Conditions that Cause Hepatitis in Humans

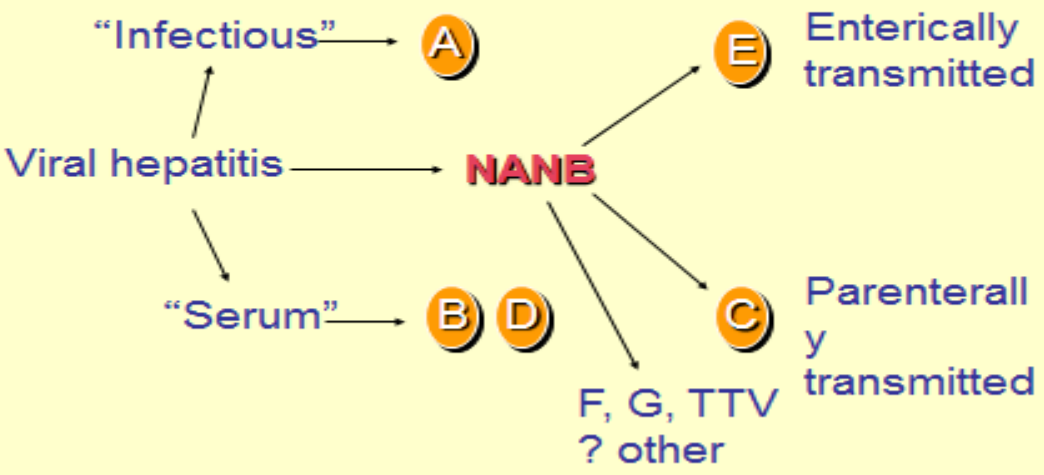
Hepatitis Viruses
- Hepatitis A virus
- Hepatitis B virus
- Hepatitis C virus
- Hepatitis D virus
- Hepatitis E virus

Other Viruses
- Epstein-Barr virus
- Human immunodeficiency virus
- Lassa fever virus
- Yellow fever virus
- Adenovirus
- Herpes simplex virus
- Human herpes-6 virus
- Ebola virus

Nonviral Infectious Agents
- Pneumococcal pneumonia
- Leptospirosis
- Syphilis
- *Coxiella burnetti*
- Toxoplasmosis

Noninfections
- Alcohol
- Medications
  - Dilantin
  - Isoniazid
  - Ritonavir
  - Chlorpromazine
  - Rifampin, etc.
- Anesthesia (halothane)

Viral Hepatitis - Historical Perspectives



Type of viral Hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water

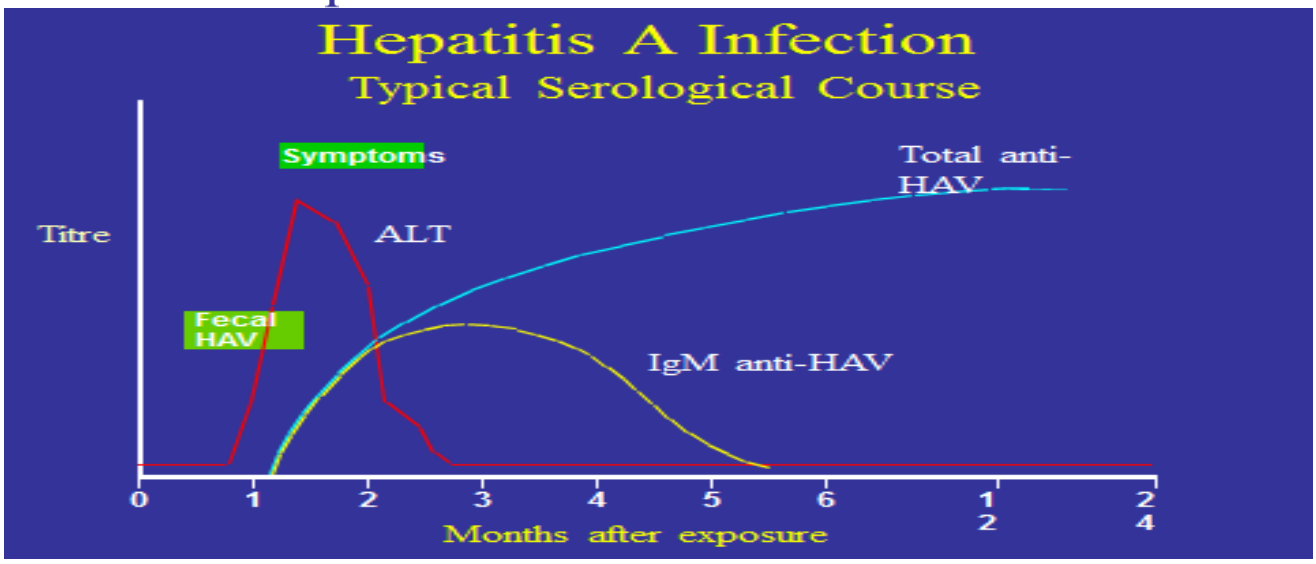
Characteristics of Hepatitis Viruses

Virus	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.

Hepatitis A - Clinical Features

- Incubation period: Average 30 days
  Range 15-50 days
- Jaundice by age group: <6 yrs, <10%
  6-14 yrs, 40%-50%
  >14 yrs, 70%-80%
- Complications: Fulminant hepatitis
  Cholestatic hepatitis
  Relapsing hepatitis
- Chronic sequelae: None



Hepatitis A Virus Transmission

- Close personal contact
  (e.g., household contact, sex contact, child day care centers)
- Contaminated food, water
  (e.g., infected food handlers, raw shellfish)
- Blood exposure (rare)
  (e.g., injecting drug use, transfusion)

Laboratory Diagnosis

-**Acute infection** is diagnosed by the detection of HAV-IgM in serum by EIA.

-**Past Infection** i.e. immunity is determined by the detection of HAV-IgG by EIA.

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

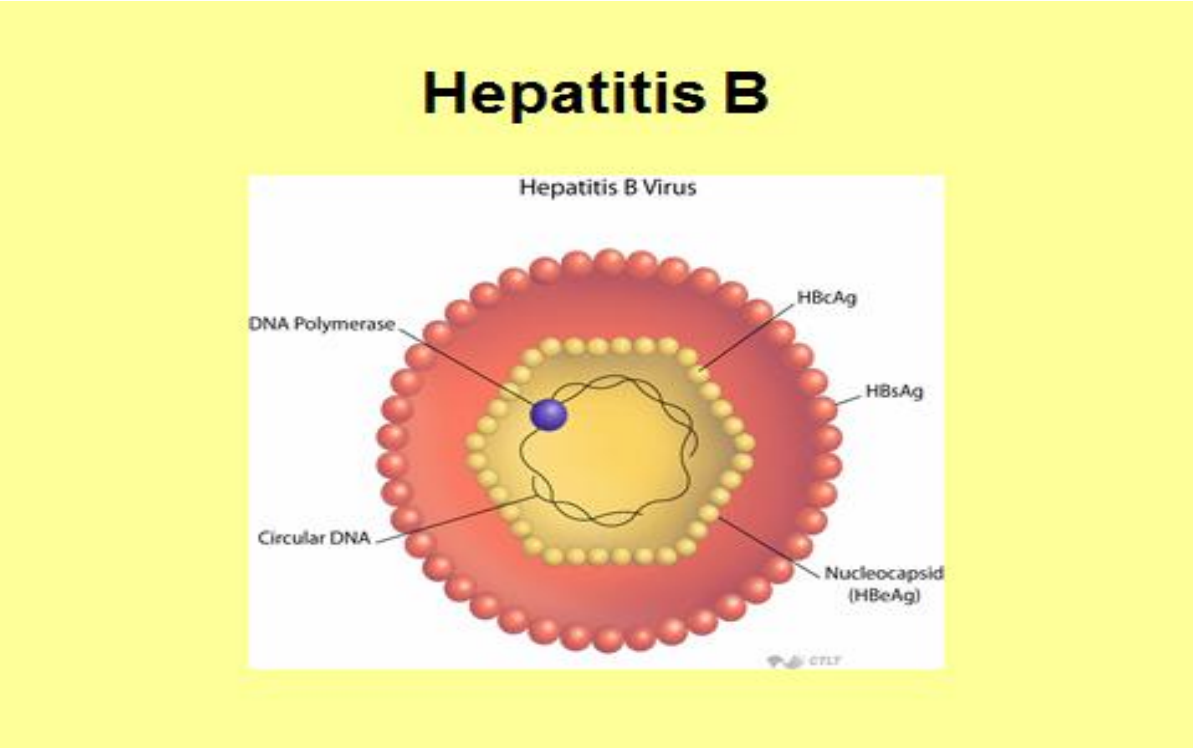
-HBcAg – localized within liver cells, identifies acute infection, anti-HBcAg persists for life and is a marker of past infection

-HBeAG – a marker of active replication and infectivity

Hepatitis *B* - *Clinical Features*

- *Incubation period:* *Average 60-90 days*
  Range 45-180 days
- Clinical illness (jaundice): <5 yrs, <10%
  5 yrs, 30%-50%
- Acute case-fatality rate: 0.5%-1%

- Chronic infection: <5 yrs, 30%-90%
  5 yrs, 2%-10%
- Premature mortality from chronic liver disease: 15%-25%



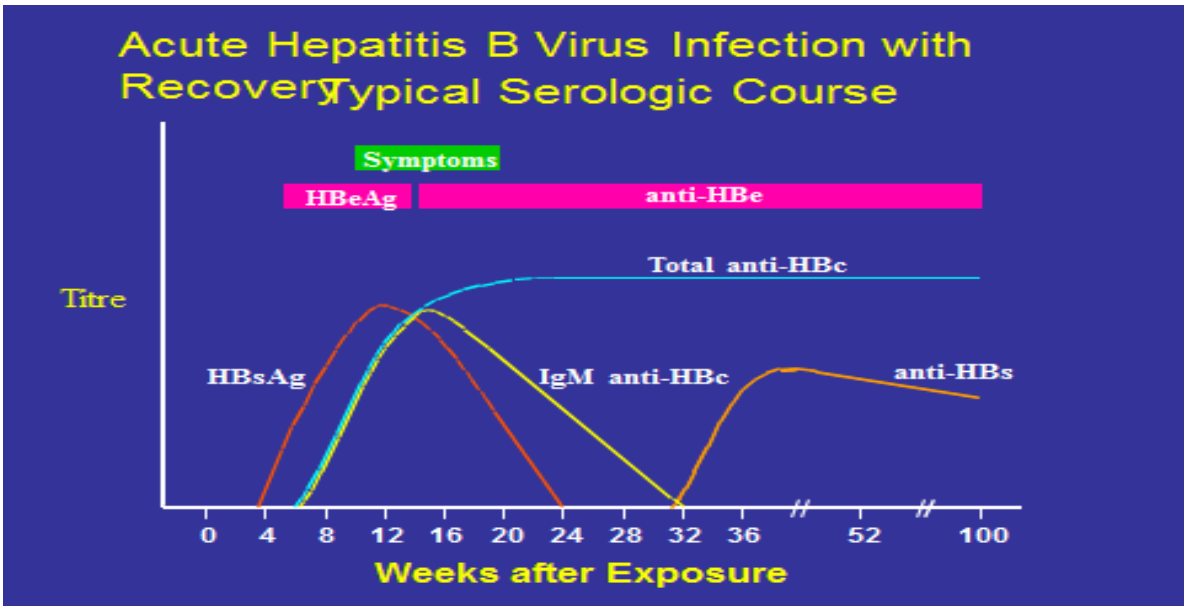
Spectrum of Chronic Hepatitis B Diseases

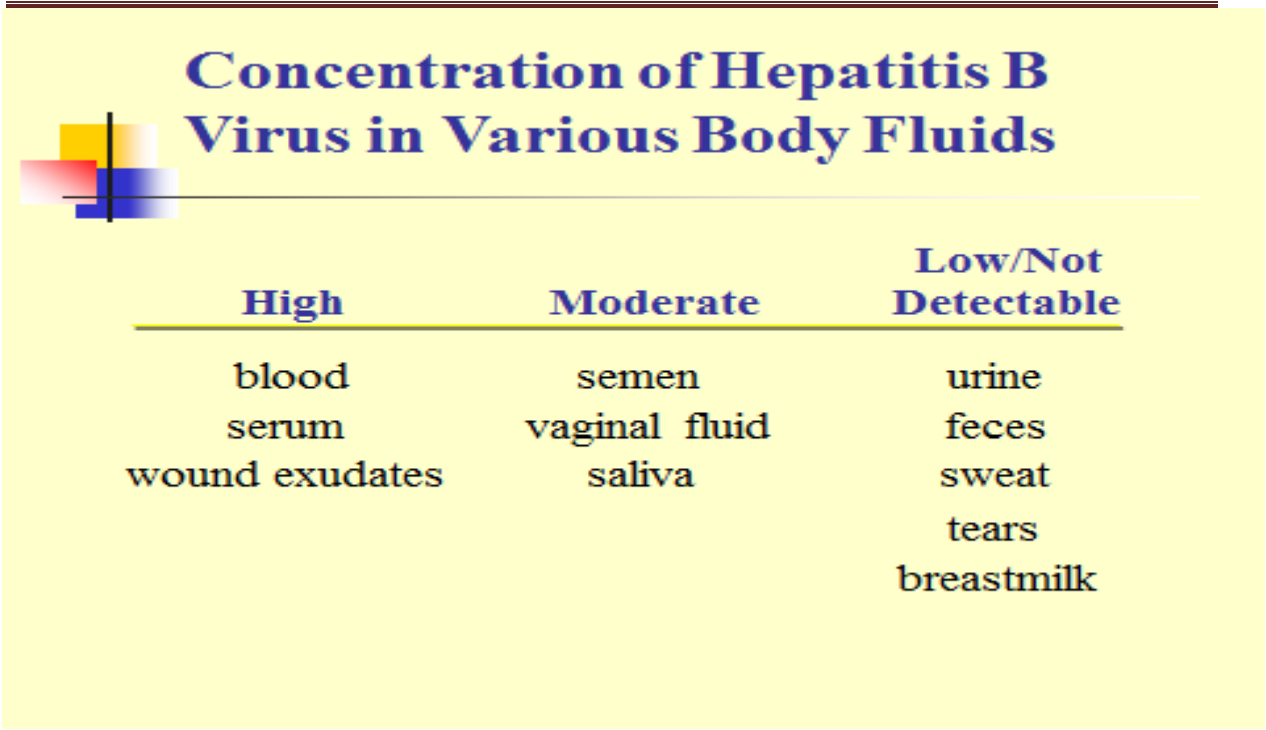
1. Chronic Persistent Hepatitis - asymptomatic

Chronic Active Hepatitis - symptomatic exacerbations of hepatitis 2.

3. Cirrhosis of Liver

4. Hepatocellular Carcinoma





- **Diagnosis Hepatitis B**

-Hepatitis B is detected by looking for a number of different antigens and antibodies:

1-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

2-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.

3-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

4-IgM antibody to Hepatitis B core antigen (IgM anti-HBc):

Positivity indicates recent infection with HBV (≤6 months).

Its presence indicates acute infection.

5-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.

6-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.

Typical interpretation of serologic test results for hepatitis B virus infection

Serologic Marker				Interpretation
HBsAg[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
–	+	+	+ or –	Acute resolving infection
–	+	–	+	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 HBsAg-positive mother
–	–	–	+	Immune if concentration is ≥10 mIU/mL after vaccine series completion;[9] passive transfer after hepatitis B immune globulin administration

-**HBsAg** - used as a general marker of infection.

-**HBsAb** - used to document recovery and/or immunity to HBV infection.

-**anti-HBc IgM** - marker of acute infection.

-**anti-HBcIgG** - past or chronic infection.

-**HBeAg** - indicates active replication of virus and therefore infectiveness.

-**Anti-Hbe** - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.

-**HBV-DNA** - indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy.

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 - Clinical Features

Incubation period: Average 6-7 wks

Range 2-26 wks

Clinical illness (jaundice):	30-40% (20-30%)
Chronic hepatitis:	70%
Persistent infection:	85-100%
Immunity:	No protective antibody response identified

Risk Factors Associated with Transmission of HCV

-Transfusion or transplant from infected donor

-Injecting drug use

-Hemodialysis (yrs on treatment)

-Accidental injuries with needles/sharps

-Sexual/household exposure to anti-HCV-positive contact

-Multiple sex partners

.Birth to HCV-infected mother

Laboratory Diagnosis

-HCV antibody - generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.

-HCV-RNA - various techniques are available e.g. PCR and branched DNA. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.

-HCV-antigen - an EIA for HCV antigen is available. It is used in the same capacity as HCV-RNA tests but is much easier to carry out

-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 D

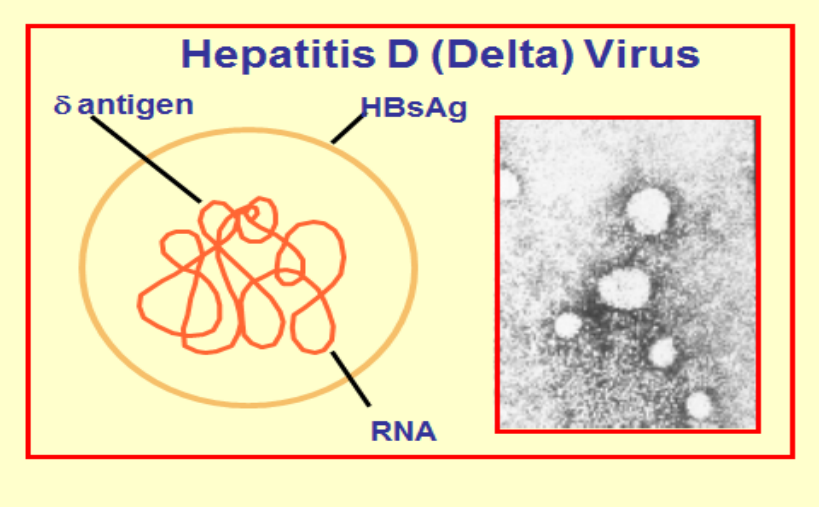
-Hepatitis D (HDV), also known as "delta hepatitis," is a single-stranded circular RNA virus structurally unrelated to the Hepatitis A, B, or C viruses

-Hepatitis D, which can be acute or chronic, is uncommon in the United States

-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 D - Clinical Features



-Coinfection

-Severe acute disease.

-low risk of chronic infection.

-Superinfection

-usually develop chronic HDV infection.

-high risk of severe chronic liver disease.

-may present as an acute hepatitis.

Hepatitis D Virus Modes of Transmission

-Percutaneous exposures

-injecting drug use

-Permucosal exposures

-sex contact

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 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 - Clinical Features

- Incubation period: Average 40 days
  Range 15-60 days
- Case-fatality rate: Overall, 1%-3%
  Pregnant women, 15%-25%
- Illness severity: Increased with age
- Chronic sequelae: None identified

Hepatitis E - Epidemiologic Features

-Most outbreaks associated with faecally contaminated drinking water.

-Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.

-In the United States and other nonendemic areas, where outbreaks of hepatitis E have not been documented to occur, a low prevalence of anti-HEV (<2%) has been found in healthy populations. The source of infection for these persons is unknown.

-Minimal person-to-person transmission.