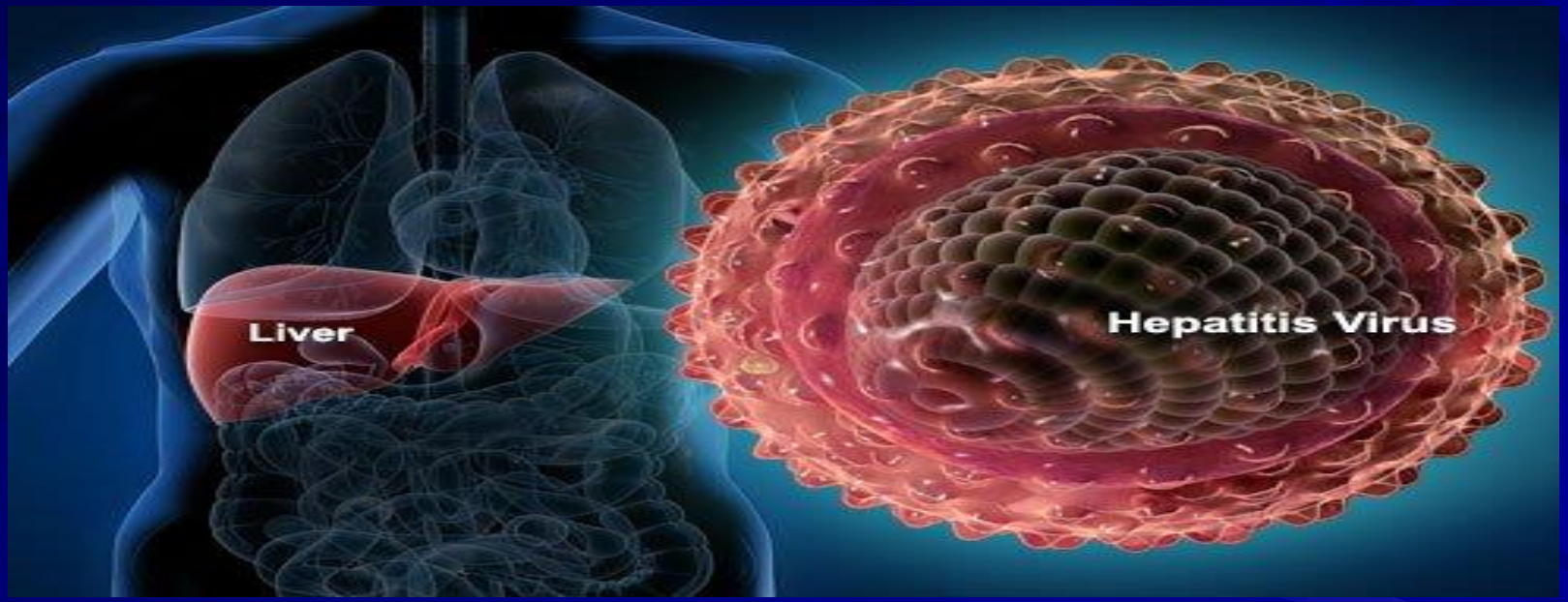
Epidemiology of Viral Hepatitis



Assistant Prof

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OBJECTIVES

- TO KNOW THE TYPES AND CASE DEFINITIONS OF VIRAL HEPATITS
- DEFINE THE EPIDEMIOLOGY OF VIRAL HEPATITS
- KNOW MAIN DIAGNOSTICS METHOD
- HACE IDEA ABOUT PREVENTION AND VACCINATIONS

Viral Hepatitis
Common Features

- Early Prodromal Phase
  - serum sickness like syndrome
    - occurs 2-3 weeks before jaundice
    - arthalgias, arthritis, rash, angioneurotic edema, fever
- Preicteric Phase
  - GI symptoms
    - nausea, vomiting, abdominal pain, anorexia, changes in taste and smell, weight loss
  - generalized malaise, myalgias, headache, fever
- Icteric Phase
  - fever declines
  - constitutional symptoms improve
- Convalescent phase
  - full recovery usually within 6 months

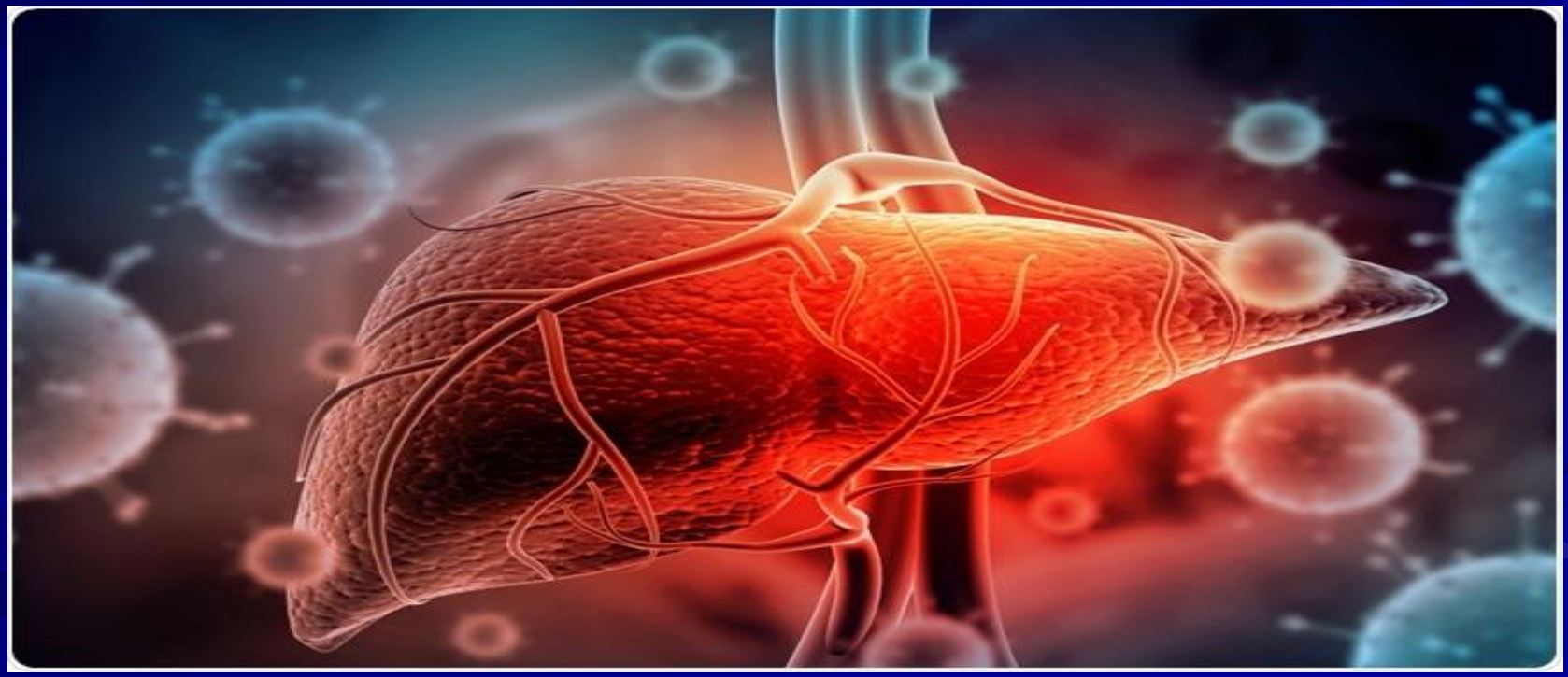
Viral Hepatitis Differential Features

Features	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Genome type	Ss RNA	Ds DNA	Ss RNA	Ss RNA	Ss RNA
Genome size	7.5 kB	3.2 kB	9.4 kB	1.7 kB	7.5 kB
Incubation period, days (mean)	15-49 (30)	28-160 (70-80)	15-160 (50)	21-140 (35)	15-65 (42)
Fecal-oral transmission	yes	no	no	no	yes
Parenteral transmission	rare	yes	yes	yes	no
Sexual transmission	no	yes, common	yes, uncommon	yes, uncommon	no
Fulminant hepatitis	<1%	<1%	rare	2-7.5%	~1%, 30% in pregnancy
Chronic hepatitis	no	10%	85%	90% with superinfection	no

Acute Hepatitis Evaluation and Recommendations

- Access for viral hepatitis A, B, C,
  - Hep A =IgM,
  - Hep B =HBsAg, HBc IgM
  - HCV =Ab (or PCR)
  - Consider alcohol and drug toxicity, autoimmune hepatitis, ischemia
  - Consider other viruses: CMV, EBV, HSV, etc.

Hepatitis A



- Picornaviridae
- Transmitted by fecal oral route, contaminated food, water, shellfish
- Most infections are sub clinical
  - Incidence peaks in fall and winter
  - 80% infected children are anicteric
  - 10-50% infected college students are anicteric
  - 30-50% adults are HAV IgG+, but only 3-5% recall prior jaundice
  - High attack rate: 70-90% exposed become infected

ACUTE HEPATITIS A CASE DEFINITION FOR SURVEILLANCE

- **Clinical criteria**

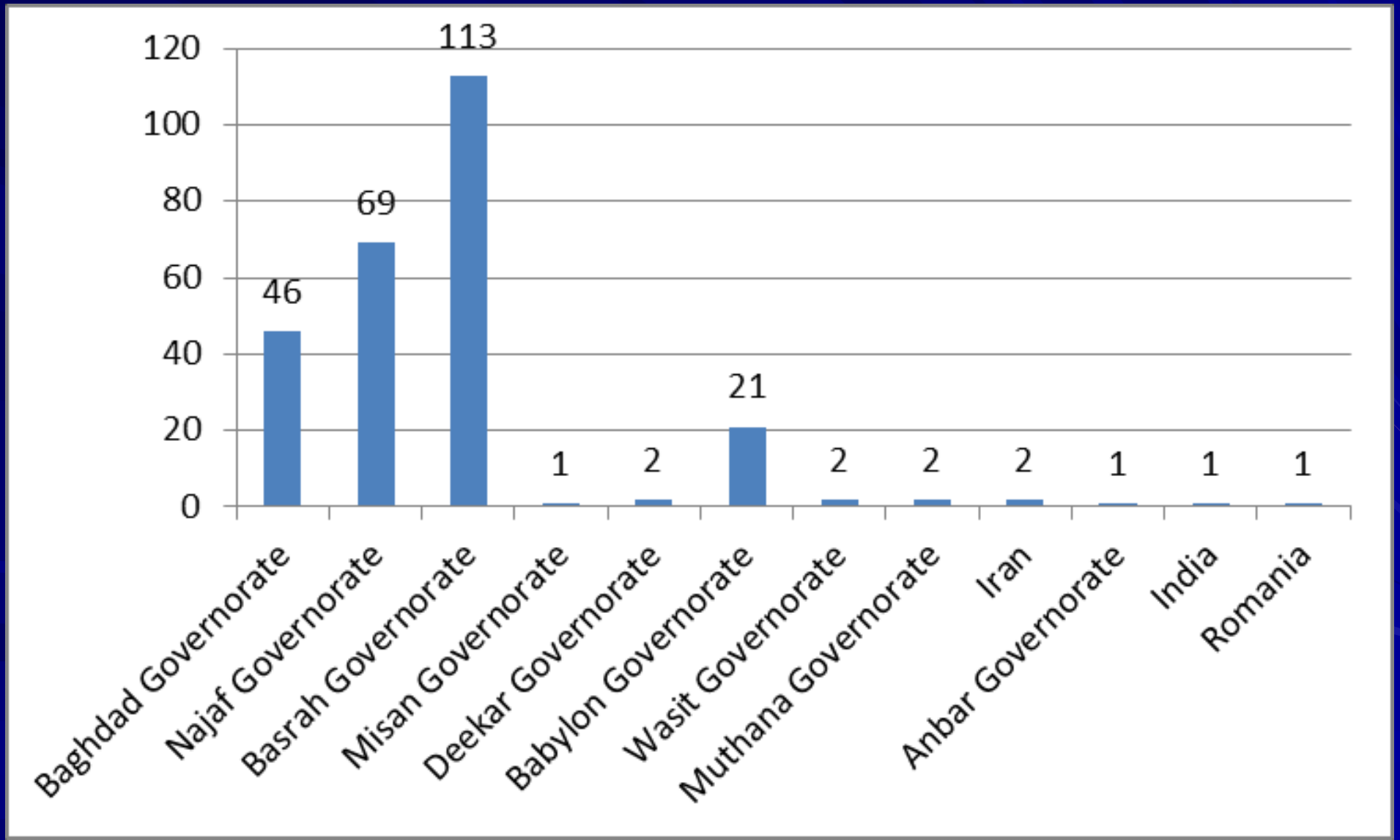
  An acute illness with:
  - discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting), **and**
  - jaundice or elevated serum aminotransferase levels

- **Laboratory criteria**
  - IgM antibody to hepatitis A virus (anti-HAV) positive

- **Case Classification**
  - Confirmed. A case that meets the clinical case definition and is laboratory confirmed or a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15-50 days before the onset of symptoms).

CDC

The incidence of hepatitis A per 10,000 population in different Iraqi governorate



- >60,000 clinical cases per year
  - Incubation 15-49 days (mean 30 days)
  - HAV Ag appears in liver at 1-2 weeks
  - HAV then appears in bile and stool
  - Fecal infectivity begins 2-3 weeks before jaundice, lasts 4-5 weeks, ends 2 weeks after peak transaminitis
- Chronic infection never occurs
  - 60% have normal LFT's at 2 months; 100% normal at 6 months

Transmission of hepatitis A virus

- HAV is spread via the fecal-oral route, personal contact, or ingestion of contaminated water/food
  - HAV is more **prevalent** in low socioeconomic areas in which a lack of adequate sanitation and poor hygienic practices facilitate spread of the infection

Risk factors:

- Most common is international travel
- Sexual & household contact with another person with hepatitis A
- Homosexual activity in men
- Chronic liver disease
- Foods contaminated by infected food handlers
- No identifiable risk factor

- Children pose a particular problem with the spread of the disease because they often remain clinically asymptomatic and are infectious for longer periods of time than adults.

Hepatitis A Prevention

- General prevention
  - –Water chlorination
  - –Boil water 20 minutes
  - –Wash hands
  - –Avoid contaminated food

- HAV Immunoglobulin
  - Can prevent 85-95% infections if given within two weeks of exposure

  Indicated in:
  - Household and sexual contacts
  - Day care contacts
  - Prison contacts
  - Common source outbreaks

- HAV Vaccine
  - 90-98% successful with one injection, 100% with two injections
  - Protection begins after 1-2 weeks, may last 20 years
  - Give to all of the above
  - Travelers to endemic areas
  - Homosexuals, IV drug abusers
  - Persons with HCV and HBV
  - Military

Hepatitis B

Acute Hepatitis B Case Definition

- **Clinical Description**
  - An acute illness with a discrete onset of any sign or symptom* consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), and either a) jaundice, or b) elevated serum alanine aminotransferase (ALT) levels > 100 IU/L.

  - *a documented negative hepatitis B antigen (HBsAg) laboratory test result within 6 months prior to a positive test (either HBsAg, hepatitis B "e" antigen (HBeAg), or hepatitis B virus nucleic acid testing (HBV NAT) including genotype) result does not require an acute clinical presentation to meet the surveillance case definition.
- **Laboratory Criteria**
  - HBsAg positive, AND
  - Immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM anti-HBc) positive (if done)
- AND patient not known to have chronic hepatitis B

Chronic Hepatitis B : [redacted] Case Definition

- **Clinical Evidence**
  No symptoms are required. Persons with chronic HBV infection may have no evidence of liver disease or may have a spectrum of disease ranging from chronic hepatitis to cirrhosis or liver cancer.

- **Laboratory Criteria for Diagnosis**
  IgM antibodies to hepatitis B core antigen (IgM anti-HBc) negative AND
  a positive result on one of the following tests: hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), or hepatitis B virus (HBV) DNA
  OR
  HBsAg positive or HBV DNA positive or HBeAg positive two times at least 6 months apart (Any combination of these tests performed 6 months apart is acceptable

- **Case Classification**
  Confirmed: a case that meets either of the above laboratory criteria for diagnosis
  Probable: a person with a single HBsAg positive or HBV DNA positive or HBeAg positive lab result and does not meet the case definition for acute hepatitis B.

Source: CDC and Prevention. CSTE Position Statement Number: 10-ID-10.

- Epidemiology
  - Worldwide
    - 2 billion people have markers of infection
    - 400 million have chronic infection (5%)
    - 1.25 million chronic infections (50% Asian)
    - 200 thousand acute infections per year
    - 250 deaths/year from fulminant HBV
    - 4000 deaths/year from chronic HBV
    - 800 deaths/year from HBV related hepatomas

Hepatitis B

- 90% cases are self-limited with spontaneous resolution
  - >50% are anicteric
  - 10% become chronic
  - <1% are fulminant (10% if “E Ag mutant”)
  - 3-5% have HBV markers

- Surface Ag appears 1-12 weeks after exposure
  - Clinical hepatitis and Core IgM occur 4 weeks after Surface antigen
  - HBe Ag indicates period of infectivity
  - HBs Ab indicates resolving infection
  - Rare “window period” occurs when Surface Ag disappears and before Surface Ab appears so HBc Ab will be positive

- Extrahepatic manifestations
  - Arthralgias and rash (25%)
  - Angioneurotic edema, polyarteritis nodosa, mononeuritis, membranoproliferative GN, arthritis, Raynaud's phenomena, Type II mixed essential cryroglobulinemia, Guillan Barre Syndrome, pancreatitis, pericarditis

Chronic Hepatitis B

- Persistent HBs Ag, HBe Ag, PCR=DNA > 6 months
- Risk of chronicity is dependent on host age and immune status
  - –90% perinatal infection
  - –30% childhood infection age < 6 years
  - –5% adult acute infection
  - –30% with HIV co-infection

- Prognosis is dependent on HBV stage
  - Immune tolerant:
  - HBs Ag +, HBe Ag +, DNA +, ALT=GPT normal
    - Prognosis good, hepatoma risk is low
  - Integrated state: HBs Ag +, HBe Ag
  - neg, PCR=DNA neg, ALT usually normal
    - Prognosis good, hepatoma risk low

– Chronic active hepatitis:

HBs Ag +, HBe Ag +,PCR=DNA +, ALT >2x normal

- 20% develop cirrhosis in 5 years
- 10% per year lose E Ag
- 1% per year lose S Ag
- Increased risk of hepatoma 500 x

Hepatitis B Prevention

- Modify risk factors
  - Eliminate high risk behavior; specialy for STI
  - Incidence of acute HBV has decreased by 40% . over 15 years
- Screen pregnant mothers for HBs Ag
  - HBIG + HBV vaccination at birth prevents 80-90% perinatal transmission

Hepatitis B Immune Globulin

- indicated for :
  - –Perinatal exposure
  - –Needle stick exposure
  - –Sexual, mucosal or percutaneous exposures

HBV Vaccination

Indications:

- Perinatal exposure
- Persons with sexual, mucosal, percutaneous exposures
- Persons with HCV or IV drug abuse
- Homosexuals
- Health care workers
- Hemodialysis
- Universal vaccination for children

Infant Hepatitis B Vaccine Schedules

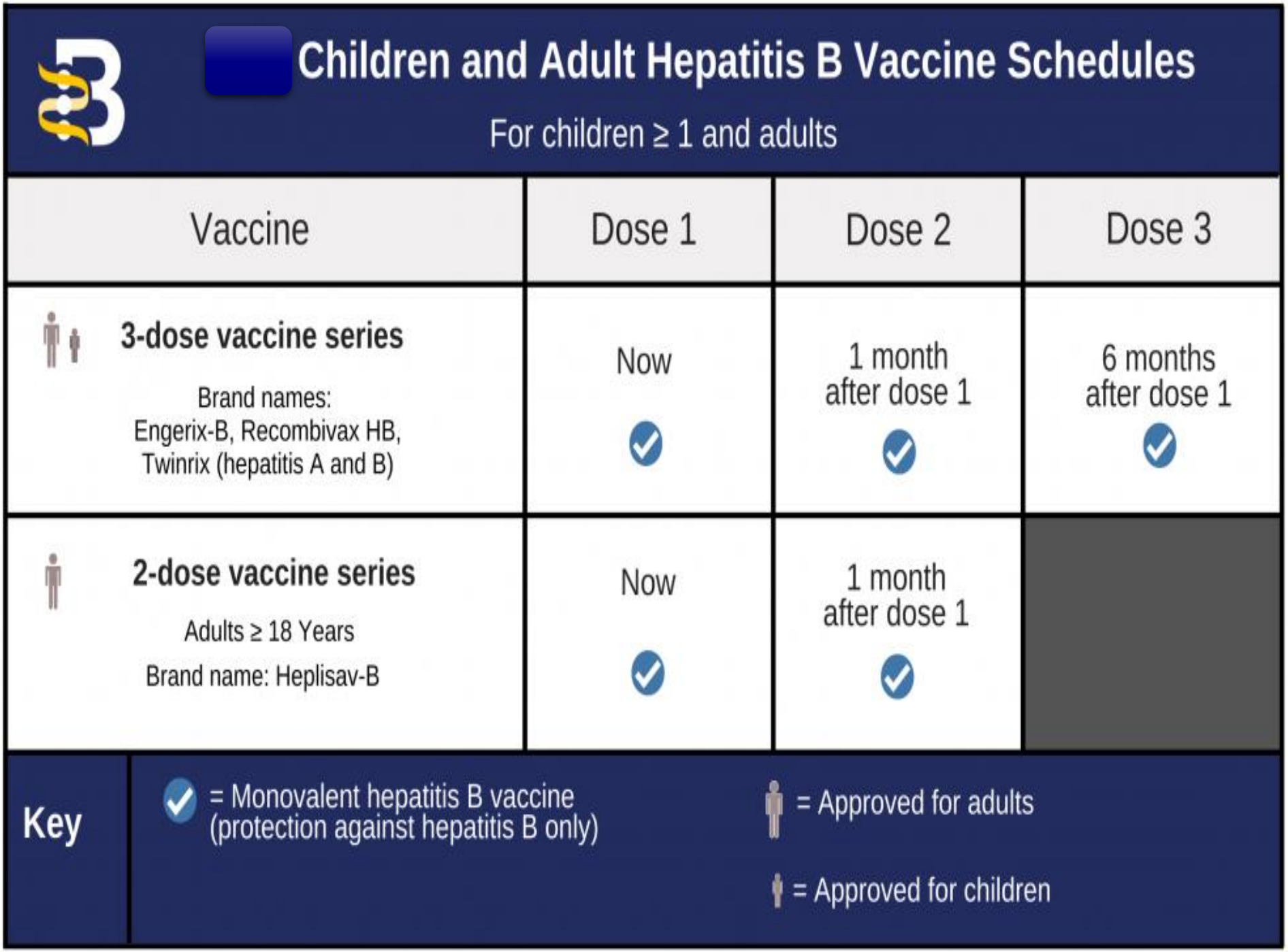
For infants < 1 year of age

Vaccine	Dose 1 "Birth Dose"	Dose 2	Dose 3	Dose 4
3-dose vaccine series Brand names: Engerix-B, Recombivax HB	Within 24 hours of birth	1 month after dose 1	6 months after dose 1	
4-dose combination vaccine series (pentavalent or hexavalent) Brand names: Vaxelis, Pediarix	Within 24 hours of birth (Hepatitis B vaccine)	6 weeks of age (Combination vaccine)	14 weeks of age (Combination vaccine)	6 months of age (Combination vaccine)

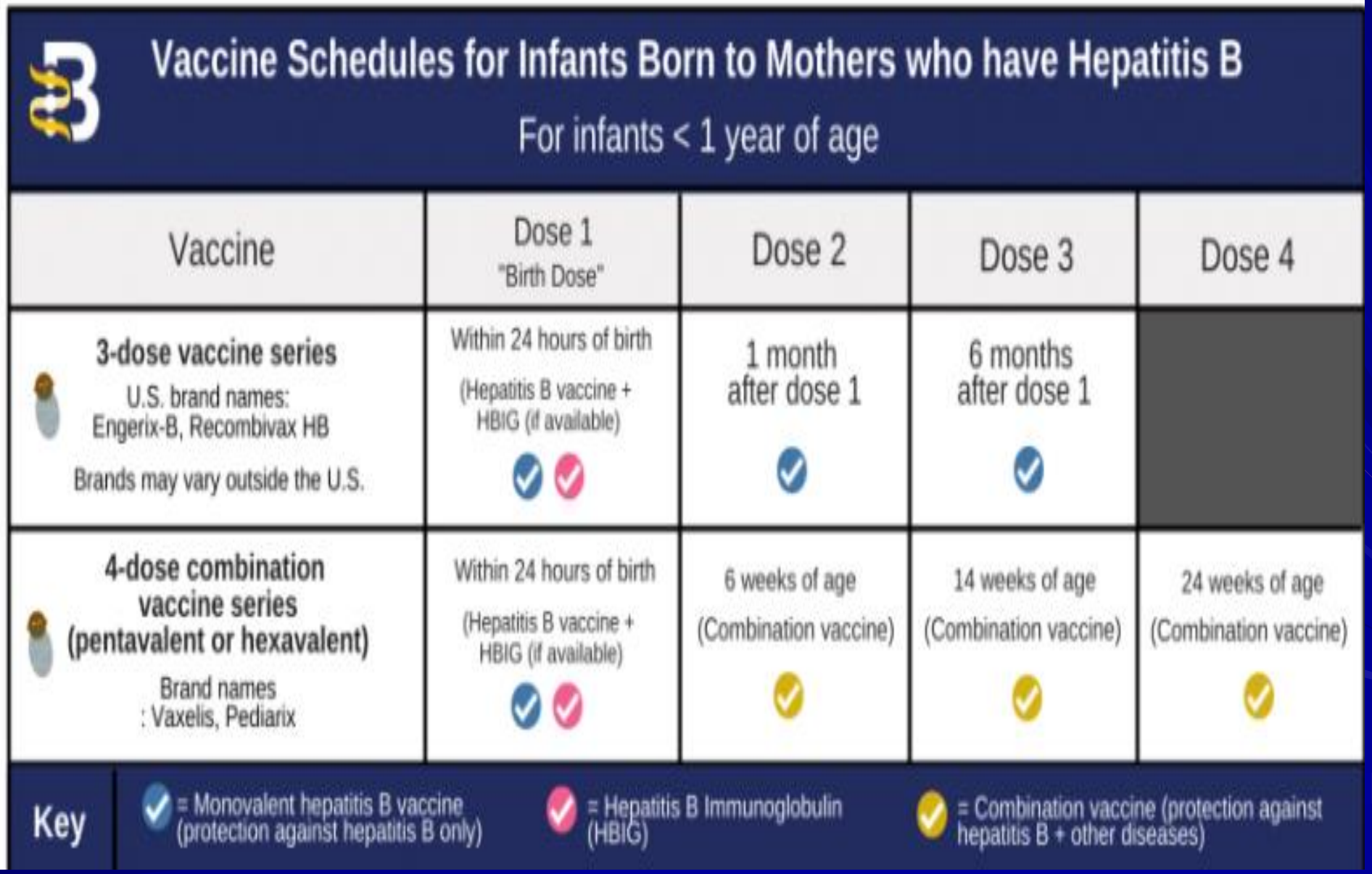
Key

= Monovalent hepatitis B vaccine (protection against hepatitis B only)

= Combination vaccine (protection against hepatitis B + other diseases)


Children and Adult Hepatitis B Vaccine Schedules
For children ≥ 1 and adults
Vaccine
Dose 1
Dose 2
Dose 3
3-dose vaccine series
Brand names:
Engerix-B, Recombivax HB,
Twinrix (hepatitis A and B)
Now
1 month
after dose 1
6 months
after dose 1
2-dose vaccine series
Adults ≥ 18 Years
Brand name: Heplisav-B
Now
1 month
after dose 1
Key
= Monovalent hepatitis B vaccine
(protection against hepatitis B only)
= Approved for adults
= Approved for children

Infants Born to Mothers who Have Hepatitis B: Hepatitis B Vaccine Schedules



Vaccine and HBIG Shot Administration Sites for Infants

Shots must be administered in opposite limbs

	HBsAg	Anti-HBs	Anti-HBc
Susceptible	Negative	Negative	Negative
Vaccinated	Negative	Positive	Negative
Past Infection	Negative	Positive	Positive
Acute Infection	Positive	Negative	IgM Positive
Chronic Infection	Positive	Negative	IgG Positive

PART 2

HBV Vaccination

- Pregnant or breastfeeding people should be vaccinated if they are at risk for getting hepatitis B.
- Pregnancy or breastfeeding are not contraindication to avoid hepatitis B vaccination.
- People with minor illnesses, such as a cold, may be vaccinated.
- People who are moderately or severely ill should usually wait until they recover before getting hepatitis B vaccine.

Risks of a vaccine reaction

- Soreness where the shot is given or fever can happen after hepatitis B vaccination.
- People sometimes faint after medical procedures, including vaccination.
- Tell your provider if you feel dizzy or have vision changes or ringing in the ears.
- There is a very remote chance of a vaccine causing a severe allergic reaction, other serious injury, or death

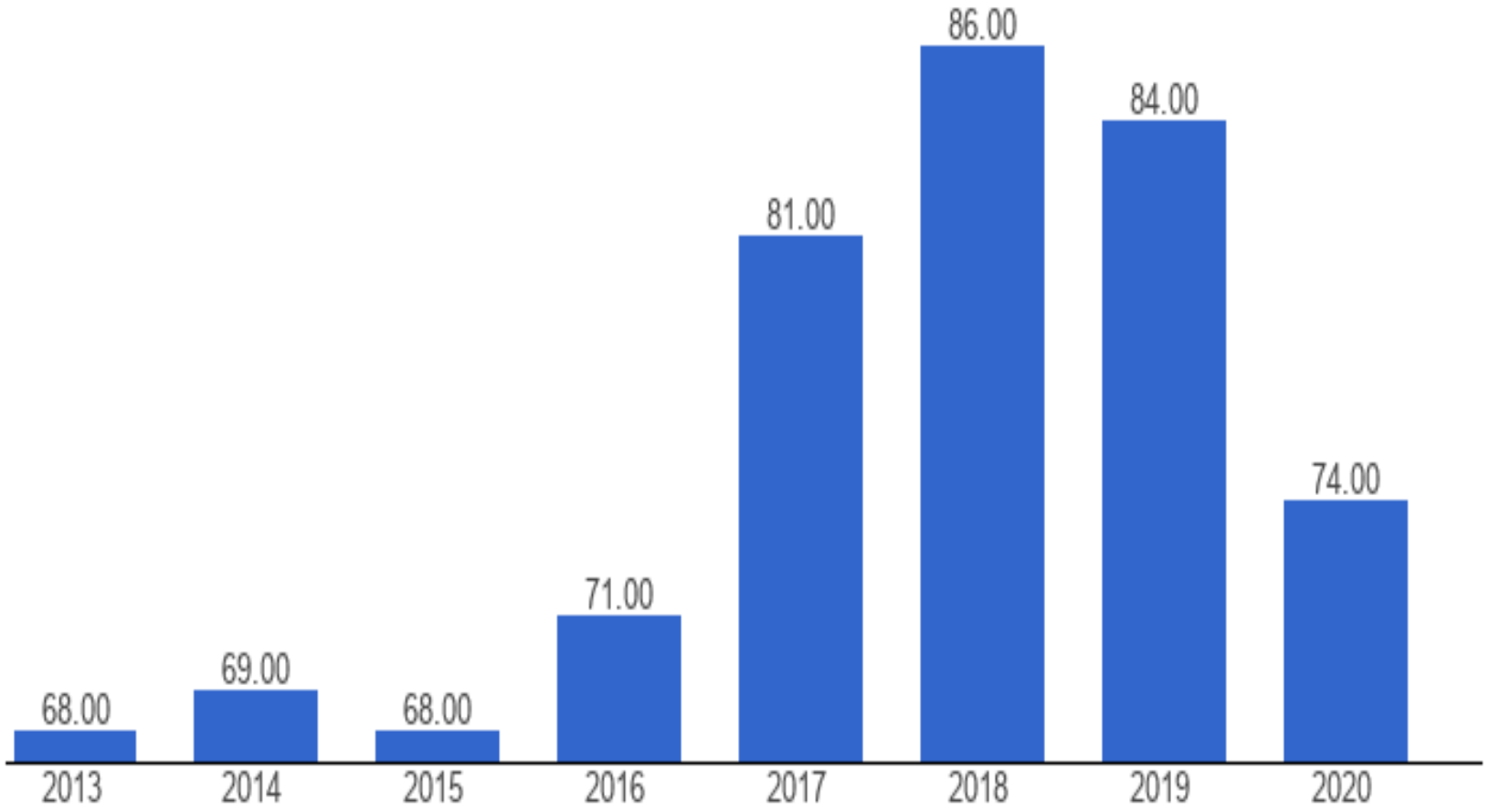
Iraq Hepatitis profile

- Hepatitis B is endemic to Iraq
- **A reported prevalence ranging from approximately 1% in the northern region to 3.5% in the southern region**

Prevalence of hepatitis B virus infection and genotype distribution in some Asian countries

Countries	HBsAg-positive prevalence[16,85-92,96,99,105-108]	HBV genotype distribution[109-118,121,123,125]
Cambodia	4.6%	A: India A1 India B: China
China	7.18%	B2 southern China
Gaza Strip	3.5%	C: China
India	3.7%	C1 southern China, India
Iraq	0.6%	C2 northern China
Jordan	1.4%	D: Arabian countries and India
Kazakhstan	3.8%	D1 Persian Gulf (Iran, Syria, Turkey), India, Pakistan D2, D3, D4, D9 India
Kuwait	3.5%	
Saudi Arabia	1.5%-2.6%	
Singapore	3.6%	C/D1-CD2 western China
South Korea	4.0%	
United Arab Emirates	2%-7%	
Yemen	5.1%	

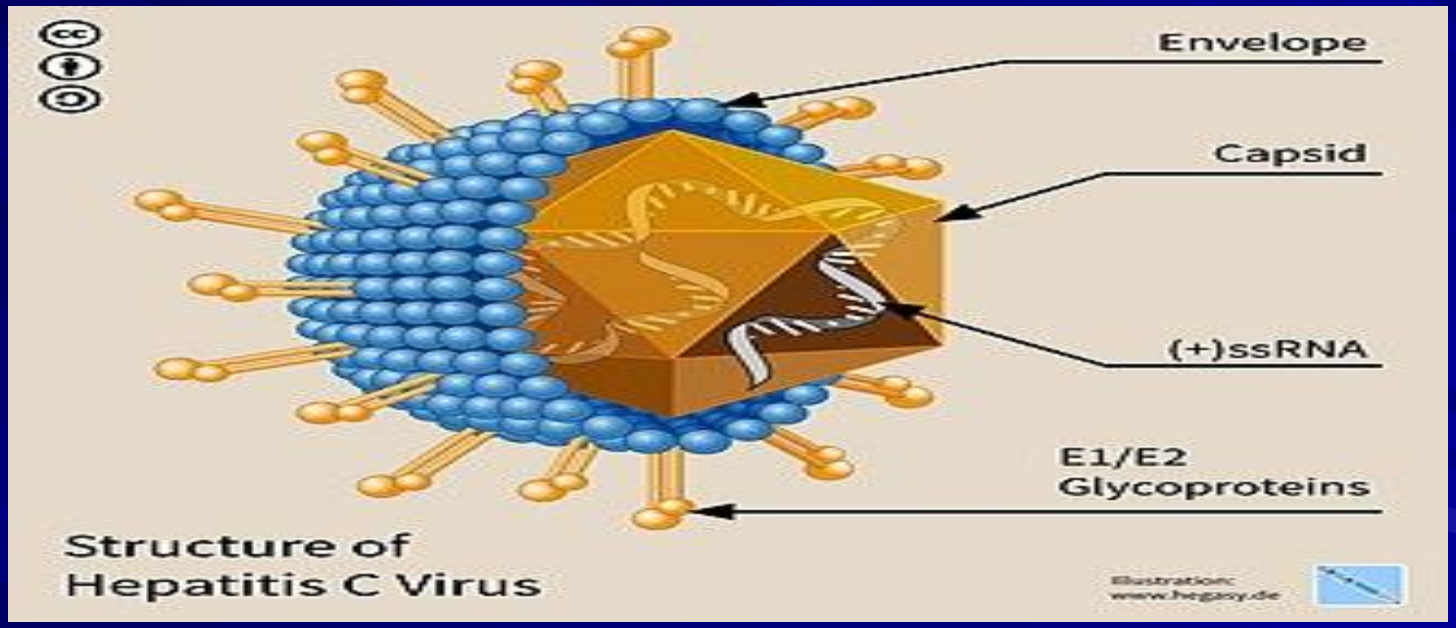
Percent of one-year-old children with Hepatitis B immunization



Hepatitis B Treatment

- Who to treat?
  - Chronic active disease > 6 months
  - Surface Ag +, DNA +, E Ag + or – (if E Ag mutant)
  - ALT > 100, and/or active hepatitis on biopsy
- Goal of treatment
  - Stop viral replication, HBV DNA becomes neg
  - Convert E Ag pos to neg, E AB becomes pos
  - Improvement in histology, prevention of progression to cirrhosis
  - With successful treatment, loss of Surface Ag may occur in 1-2% per year

Hepatitis C


Envelope
Capsid
(+)ssRNA
E1/E2
Glycoproteins
Structure of
Hepatitis C Virus
Illustration:
www.hegasy.de

Acute Hepatitis C: 2020 Case Definition

Clinical Criteria

All hepatitis C virus cases in each classification category should be >36 months of age, unless known to have been exposed non-perinatally.

One or more of the following:

- Jaundice, **OR**
- Peak elevated total bilirubin levels ≥3.0 mg/dL, **OR**
- Peak elevated serum alanine aminotransferase (ALT) level >200 IU/L

AND

The absence of a more likely diagnosis (which may include evidence of acute liver disease due to other causes or advanced liver disease due to pre-existing chronic HCV infection or other causes, such as alcohol exposure, other viral hepatitis, hemochromatosis, etc.)

Laboratory Criteria for Diagnosis

Confirmatory laboratory evidence:

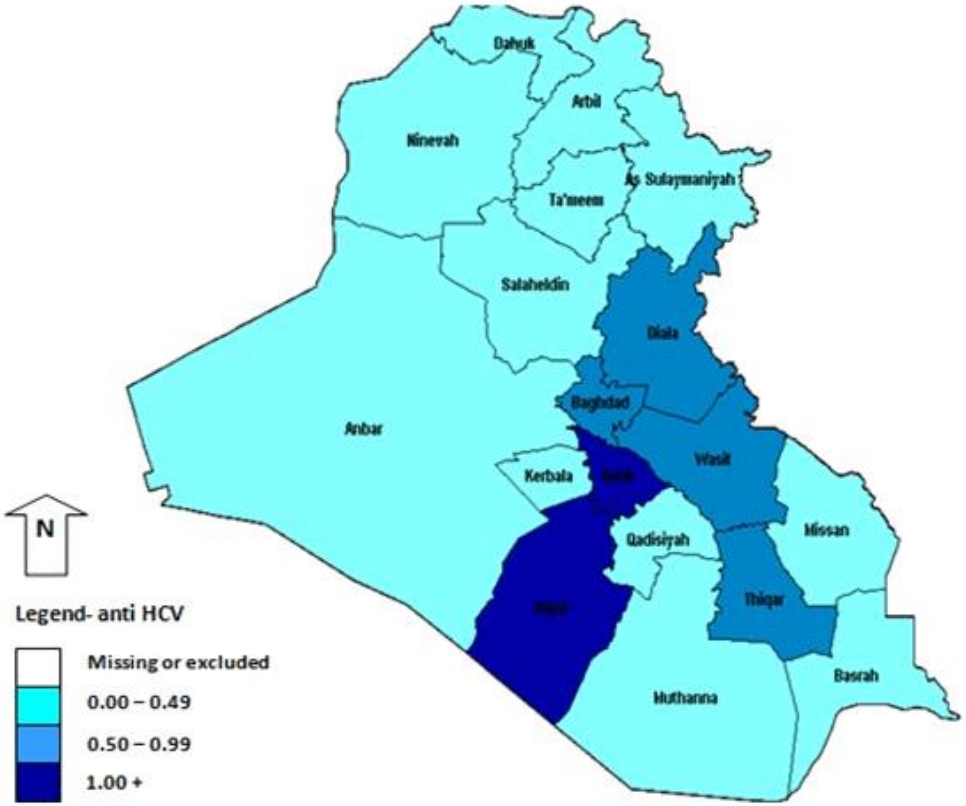
- Positive hepatitis C virus detection test: Nucleic acid test (NAT) for HCV RNA positive (including qualitative, quantitative, or genotype testing), **OR**
- A positive test indicating presence of HCV antigen

Presumptive laboratory evidence:

- A positive test for antibodies to hepatitis C virus (anti-HCV)

- Flaviviridae
- Transmission is primarily percutaneous; sexual and perinatal infection can occur
  - Transfusional HCV risk is now low: 1:1,935,000
  - 50-90% of IV drug abusers have HCV
  - 10% needle stick injuries transmit HCV
  - 4% sexual partners have HCV; Risk of sexual transmission <0.5%/year
  - Perinatal transmission 1-10%

Map diagram showing the anti-HCV antibodies prevalence rate in 18 Iraqi provinces



- 100 million chronic carriers world wide (>3%)
- 4 million with chronic HCV (1.5-2%)
  - 30 thousand new HCV cases per year (incidence decreasing)
  - 10 thousand deaths/year from HCV (incidence increasing)

- Acute hepatitis is rare
  - Fulminant hepatitis is extremely rare
  - 15% can spontaneously resolve infection
  - 85% develop chronic infection
  - HCV RNA becomes + 2 weeks after exposure
  - “incubation” period is 6-7 weeks
  - HCV Ab becomes + by 12 weeks in most

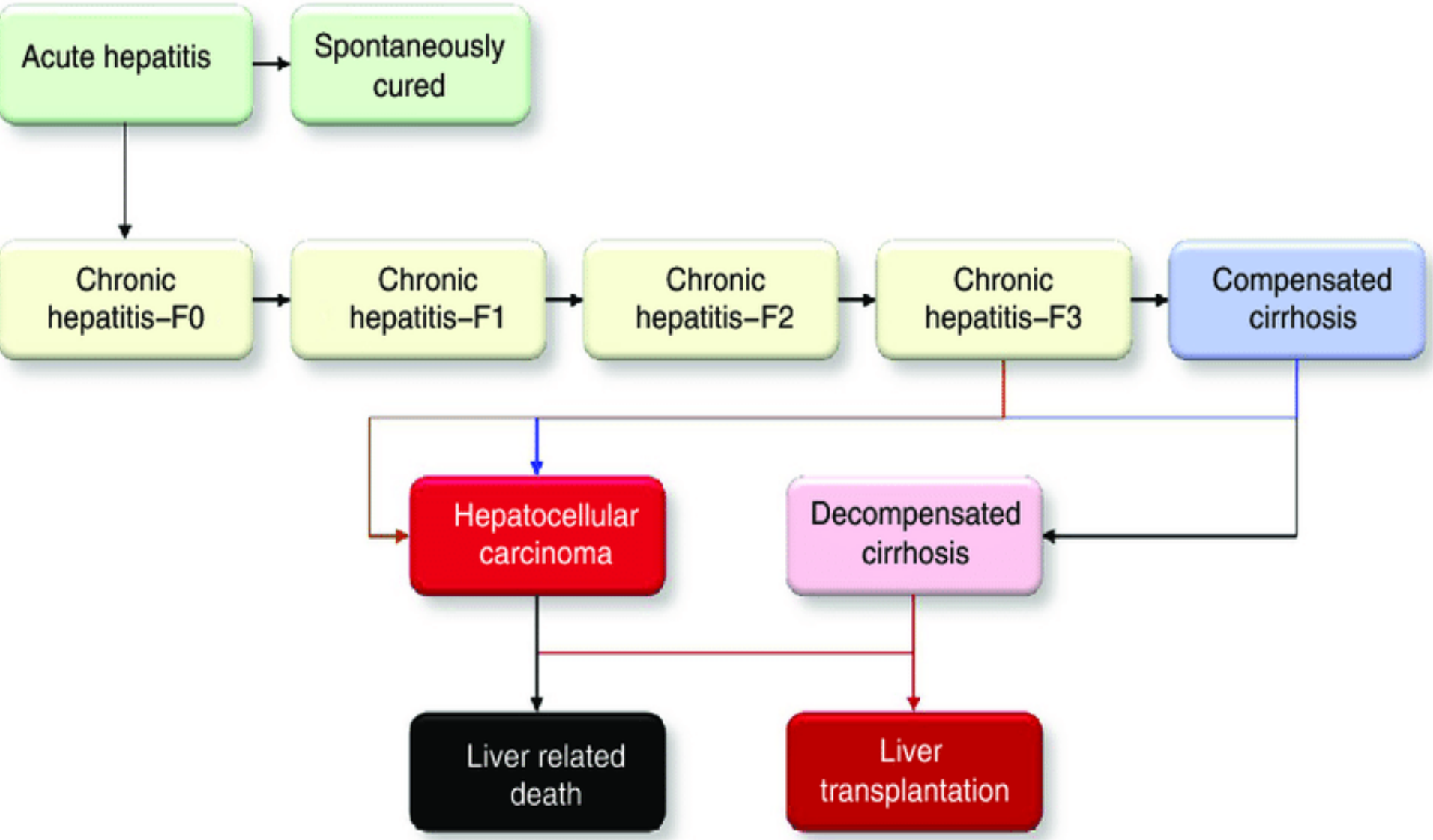
Hepatitis C Prevalence

Risk Factor	Prevalence (%)
Clotting factors < 1987	87
IVDA=IV drug abuse	79
HIV +	25
Increased ALT	15
Hemodialysis	10
> sexual partners	9
History of STD	6
Homosexual	4
General population	1.8
Health care workers	1.0
Healthy blood donors	0.16

HCV Natural History

- 30% with HCV have normal ALT
  - 20% have normal or minimal histology
  - 80% have abnormal histology
  - 15% have advanced histology
  - Disease progression is slower
- Mean progression =
  - Chronic hepatitis 13.7 years
  - Cirrhosis 20.6 years
  - Hepatoma 28.3 years
  - 20% have cirrhosis at 20 years

HCV Natural History



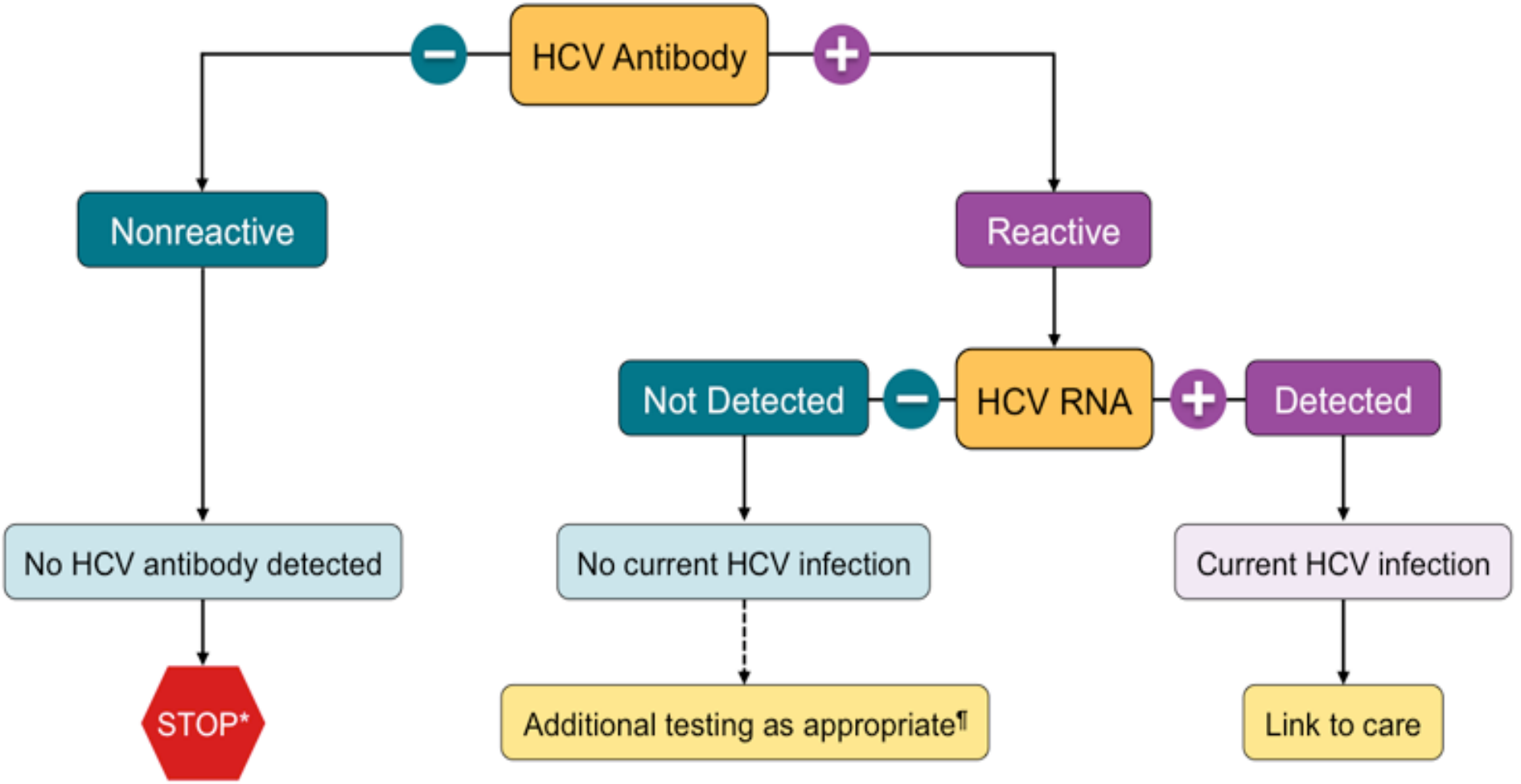
- Other studies
  - Post-transfusion HCV in Italy: 32% have cirrhosis at 7.5 years
  - HCV infected sera given to Irish women: 2% have cirrhosis at 18 years
  - HCV infected RH Ig given to German women: 0% have cirrhosis at 15 years
- Complications of HCV Cirrhosis
  - Decompensation 5% per year
  - Hepatoma 1-4% per year

Hepatitis C

Factors Associated with Disease Progression

- Age > 40
- Male
- Alcohol > 50 gm/d
- Immunosuppression: HIV, transplant, etc.
- Infection by blood transfusion
- Co-infection with HBV
- Genotype 1

Recommended Testing Sequence for Identifying Current HCV Infection



* 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.

Hepatitis C
Goals of Therapy

- Biochemical response — normal ALT
- Virological response — loss of HCV RNA
- End of treatment response — loss of HCV RNA at end of treatment
- Early Virological response (EVR)
  - HCV RNA neg or 2 log reduction at 12 weeks
    - Overall 67 % with EVR achieve SVR
    - 80% who are HCV RNA neg achieve SVR
    - 40% who are RNA +, but have 2 log reduction achieve SVR
  - Patients w/o EVR
    - Only 1.6% achieve SVR
- Sustained virological response (SVR)
  - Undetectable HCV RNA 6 months after treatment ends
  - 95% have persistent SVR over 10 years
  - 80% have reduction in fibrosis

Delta Hepatitis
Hepatitis d

- Defective RNA virus, requires presence of HBV Surface Ag
- 7500 new cases/year .
  - More common in southern, eastern Europe, Middle East, and South America
- Transmission is similar to HBV

Hepatitis D

Can be contracted 2 ways

	Coinfection	*Superinfection*
Contracted by:	Getting Hepatitis B and D simultaneously	Being chronically infected with hepatitis B and contracting Hepatitis D
Likelihood of becoming chronic:	5% (Unlikely)	70-90% (Likely)

Clinical Features of Hepatitis D

Jaundice	Unknown
Fulminant	2 – 7.5%
Diagnostic tests	
Acute infection	IgM anti-HDV
Chronic infection	IgG anti-HDV, HBsAg +
Immunity	Not applicable
Case-fatality rate	1 – 2%
Chronic infection	Superinfection – 80% Coinfection < 5%

- Diagnosis: HDV Ag, HDV RNA, HDV IgG and IgM
- Acute Hepatitis
  - Co-infection with HBV
    - Fulminant hepatitis more common (34%)
    - Progression to chronic infection is uncommon
  - Super-infection of HBV
    - Acute exacerbation of ongoing hepatitis
    - Chronic liver disease occurs in 90%

Hepatitis E

Case definition of HEV

Diário da República, 2.ª série — N.º 82 — 29 de abril de 2014

_Clinical Criteria

Any person with a onset of symptoms compatible with acute viral hepatitis (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting)

AND

At least one of the following three:

a) Fever

b) Jaundice

c) Elevated serum aminotransferase levels

_Laboratory Criteria

At least one of the following two:

a) Detection of hepatitis A virus nucleic acid in plasma or stool

b) Hepatitis A virus specific antibody response

_Epidemiological Criteria

At least one of the following five:

a) Human to human transmission

b) Exposure to a common source of one or more cases

c) Exposure to contaminated food/drinking water

d) Environmental exposure

c) Recent travel to endemic region in less than 3 months

_Case Classification

a) Possible case NA

b) **Probable case**

Any person meeting the clinical criteria and with an epidemiological link

c) **Confirmed case**

Any person meeting the clinical and the laboratory criteria

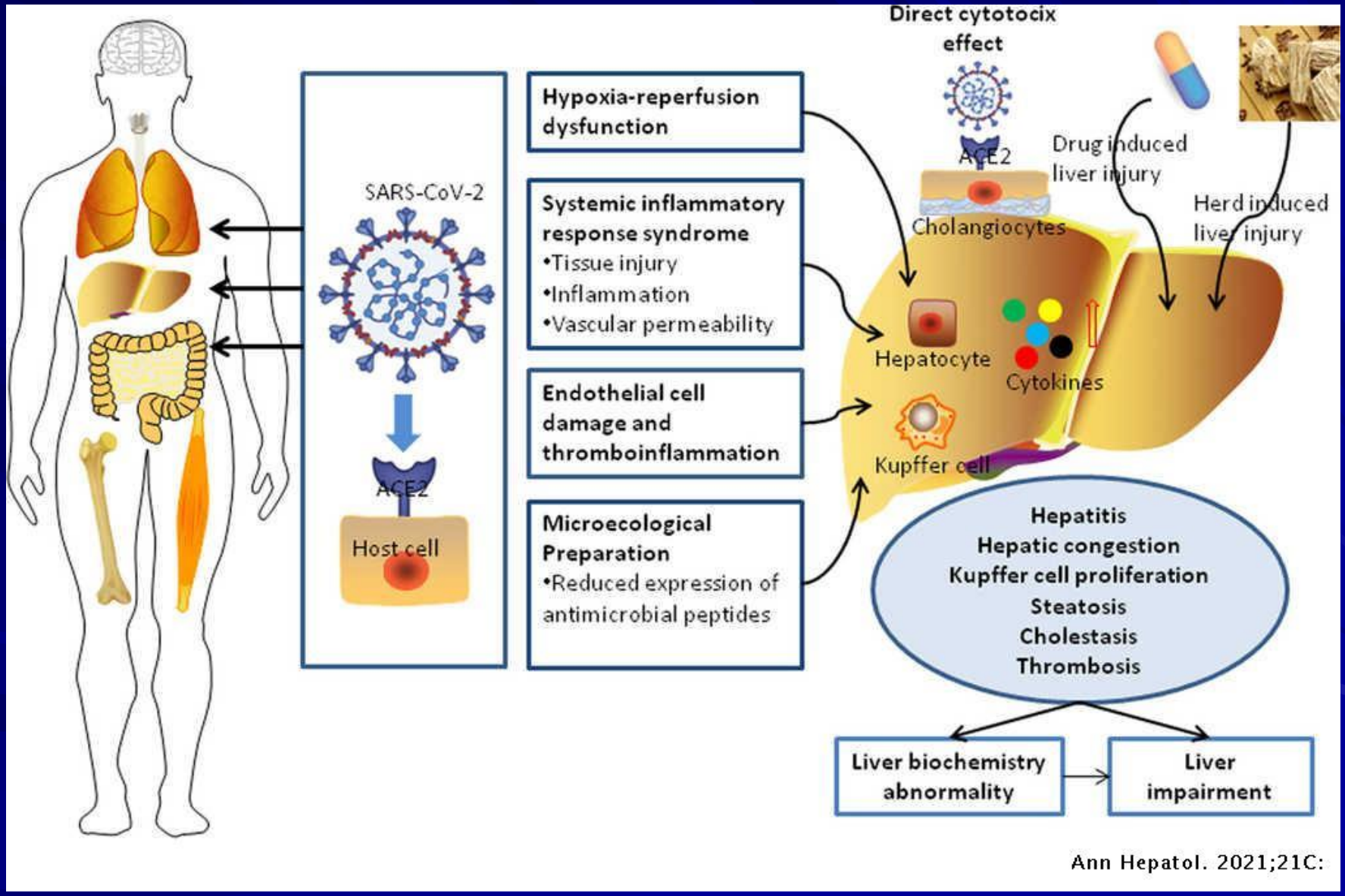
- Related to Rubella virus
- Endemic in equatorial regions of world
  - India, Africa, Central America, Asia
  - May account for 50% hepatitis cases in endemic areas
  - Antibodies found in pigs, other mammals

- Fecal oral transmission
  - Contaminated water
  - Household transmission rates are low 1-2%
- Rare except travelers to endemic regions
- Incubation period is 15-60 days (mean 40)
- HEV IgM + at 27-39 days
- 1-4% overall mortality; 20-30% mortality if pregnant

Other Viruses Causing Hepatitis

- Hepatitis G and GB — related to HCV
- TT Virus — post-transfusional hepatitis in Japan
- Sanban, Yonban, TLMV — related to TT virus, post-transfusional hepatitis in Japan
- Giant Cell Hepatitis — paramyxovirus; 7 small series ~100 patents
- Herpes Viruses
  - HSV 1 and 2 — 90% are immunosupressed or in last trimester of pregnancy
  - HSV 6 and 7 — case reports
  - Cytomegalovirus — after transfusion or transplant
  - Epstein Barr Virus — 11% become jaundiced

COVID-19 HEPATITIS



Ann Hepatol. 2021;21C:

A 15-year-old male presents after 1 week of progressive fatigue,nausea followed by 2 days of jaundice. No Past history of blood transfusion, Laboratory studies demonstrate serum ALT 225 IU/l, ALP of 330 IU/l and bilirubin of 5.2 mg/dl with normal albumin and INR. A liver ultrasound was normal. A positive value for which of the following tests most likely explains this situation?

- a. Anti-HAV IgM
- b. Anti-HB surface
- c. Anti-HCV
- d. Anti-HDV
- e. Anti-HEV

THANK YOU