires the helper function of HBV to replicate and only occurs among people who are infected with the Hepatitis B virus (HBV).
- HDV is transmitted through percutaneous or mucosal contact with infectious blood and can be acquired either as a coinfection with HBV or as superinfection in persons with HBV infection.

Hepatitis E

- Hepatitis E virus (HEV), the major etiologic agent of enterically transmitted non-A hepatitis worldwide, is a spherical, non-enveloped, single stranded RNA virus that is approximately 32 to 34 nm in diameter.
- HEV is the sole member of the genus Hepevirus.
 - Two major species of the virus are recognized:
 - Mammalian HEV, a virus that causes acute hepatitis in humans and has a reservoir in pigs and possibly a range of other mammals
 - Avian HEV, causing big liver and spleen disease in chickens

Hepatitis E

- Hepatitis E is a serious liver disease caused by the Hepatitis E virus (HEV) that usually results in an acute infection.
- It does not lead to a chronic infection.
- While rare in the United States, Hepatitis E is common in many parts of the world.
- Hepatitis E is transmitted through the fecal oral route and outbreaks are usually associated with contaminated water supplies in countries with poor sanitation.

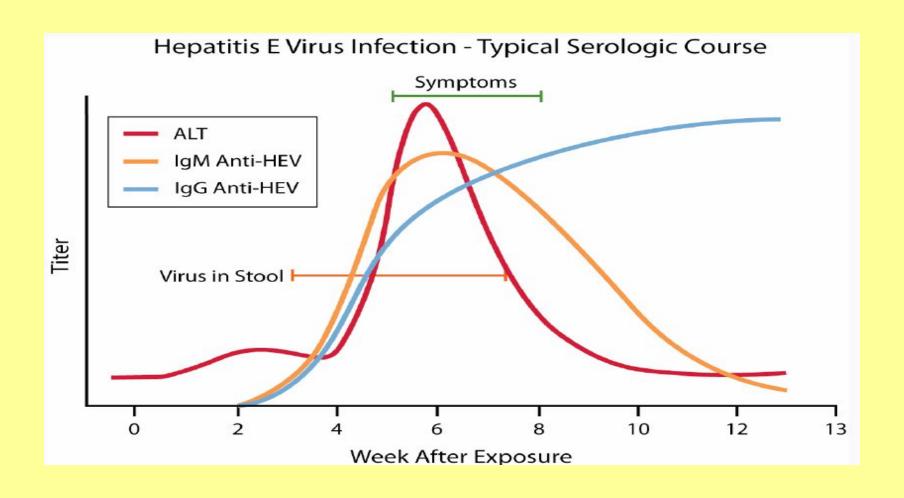
Hepatitis E Acute Illness

- The incubation period following exposure to HEV ranges from 15 to 60 days (mean, 40 days).
- Typical clinical signs and symptoms of acute hepatitis E are similar to those of other types of viral hepatitis and include abdominal pain anorexia, dark urine, fever, hepatomegaly, jaundice, malaise, nausea, and vomiting.

Hepatitis E

- Most people with Hepatitis E recover completely.
- The overall case-fatality rate is ≤4%.
- However, for pregnant women, Hepatitis
 E is more serious and the disease is
 fatal in 10%–30% of pregnant women,
 particularly those in their third trimester.

Hepatitis E Diagnosis



Hepatitis E Epidemiology

- The highest attack rate is seen among persons aged 15-40 years.
 - In most hepatitis E outbreaks, the highest rates of clinically evident disease have been in young to middle-age adults; lower disease rates in younger age groups may be the result of an icteric and/or subclinical HEV infection.
- The case fatality rate overall is 1%-3%.
 - In pregnant women, the case fatality rate can be as high as 15%-25%.
- HEV is found in the stool (feces) of persons and animals with hepatitis E.
- HEV is spread by eating or drinking contaminated food or water.
- Transmission from person to person occurs less commonly than with hepatitis A virus.

Hepatitis E Levels of Endemicity, 2010



Source: CDC DVH

Hepatitis E Prevention

- A Hepatitis E vaccine was just approved for use (but only in China).
- Good sanitation measures are essential for preventing environmental contamination.
- Good personal hygiene is also essential for prevention and control including:
 - Hand washing with soap:
 - After using the bathroom
 - After changing a diaper
 - Before preparing and eating food