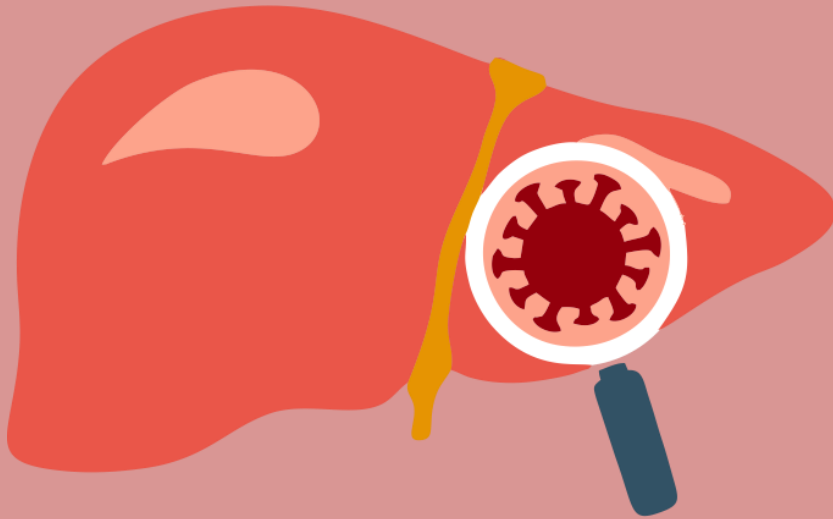


PRAKASH

PRogrammed **A**pproach to **K**nowledge
And **S**ensitization on **H**epatitis



HEPATITIS INDUCTION PROGRAM

Viral Hepatitis

A Pediatrician's Perspective

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New Delhi

Outline

- What are the causes ?
- How to identify them ?
- How to manage ?

ETIOLOGICAL SPECTRUM

Hepatotropic	Non Hepatotropic
Hepatitis A	Cytomegalovirus
Hepatitis B	Parvovirus B19
Hepatitis C	Epstein Barr virus
Hepatitis D	Herpes viruses (HSV 1 & 2)
Hepatitis E	Others: Dengue, VZV, Adeno, HHV etc

Study	HAV	HEV	HBV	Coinfection	Others
Panda et al Delhi, 1989 (n=456)	55.8 %	-	20.2 %	-	23.2 % (NANB)
Malathi et al Chennai, 1998 (n=127)	38.6 %	15.7 %	13.4 %	21.3 %	-
Poddar et al, Chandigarh, 2002 (n=172)	64.5 %	16.3 %	7.6 %	8 %	-
Srivastava et al, Lucknow (n=130)	53.1 %	6.9 %	13.8 %	26.2 %	-

Trop Gastroenterol. 1989 Apr-Jun;10(2):106-10.

[J Trop Pediatr.](#) 1998 Oct;44(5):275-8.

[J Trop Pediatr.](#) 2002 Aug;48(4):210-3

Journal of Viral Hepatitis, 2012, 19, e194–e201

Summary

- Hepatitis A: **38-55 %**
- Hepatitis E: 7-16 %
- Hepatitis B: 7-14 %
- Coinfection: **8-26 %**
- **Unknown: 23 % → 11 % → 3.5 % → 0 %**

Learning Points

- Always exclude HAV, HEV, HBV in all AVH cases
- Also, do Anti HCV - **Silent/Chronic cases**
- Complete evaluation in all → **Co-infection**
- **Test for Other viruses (Serology/PCR):**
 - **If acute liver injury + Negative classical serology**
 - **Choose as per clinical picture**

HEPATITIS A

Viral Characteristics

- Resistant to drying, ether, heat, cold storage, and denaturation by acidic conditions
- Inactivated by:
 - **Heating food to $> 85^{\circ}\text{C}$, &**
 - Treating surfaces with a 1:100 dilution of sodium hydrochloride (household bleach) in tap water

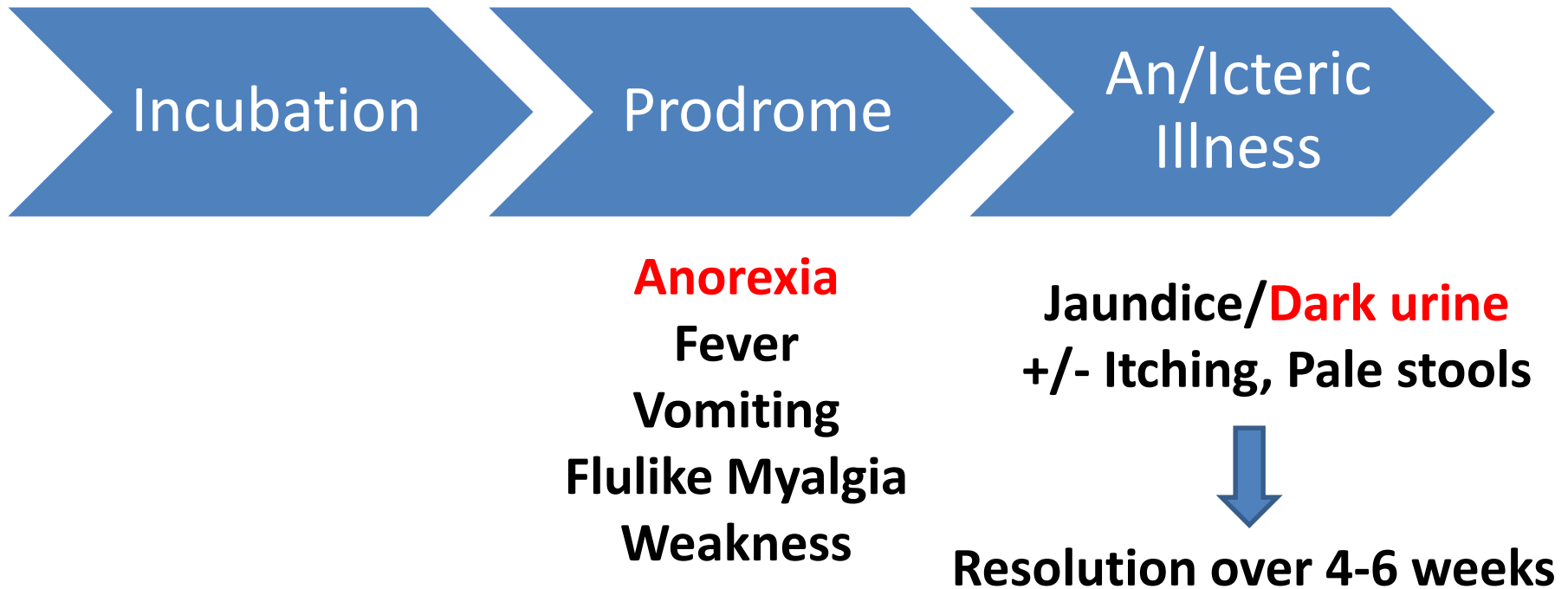
Ref: Suchy's Textbook 'Liver Disease in Children', Fourth Edition

Pediatric Liver Disease Burden

- Overall, in Indian children, HAV infection contributes:
 - 72-85 % of all Acute Viral Hepatitis (AVH) cases
 - 40-61 % of all Acute Liver Failure (ALF) cases
 - 11-42 % of all Acute on Chronic Liver Failure (ACLF) cases
- Most important single etiological agent for pediatric liver diseases

Ref: JPGN, 2010 Feb;50(2):184-7; Arch Dis Child. 2002; 87:54-6; [Liver Int.](#) 2017 Oct;37(10):1508-1514. JPGN 2016;63(4):400-5; [Hepatol Int.](#) 2011 Jun;5(2):693-7.

Clinical Features



Historical Evaluation

- Family or Neighbourhood **Contact**
- **Multisystem** Involvement:
 - Fever, Rash
 - Loose Stools
 - Red Eyes
 - Coryza/Cough/Sore Throat
 - Lymphadenopathy

Non Classical Viruses

IgM CMV/EBV/Varicella/HSV/Dengue/Parvo/Adenovirus

HEV Infection

- Rarely have prolonged cholestasis- Good outcome
- Rarely as FHF, esp pregnant women.
- High incidence of asymptomatic or inapparent HEV infection
- CFR- 0.5% to 4% (Hospital Based)
- Population surveys- 0.07% to 0.6%.

Naik SR et al. *Bull. World Health Organ.* 1992; **70**: 597–604.
Zhuang H et al. *Amsterdam: Excerpta Medica*, 1991; 277–85.

HEV and ACLF

- HEV superinfection on CLD- Superimposed acute liver injury and acute on chronic liver disease.
- Higher risk of a poor outcome.

ORIGINAL ARTICLE: HEPATOLOGY AND NUTRITION

Acute on Chronic Liver Disease in Children From the Developing World: Recognition and Prognosis

Barath Jagadisan, Anshu Srivastava, Surender Kumar Yachha, and Ujjal Poddar

Outcome- HAV

- Self resolution in almost all
 - Liver Failure in **< 1 %**
 - Atypical Manifestations (esp. HAV):
 - Prolonged Cholestasis- 15-20 %
 - Relapsing Course- 5-10 %
 - Ascites- 13-21 %
 - Severe Anemia- **Associated G6PD Deficiency**

J Pediatr Gastroenterol Nutr. 2010;50:184–7; J Trop Pediatr. 2002;48:210–3; [Trop Doct.](#) 2013 Jan;43(1):17-8.

Warning signs in AVH

- Deepening Jaundice
- Excessive sleepiness, Abnormal behaviour
- Loss of appetite, Persistent vomiting
- Coagulopathy, Bleeding from any site
- Fever
- Seizures
- Cola colored urine
- Abdominal distension

When to suspect underlying CLD

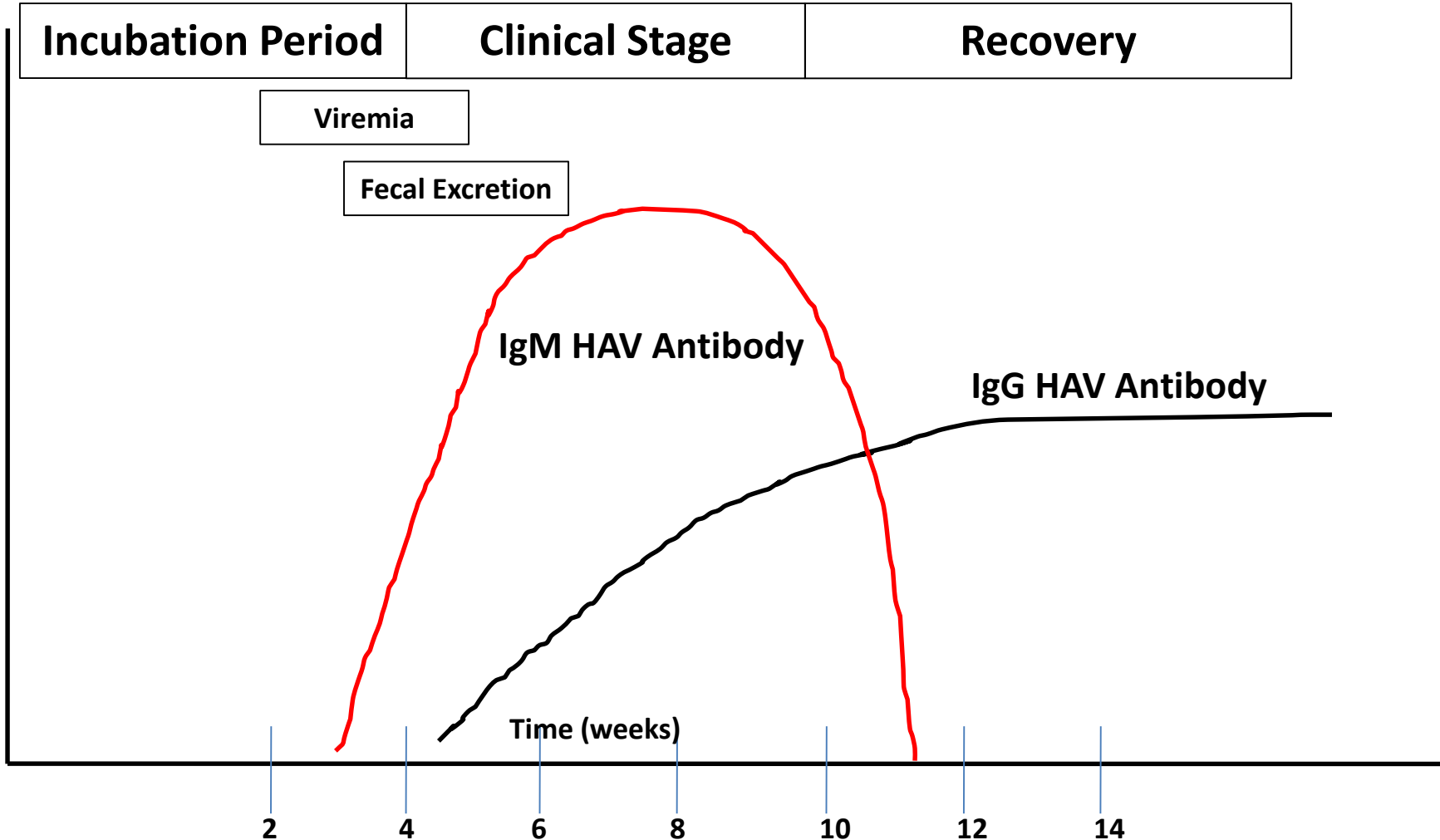
- Positive family or past history of liver disease
- Decompensation (Ascites, Encephalopathy)
- Firm Organomegaly
- USG:
 - Coarse Echotexture, Nodularity
 - Collaterals, Splenomegaly

DIAGNOSIS

Work up

Standard Work up	Etiological Work up
LFT	<p>All patients:</p> <ol style="list-style-type: none">1. IgM HAV2. IgM HEV3. HbsAg, IgM Anti Hbc4. Anti HCV
PT-INR	
USG Abdomen	
	<p>Selected patients/if above negative:</p> <ul style="list-style-type: none">• IgM CMV/EBV/VZV/HSV/Dengue/ Parvo/Adeno virus

Diagnosis



Ref: Nelson Textbook of Pediatrics, 20th Edition; Suchy's Textbook 'Liver Disease in Children', Fourth Edition^{xxxx}

Diagnosis

•Acute Infection:

- Requires IgM anti-HAV antibody testing
- Detected in serum 5–20 days following exposure
- Remains +ve for 30-420 days (average 4 months)

•Past Infection or Previous immunization:

- Associated with serum IgG anti-HAV antibodies
- Lifelong immunity

Ref: Nelson Textbook of Pediatrics, 20th Edition; Suchy's Textbook 'Liver Disease in Children', Fourth Edition^{xxxx}

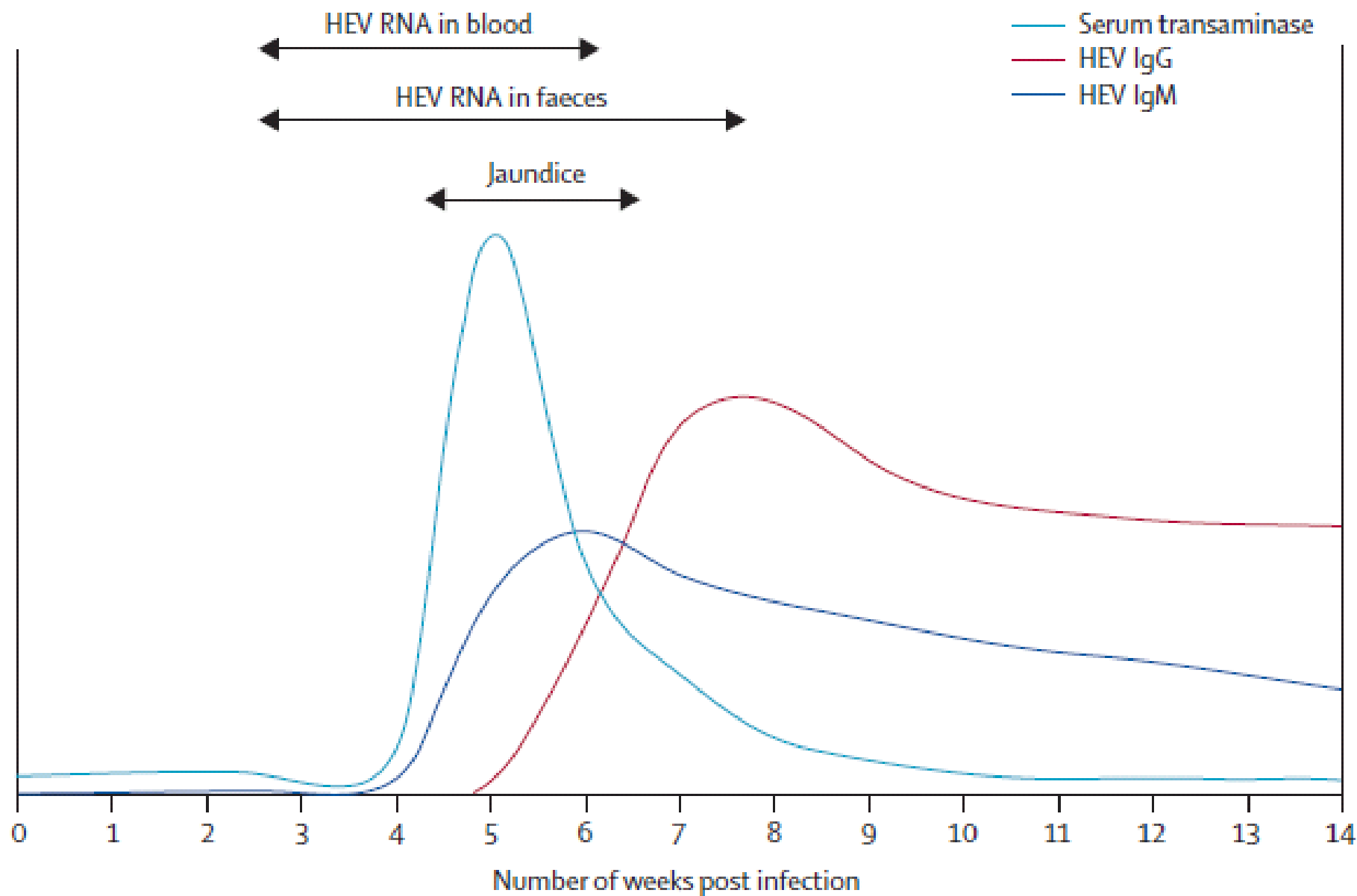


Figure 1: Schematic representation of HEV infection, showing virus detection at different sites and serological response

MANAGEMENT

General Treatment

- Parental (& Doctor's 😊) Reassurance
- Normal Diet, Plenty of Fluids
- No medications needed (in majority)

Do's & Don'ts

No restriction on Diet



No Bed Rest needed



Bland Food- Restriction of Salt, Fat, Spices, Turmeric



Herbal Medicine Intake



Glucose Water, Sugarcane Juice Intake



Specific Treatment

- Antivirals for:
 - Hepatitis B (Needed in < 5 % only)
 - Indication:
 - » ALF
 - » Severe acute hepatitis B (INR > 1.5), or a protracted course (i.e., persistent symptoms or marked jaundice for > 4 weeks)
 - Others: HSV, Varicella, CMV

Anti Viral Measures- HEV

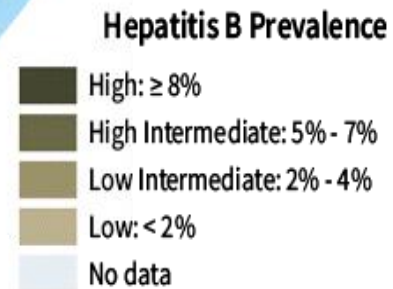
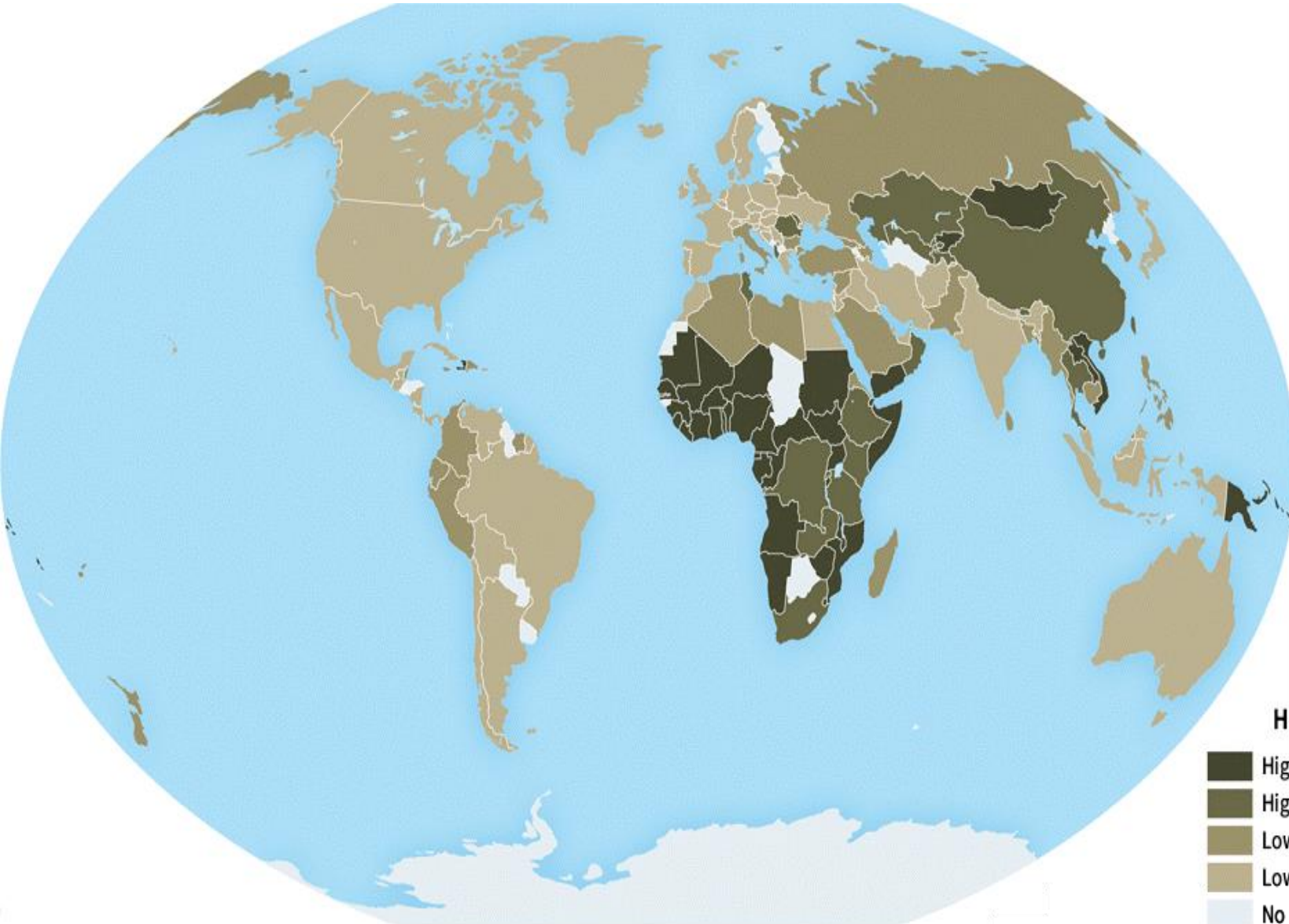
- Use of pegylated interferon, ribavirin or both in chronic HEV infection due to associated risk of progressive liver injury
- May lead to cirrhosis after < 3 years of infection
- Mostly case reports or small case series.

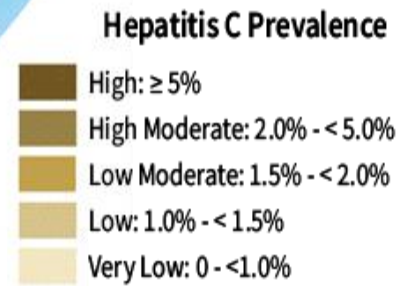
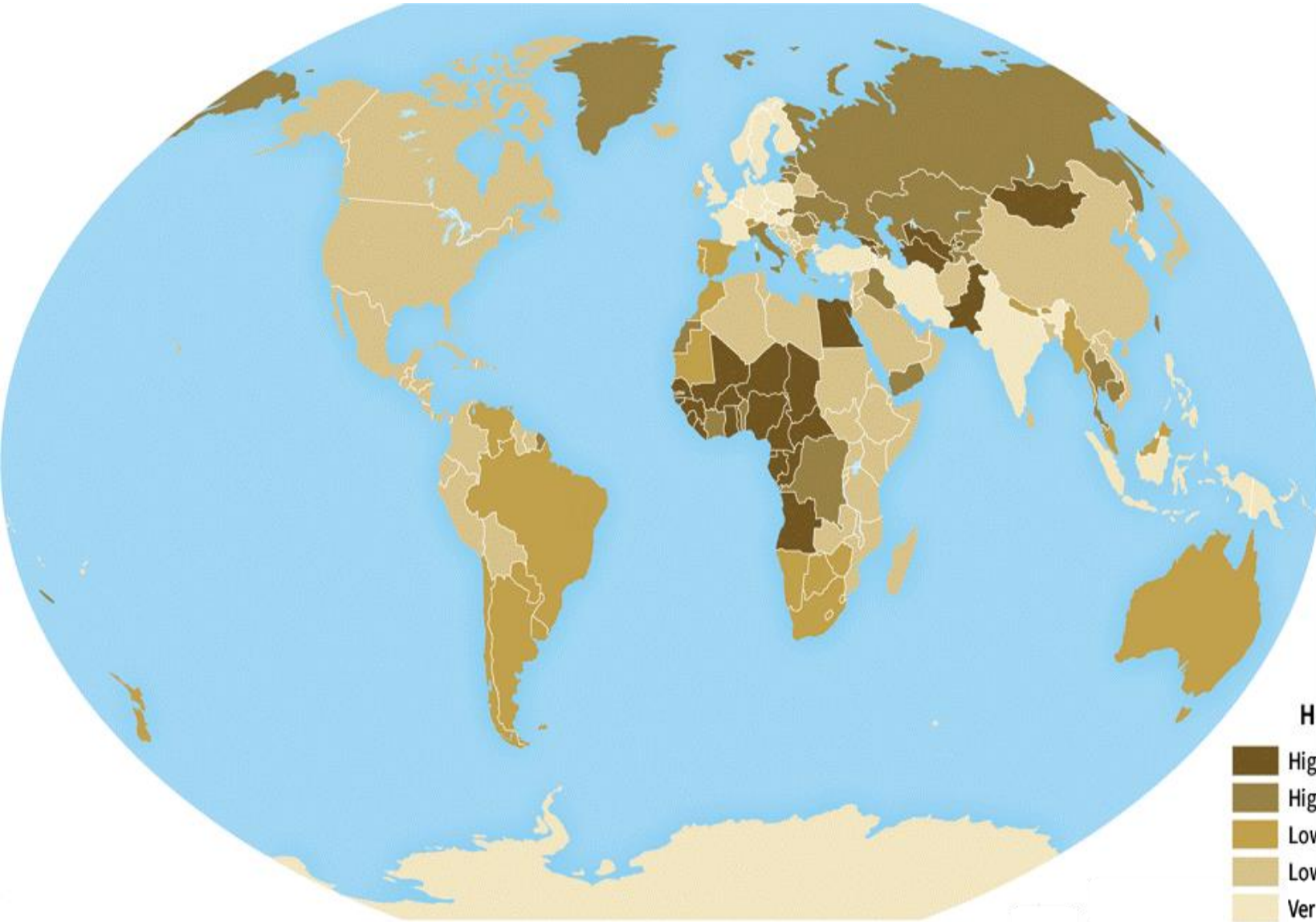
Gerolami R et al. N Engl J Med **2008; 358:859–860.**
Haagsma EB et al. Liver Transpl **2008; 14(4): 547–553.**
Kamar N et al Am J Transplant **2008; 8(8):1744–1748.**

Chronic Viral Hepatitis

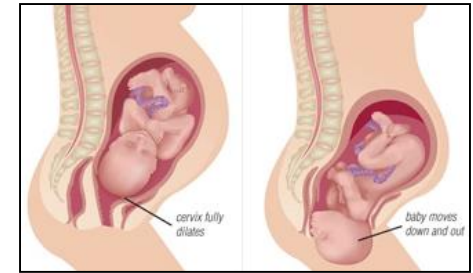
Key Facts

- **The WHO (in 2019):**
 - 296 million living with hepatitis B
 - 58 million living with hepatitis C
 - 1.5 million newly infected with chronic hepatitis B
 - 1.5 million newly infected with chronic hepatitis C
- **India:**
 - 10% to 15% of the global pool (40 million HBV carriers)





- 1) **Perinatal** - mother to baby (vertical transmission)
 - during parturition, or immediately after birth
 - major route in the developing world including India
 - Asia, sub-Saharan Africa



- 2) **Sexual** - major route in the developed world
 - U.S., Europe



- 3) **Others routes**
 - injection drug use (IDU)
 - blood transfusion (BT)
 - hemodialysis



Transmission-HBV

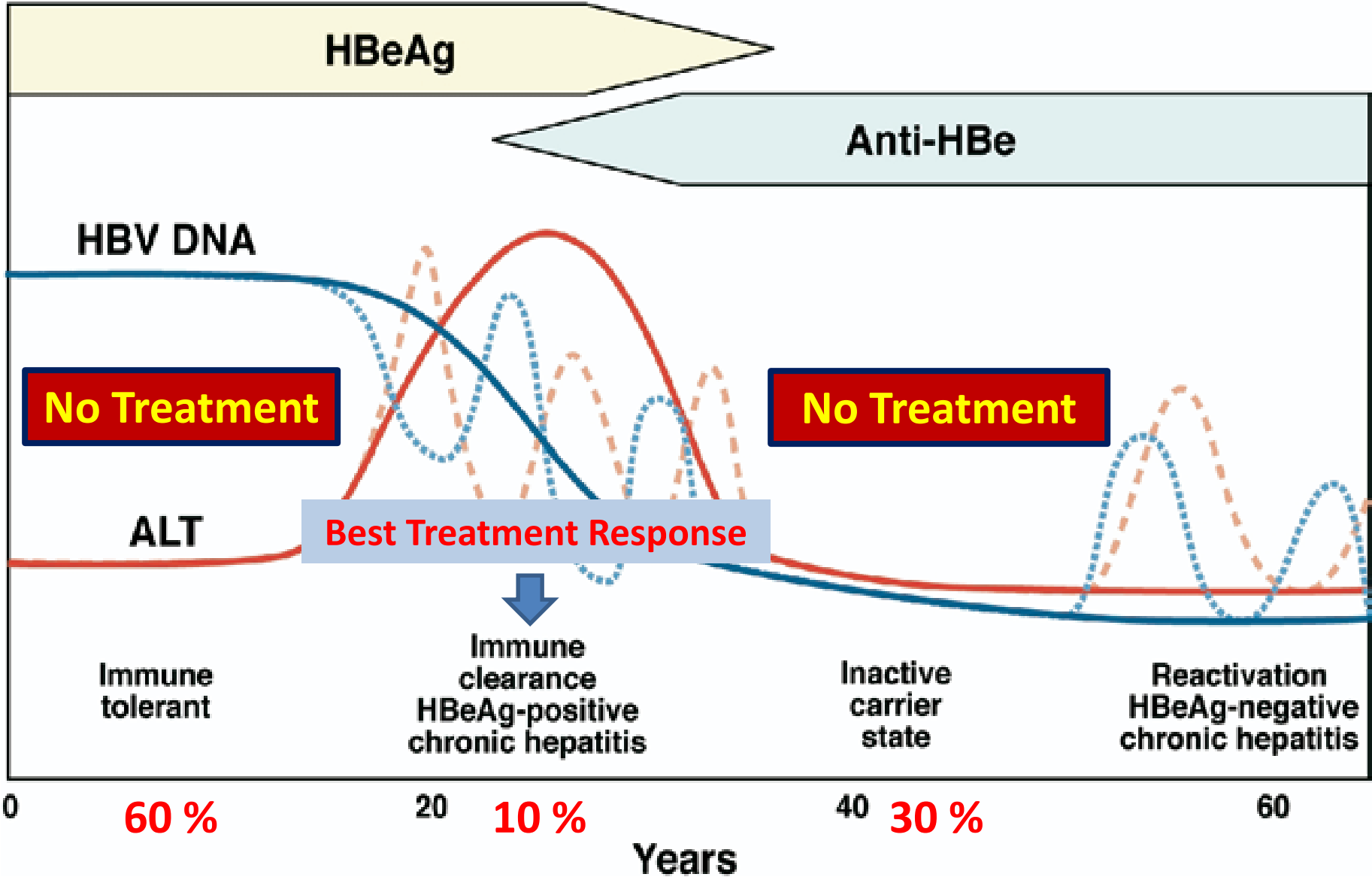
- HBV does not spread through:
 - food or water
 - sharing eating utensils
 - breastfeeding
 - hugging, kissing, hand holding
 - Coughing or sneezing

High Risk Groups-HBV

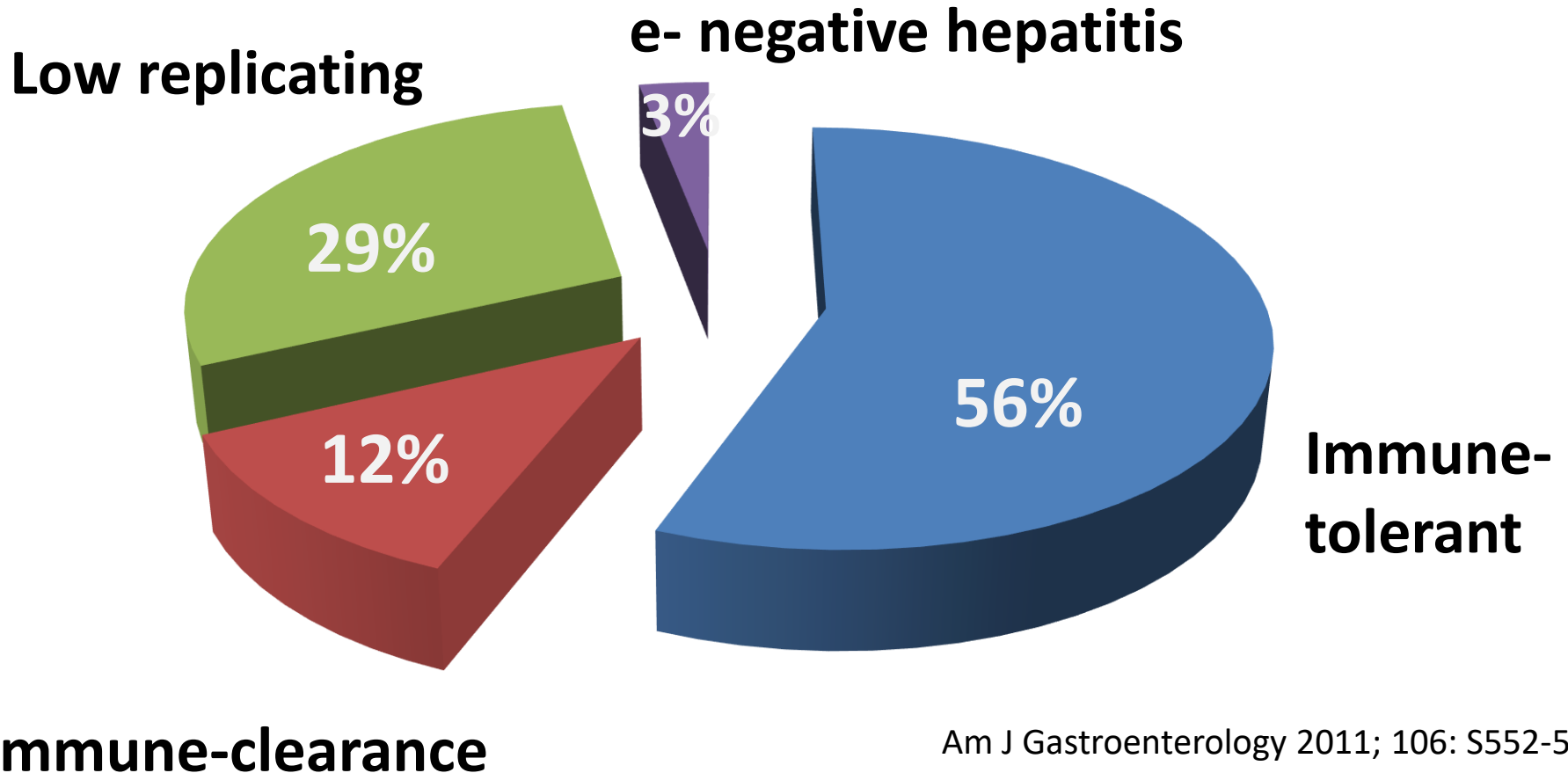
- Infants born to infected mothers
- Sex partners of infected persons
- Men who have sex with men
- Injection drug users
- Household contacts of known persons with chronic HBV infection
- Health care professionals
- Hemodialysis patients



Stages of HBV infection



Spectrum of Chr. HBV in Children (n=203)



Am J Gastroenterology 2011; 106: S552-553

Natural History in children

- Mostly Perinatal Transmission

Risk of Chronicity as per age of acquisition

1. Infancy- >90%
2. 1-5 Years- 25-50%
3. > 5 Years- 5-10 %

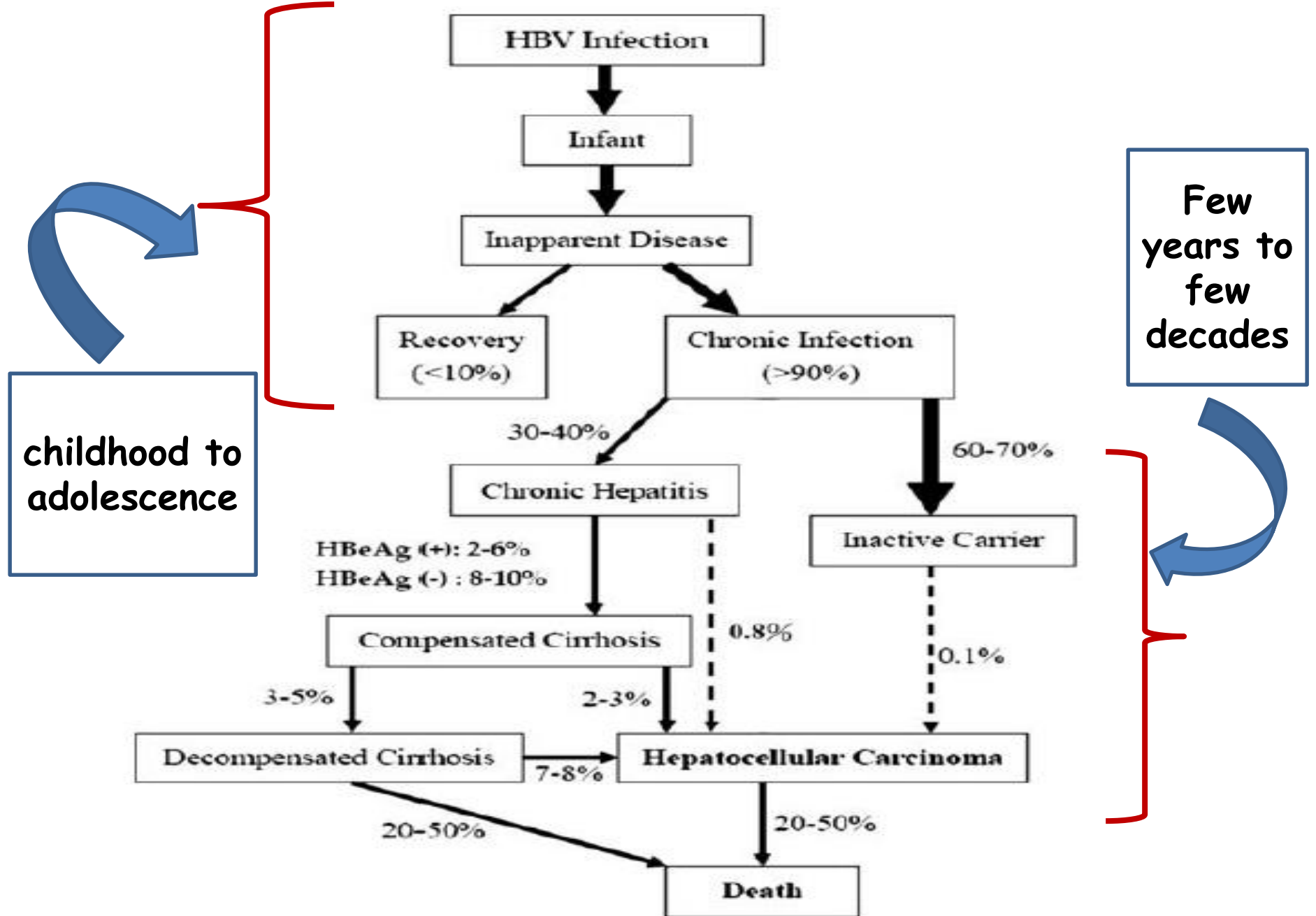
Seroconversion Rates

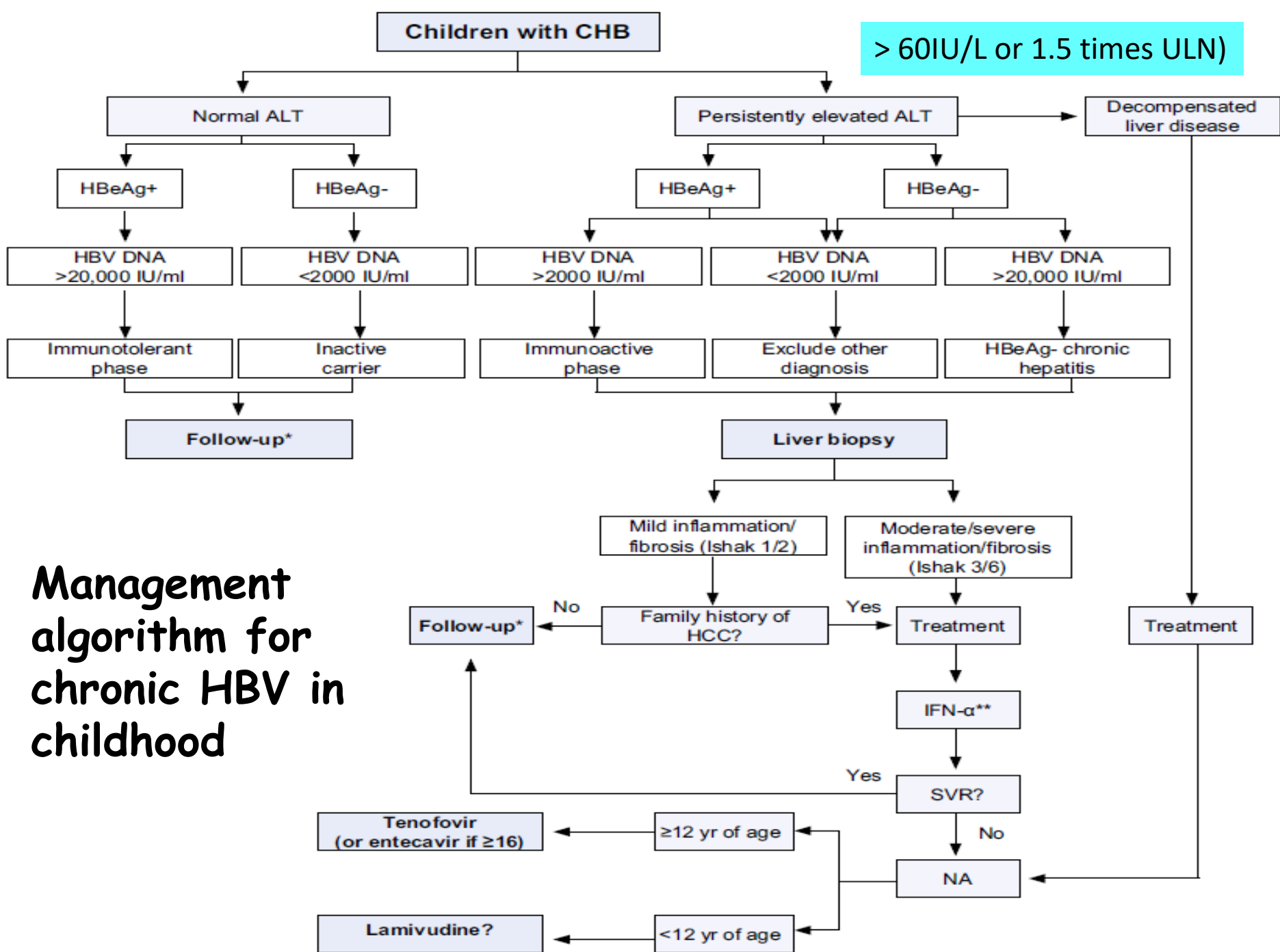
Perinatal Transmission- Asians

1. < 3 Yr Age- 2%/Year
2. > 3 Yr Age- 4-5%/Year

Horizontal Transmission- Europeans

70-80% over 20 Years



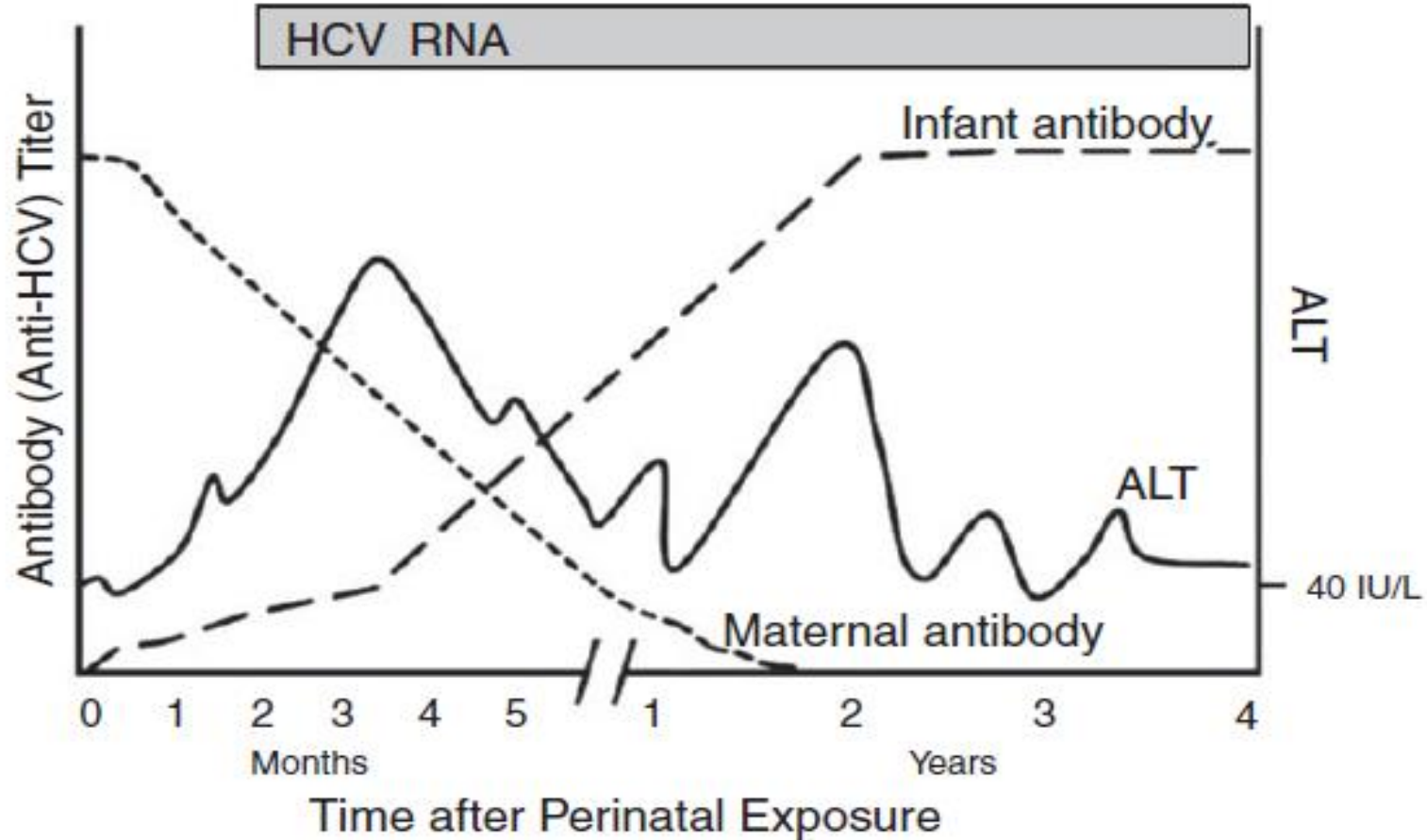


Family screening

- HBsAg
- Anti-HBs titre
- Total Anti-HBc

	HBsAg	Total Anti-HBc	Anti-HBs	Status	Remarks
1.	-	+	<10 mIU/mL	Exposed	Offer vaccination
2.	-	-	<10 mIU/mL	Unexposed Unimmunized	Offer vaccination
3.	-	-	>10 mIU/mL	Unexposed Immunized	No vaccination
4.	+	+	<10 mIU/mL	Infected	Further testing HBeAg, Anti-HBe, DNA

HCV Infection

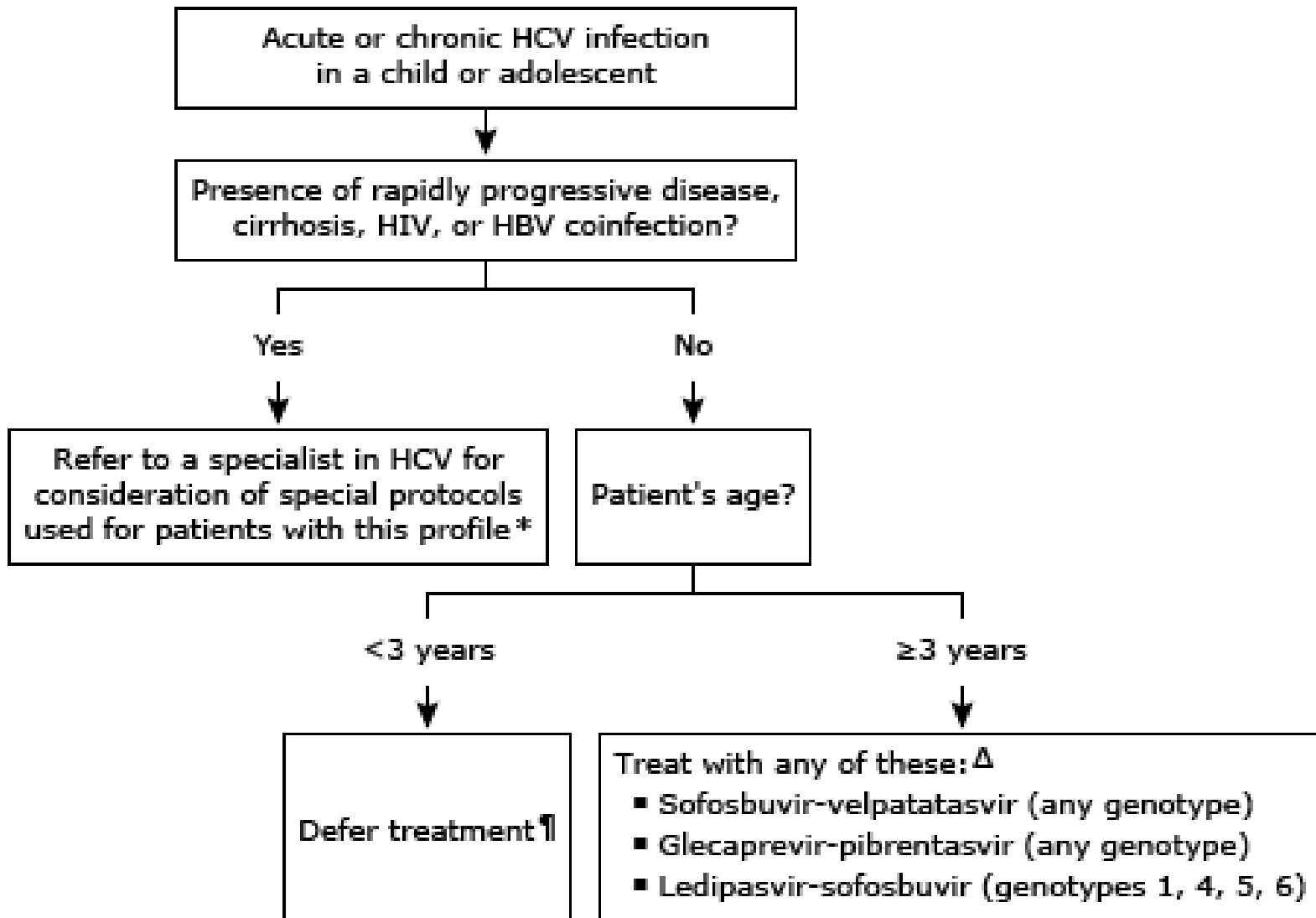


Vertical Transmission:

- 20% clear infection without any treatment (first 2-4 years of life)
- Remaining 80% → Chronic infection

Lab Diagnosis-HCV

- Anti-HCV antibody
- HCV RNA (Quant)
- HCV Genotype



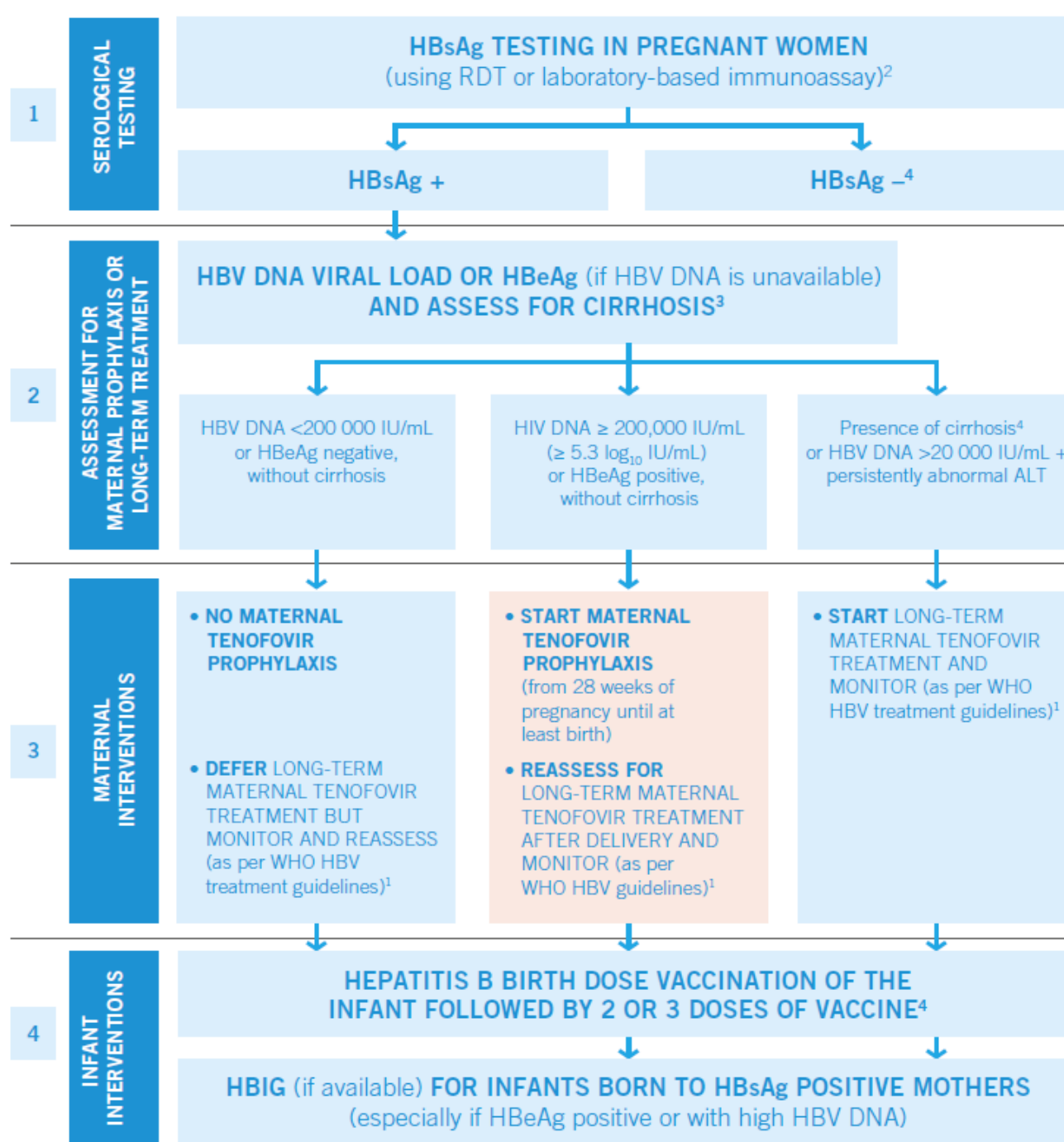
PREVENTION

Prevention

- Check (esp if doubtful vaccination history):
 - Anti Hbs titres
 - Anti HAV Total or IgG (>5 years age)
- Family Screening, if HBV infection:
 - HbsAg
 - Anti Hbc Total
 - Anti Hbs titres

Prevention-HBV

- Hepatitis B vaccine: effective
 - NFHS-4: 66.3% coverage for all 3 doses
- Maternal screening for HBsAg
- Safe sex
- Do not share needles
- Universal precautions for HCWs



Effect of elective cesarean section on the risk of mother-to-child transmission of hepatitis B virus

Hu *et al.* *BMC Pregnancy and Childbirth* 2013, **13**:119

Table 2 HBV serologic markers in 546 children of HBsAg-positive mothers who delivered their infants by ECS and VD

Serologic marker	ECS (n = 285)	VD (n = 261)	p
HBsAg+, n (%)	7 (2.5)	6 (2.3)	0.904
Anti-HBc+/HBsAg-, n (%)	7 (2.5)	10 (3.8)	0.355
Anti-HBs \geq 10 mIU/ml, n (%)	206 (72.3)	185 (70.9)	0.717

With the recommended immunoprophylaxis against hepatitis B, ECS does not reduce the risk of mother-to-child transmission of HBV.

Therefore, ECS should not be used in HBsAg-positive pregnant women to prevent mother-to-child transmission of HBV

Breast-feeding and Risk of HBV Transmission

Author	No. of infants	Population	Prophylaxis	Infected or failed seroconversion to antiHBs		P
				BF (%)	FF (%)	
Beasley <i>et al</i> ^[56]	147	USA, Taiwan (China)	No	53	60	NS
Tseng <i>et al</i> ^[57]	170	Hong Kong (China)	HBIG + Vx	7	6	NS
de Martino <i>et al</i> ^[58]	85	Italy	Vx	4.6	3.2	NS
Hill <i>et al</i> ^[59]	369	USA	HBIG + Vx	0	3	0.06

BF: Breastfeeding; FF: Formula feeding; HBIG: Hepatitis B immune globulin; NS: Nonsignificant.

Petrova M, 2010

No differences in HBV transmission regarding feeding practices

Even in cases of no active or passive prophylaxis, the risk of transmission from HBV-positive mothers to their breastfed infants is at least equal.

Hepatitis A

× Strategies:

- Adequate food/water hygiene

- **Passive prophylaxis with Immune Globulin**

- Only for children < 12 months; immunocompromised hosts; those with chronic liver disease or in whom vaccine is contraindicated

- Within 2 weeks of exposure

- Limited practical role

- **Active Immunisation with Vaccine**

Ref:

Journal of Hepatology 2018 vol. 68 j 167–184; Nelson Textbook of Pediatrics, 20th Edition

Vaccination Options

- Available vaccines (≥ 12 month age):
 - **Formalin-inactivated ('killed')**:
 - Intramuscular route, Two doses at a six-month interval
 - **Live attenuated**:
 - Single dose, Subcutaneous route
- Excellent efficacy ($>90-95\%$) and safety data
- Recommended by IAP

Ref: IAP Immunisation Schedule 2018; Indian Pediatrics Volume 55; December 2018

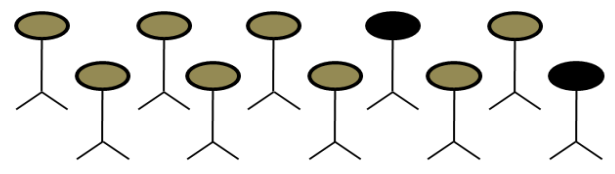
Vaccination Strategy

- × Check (esp if doubtful vaccination history):
 - + Test for Anti HAV Total or IgG (if > 5 years age)
 - + To avoid vaccinating those with natural immunity
 - + No vaccine needed if positive results

Ref: J Pediatr Gastroenterol Nutr. 2014 Sep;59(3):393-7

Significance of Vaccination against HAV Infection

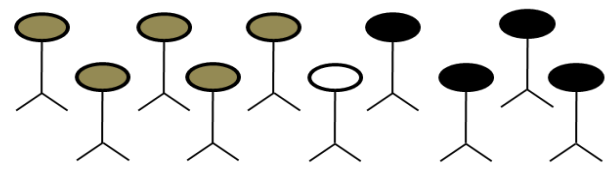
High Endemicity



Endemic Pattern
Poor Hygiene/Sanitation
Majority Population: Infected and Immune
Minority Population: Susceptible

Ongoing Epidemiological Transition in India

Intermediate Endemicity



Epidemic Pattern (Current Scenario)
Improved Sanitation (Decreased HAV Transmission)
Low Immunization Coverage
Increasing Age/Disease Severity in Susceptible Population

Goal

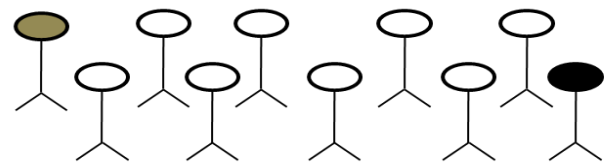
Improved Hygiene/Sanitation
High Immunization coverage
Vast Majority: Vaccinated & Immune
Minimal Susceptible Population



Sanitation



Vaccination



Ref:

Susceptible Person

Immune after Infection

Vaccine Immune

HEV Vaccine 1

- Successful in Phase II study
- 2000 Nepalese soldiers, with a 96% efficacy after administration of 3 doses(0, 1 and 6).
- After 3 vaccine doses, hepatitis E in 69 subjects (66/69 in placebo group).
- No further development

Shrestha MP et al. N Engl J Med 2007;356:895– 903

HEV Vaccine 2

- A Phase III study of 100,000 Chinese adults
- Recombinant HEV vaccine (HEV 239- 26 KDa protein encoded by ORF2 of HEV1)-30 g purified HEV antigen adsorbed to 0.8 mg aluminum hydroxide
- 94%–100% efficacy, Safe in pregnant women.
- Protects against infection with HEV genotypes 1 and 4
But ?? 3
- Approved in China in December 2011.

Wu T et al. Hepatology 2011 Dec 13

Wedemeyer H et al. Nat Rev Gastroenterol Hepatol 2011;8:8–10.

Carry Home Messages

- HAV & HEV- Commonest causes of AVH
 - Work up- Not to be limited to HbsAg/Anti HCV only
- Management of AVH
 - No dietary restrictions or medicines
 - Reassurance is the key
- Pick up HBV/HCV early- Screen family/high risk groups

THANK YOU