

NATURAL HISTORY OF HEPATITIS B AND DIAGNOSTIC: STATE OF THE ART



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*The 2nd Congress of The Federation of Arab Societies
of Clinical Microbiology and Infectious Diseases
Tunisia, 24 – 26 May 2012*

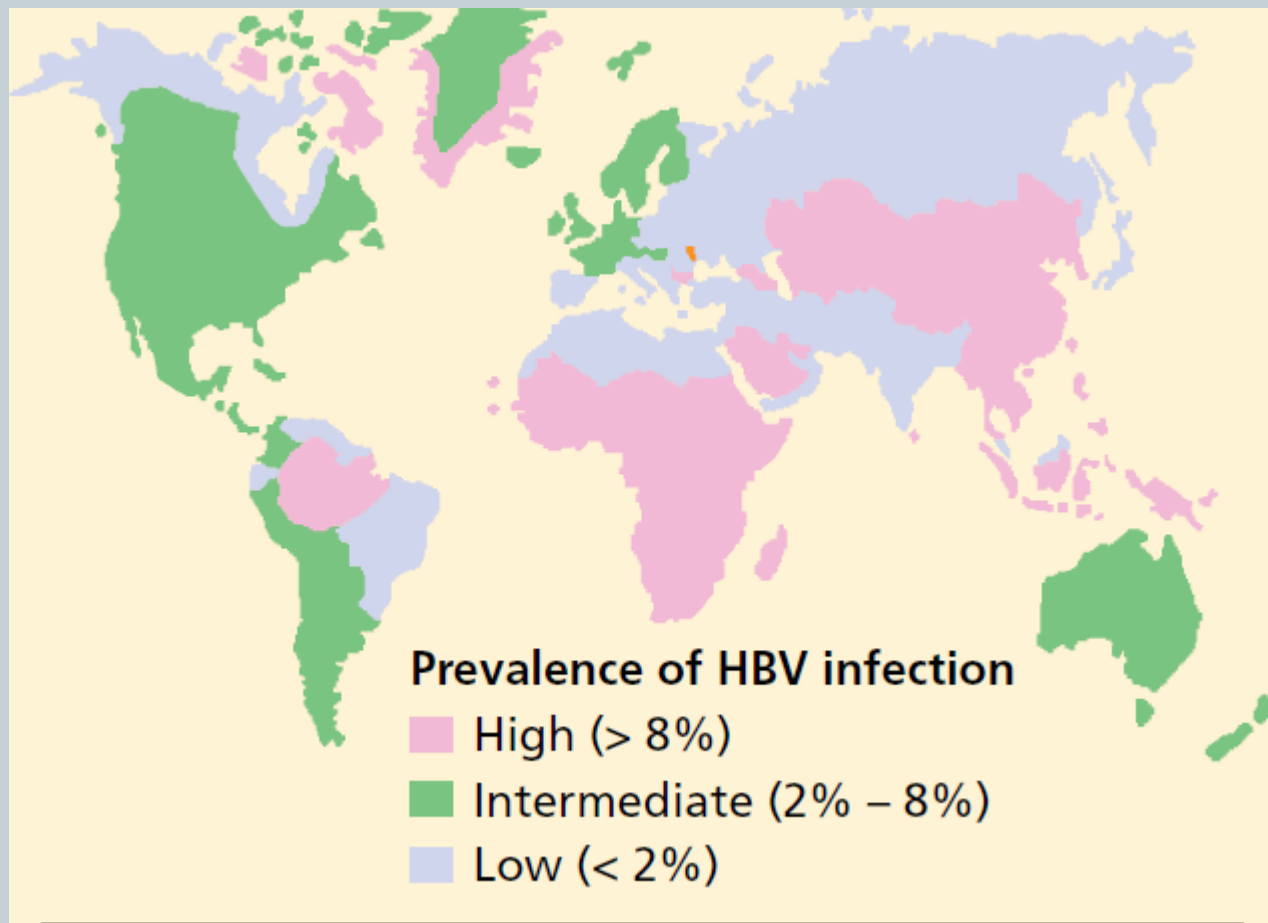
HEPATITIS B = GLOBAL HEALTH PROBLEM



One of the most common chronic viral infections

<i>HBV contact</i>	≈ 2 billion
<i>HBV chronically infected</i>	350 – 400 million
<i>Death</i>	≈ 1 million annually
<i>Ranked cause of cancer</i>	5 th worldwide
<i>Ranked cause of death by cancer</i>	3 th worldwide

HEPATITIS B = GLOBAL HEALTH PROBLEM



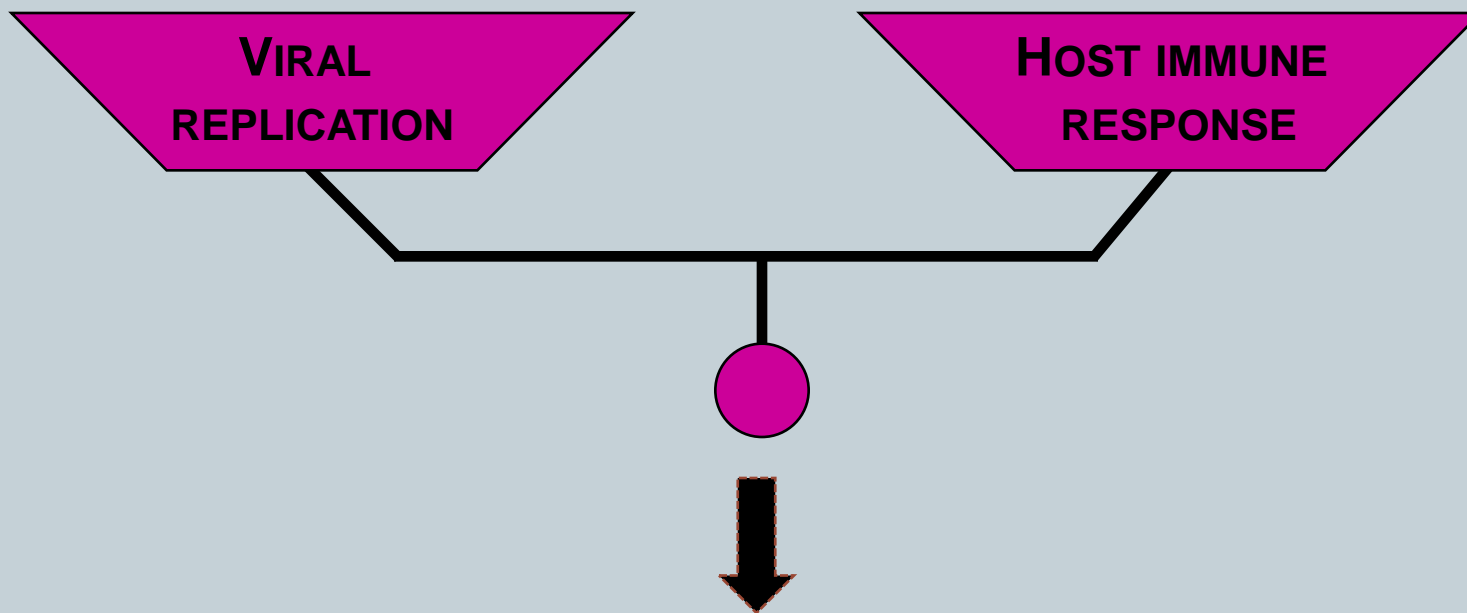
High endemicity:

- Asia
- Africa
- Parts of southern, eastern Europe

NATURAL HISTORY OF HBV INFECTION



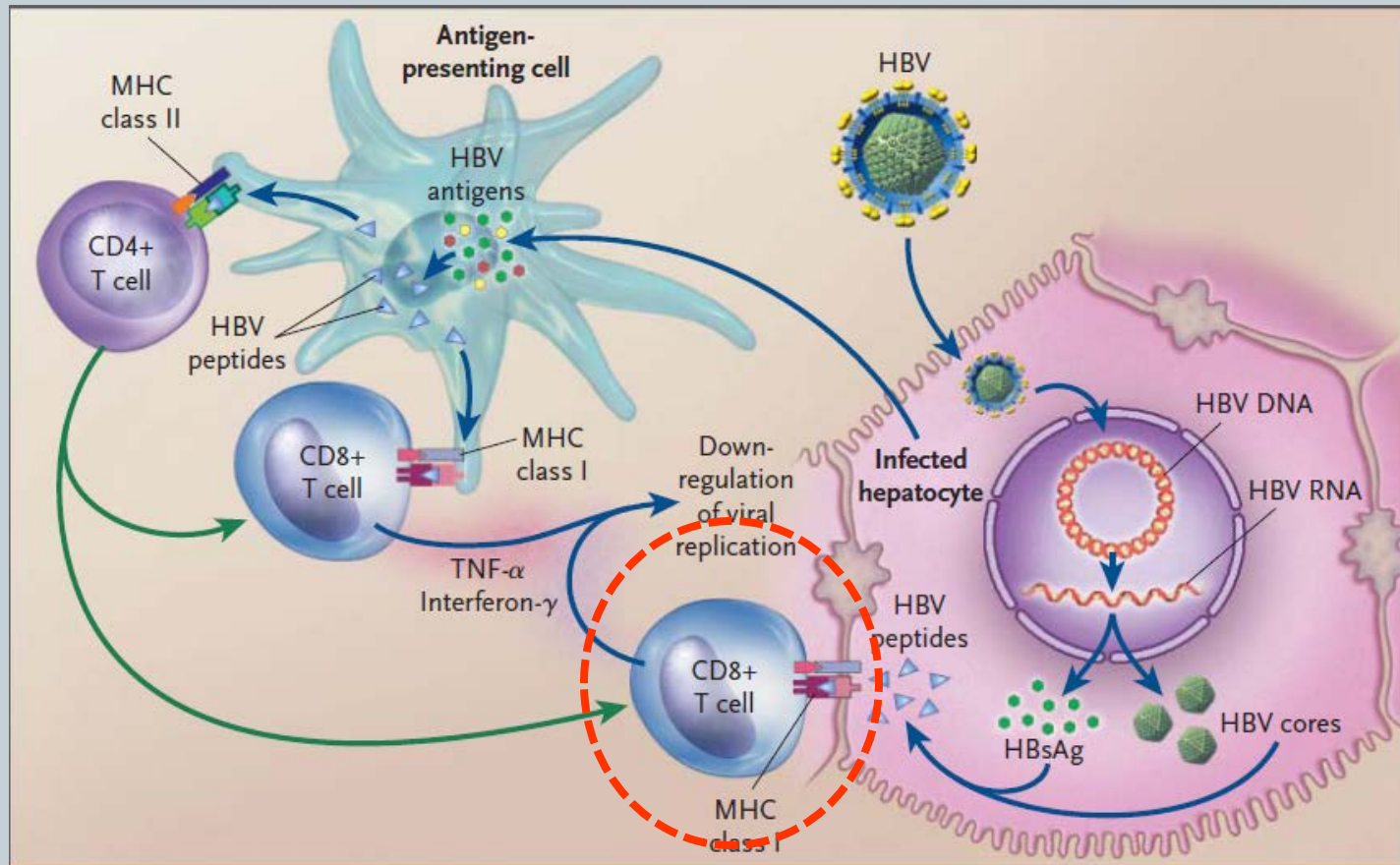
HBV infection = a dynamic process



- Course of viral infection
- Severity of liver damage

NATURAL HISTORY OF HBV INFECTION

Immune response against HBV infection



NATURAL HISTORY OF HEPATITIS B



Acute HBV infection

Immune response is
adequate

CD8+



HBV clearance
Moderate liver damage

Resolved form

Immune response is
enhanced

↑↑↑CD8+



HBV clearance
Massive liver damage

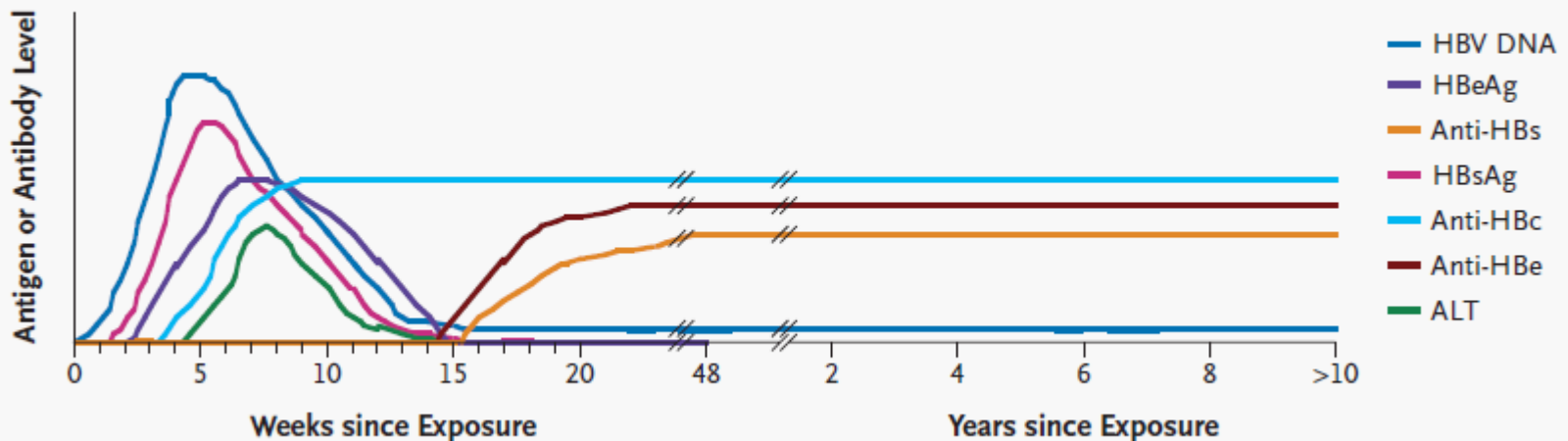
Fulminant form

NATURAL HISTORY OF HEPATITIS B



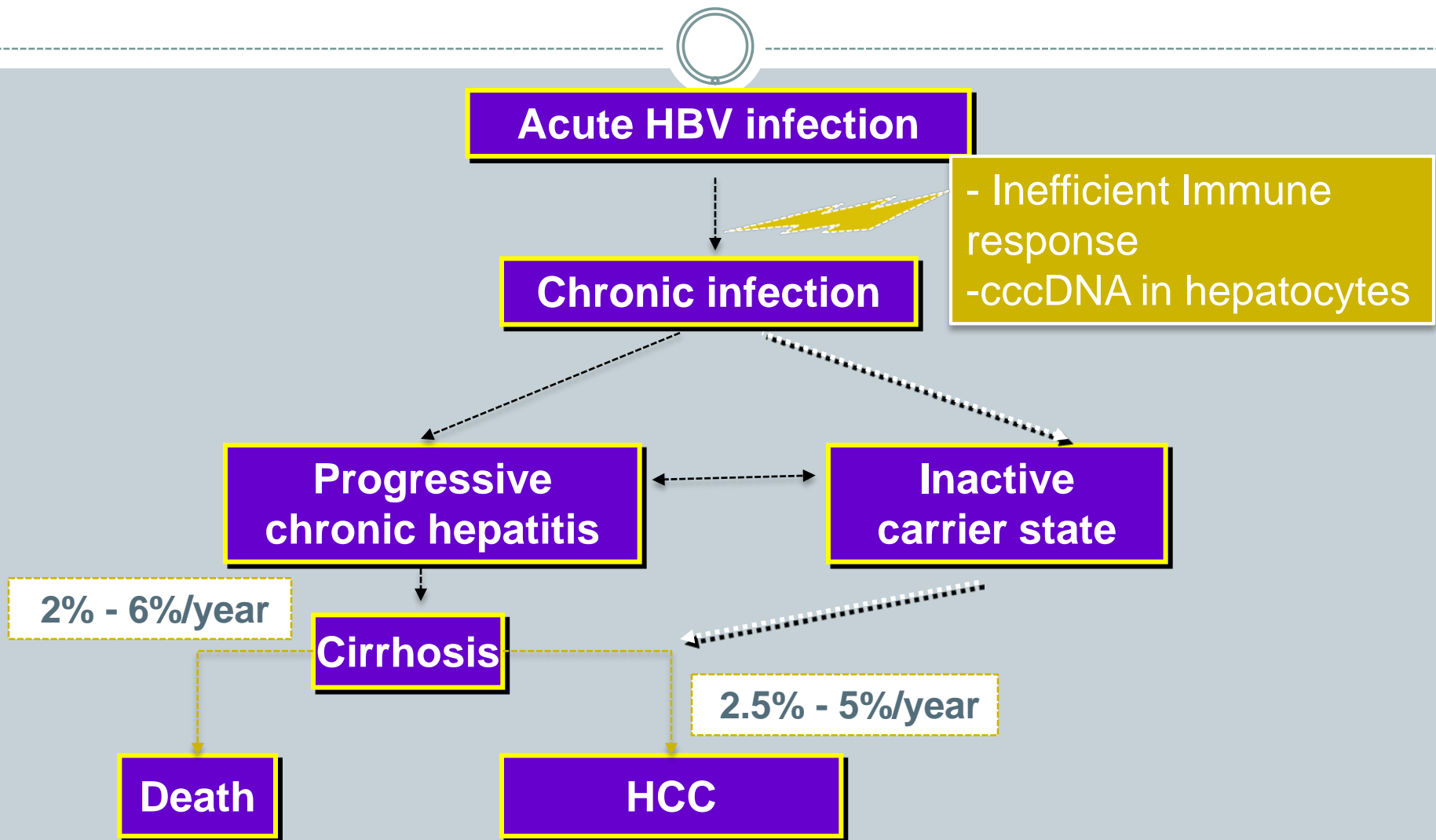
Acute HBV infection

A Acute Self-Limited HBV Infection

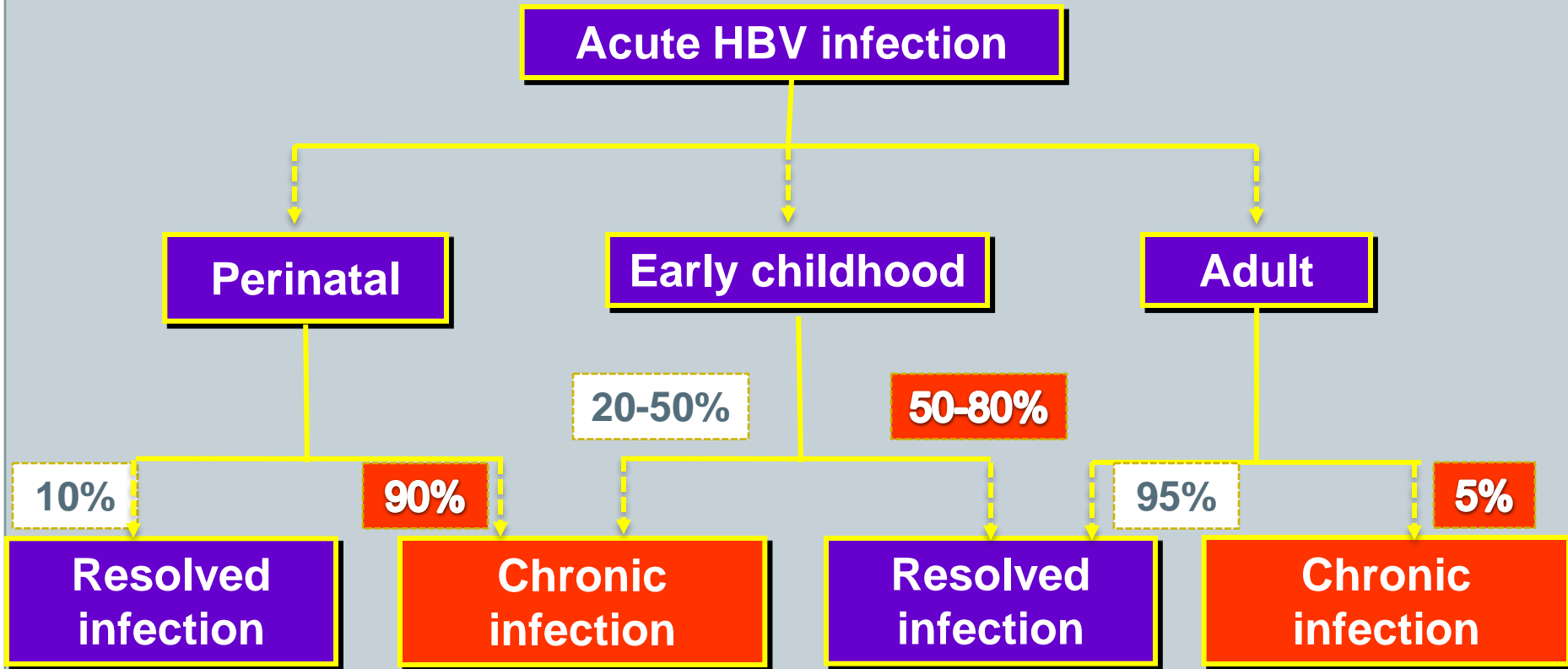


- Fulminant form is characterised by:
 - Presence of IgM against HBcAg
 - Absence of HBV DNA

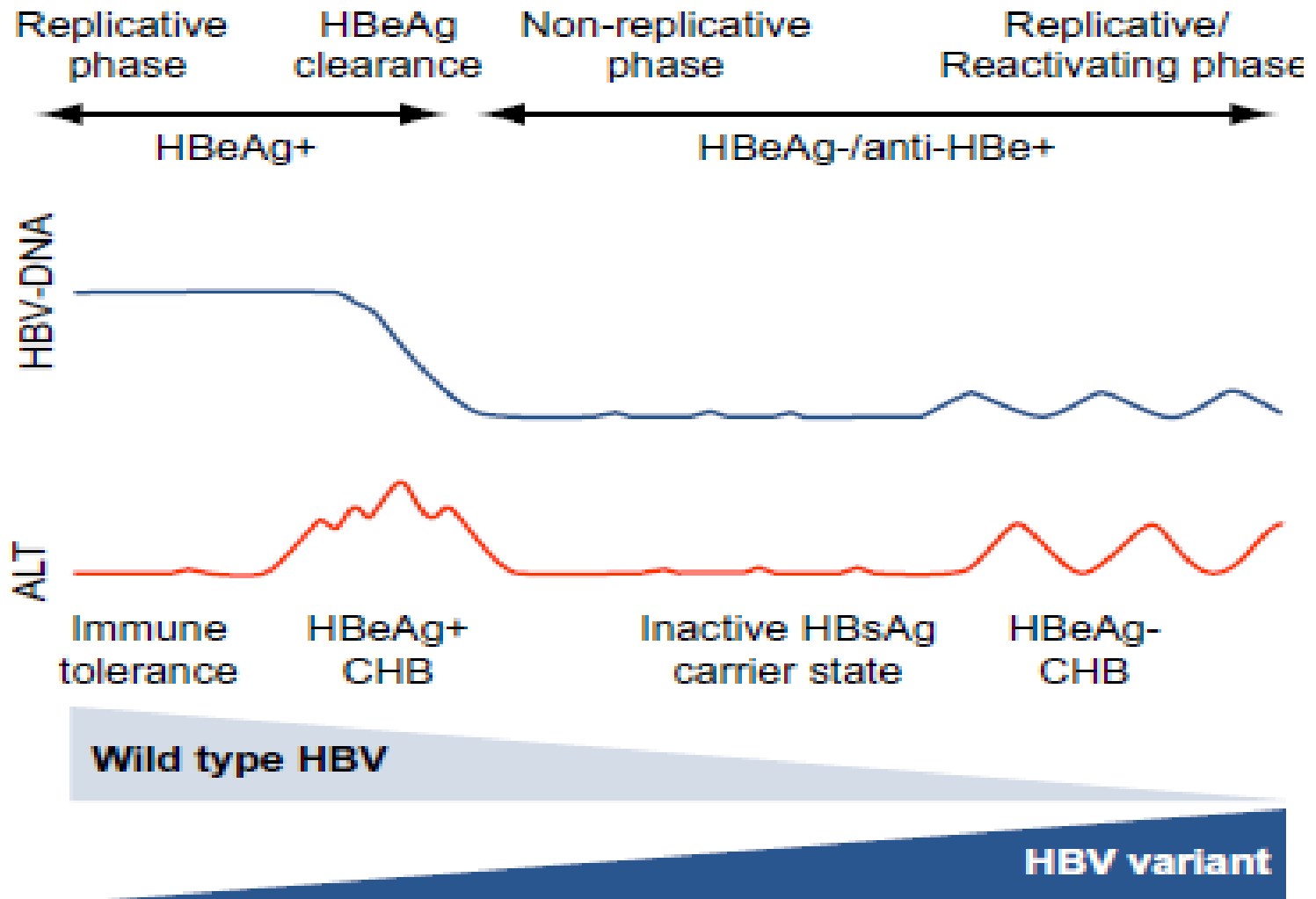
NATURAL HISTORY OF HEPATITIS B



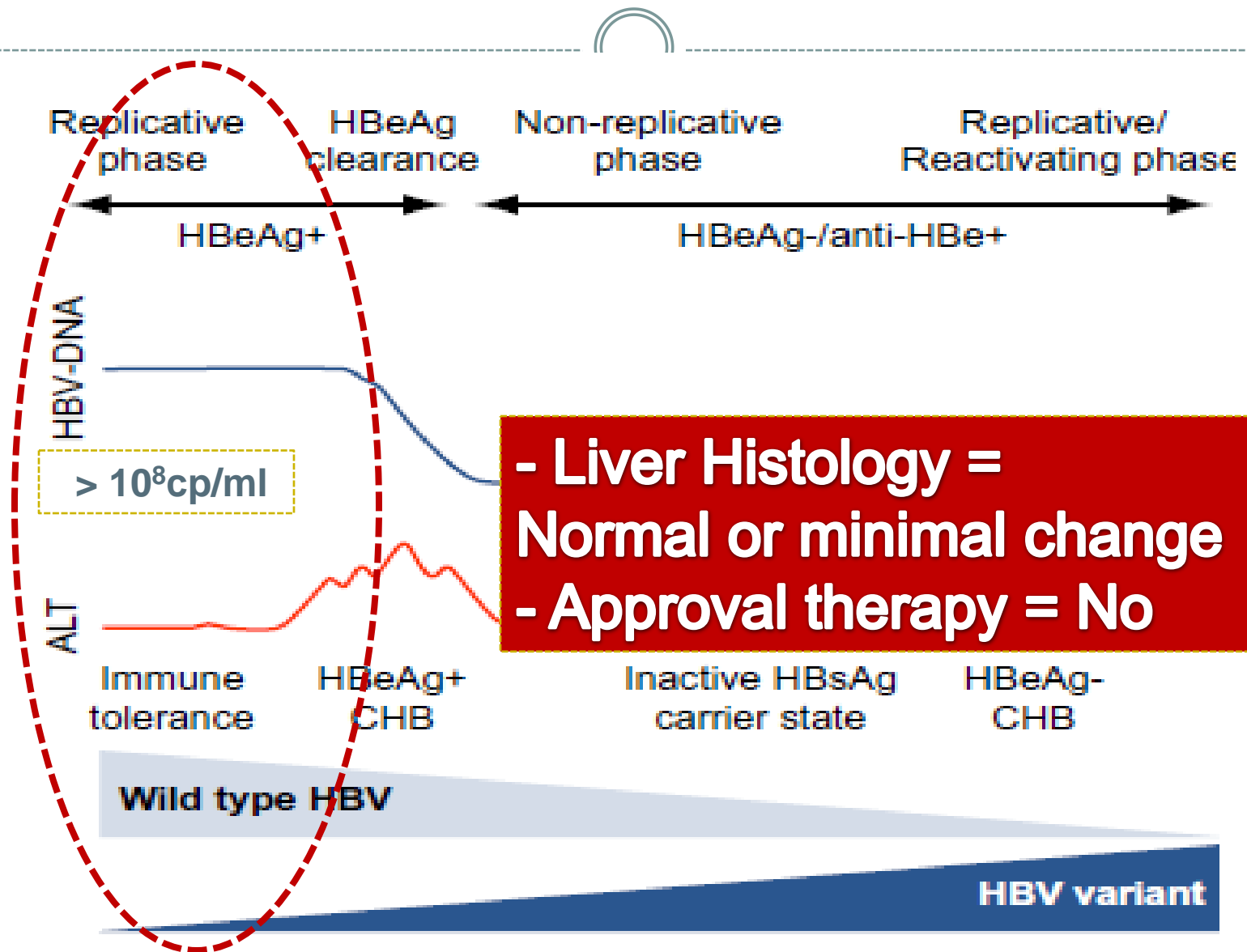
ROLE OF AGE OF CONTAMINATION IN THE EVOLUTION OF HEPATITIS B



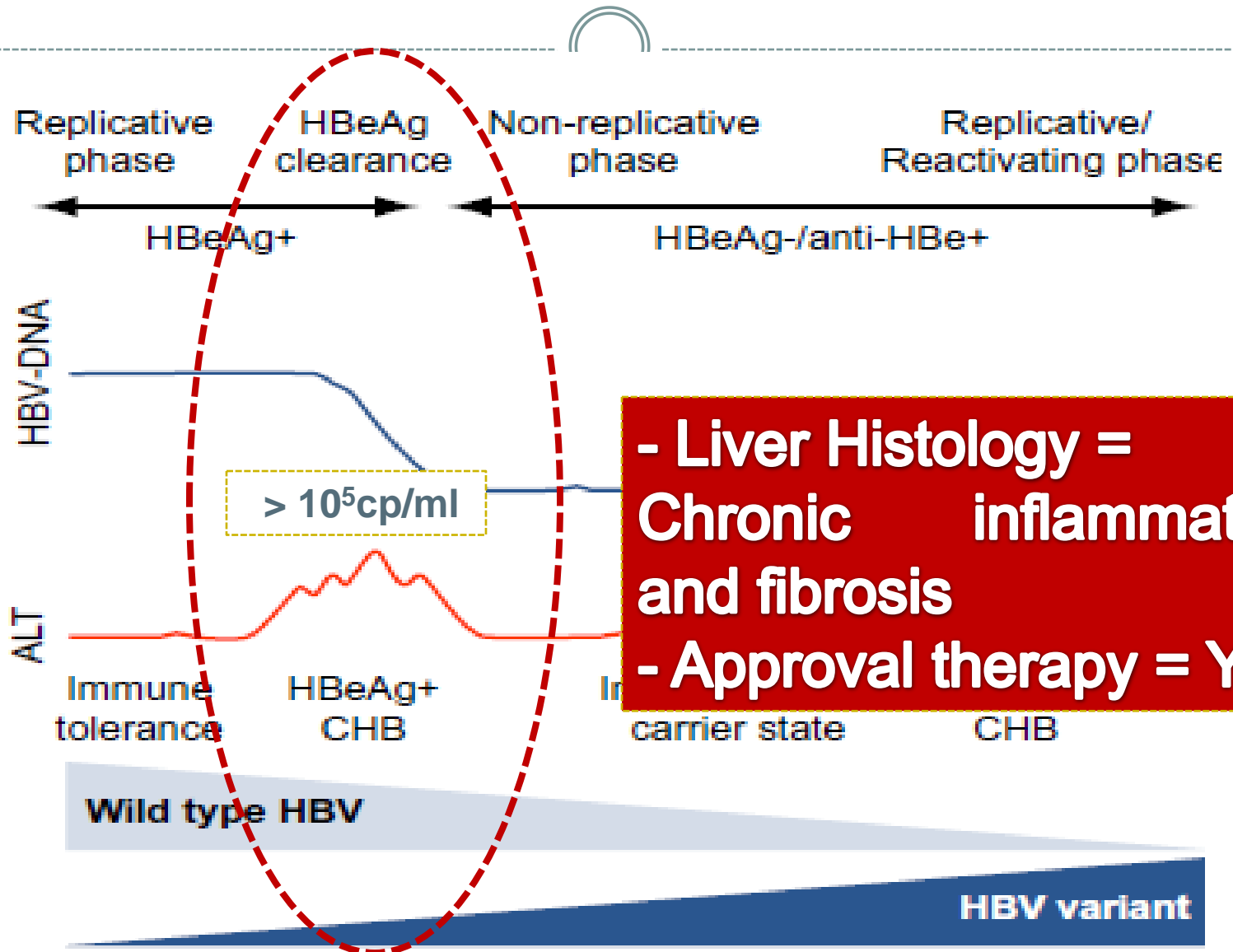
NATURAL HISTORY OF CHRONIC HEPATITIS B



IMMUNOTOLERANT PHASE

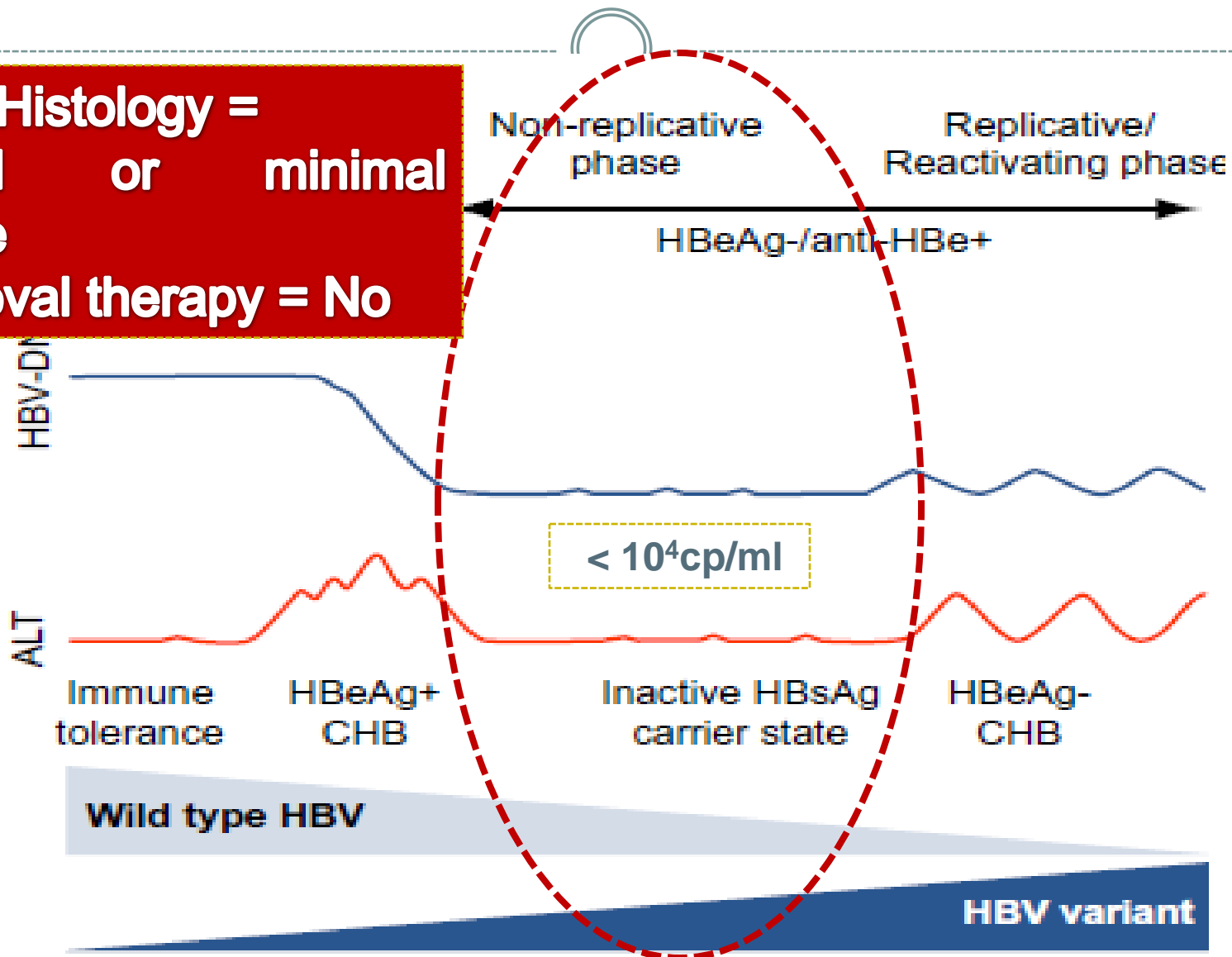


IMMUNOCLEARANCE PHASE

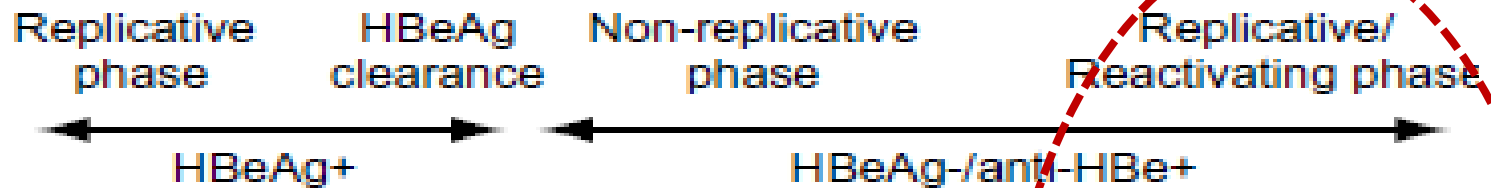


INACTIVE CARRIER STATE

- Liver Histology = Normal or minimal change
- Approval therapy = No



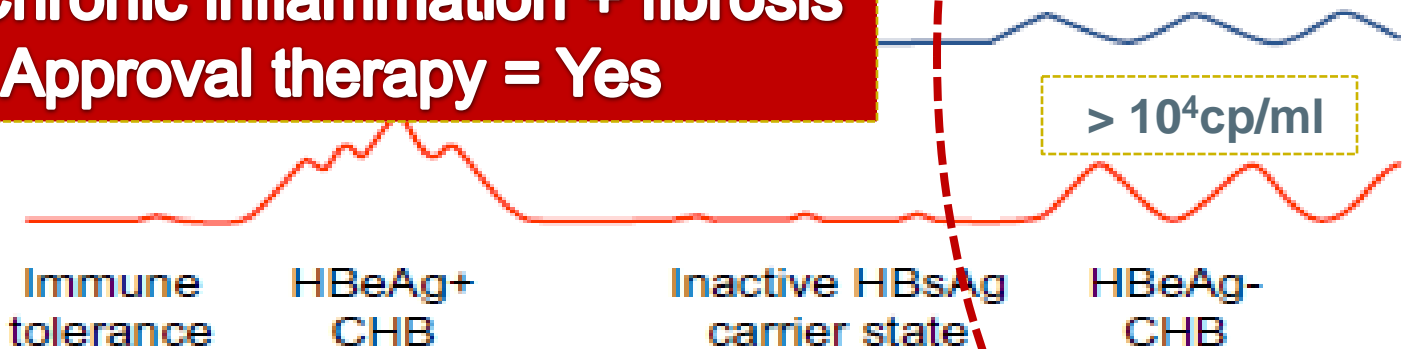
REACTIVATION PHASE



NA

- Liver Histology =
Chronic inflammation + fibrosis
 - Approval therapy = Yes

ALT



Wild type HBV

HBV variant

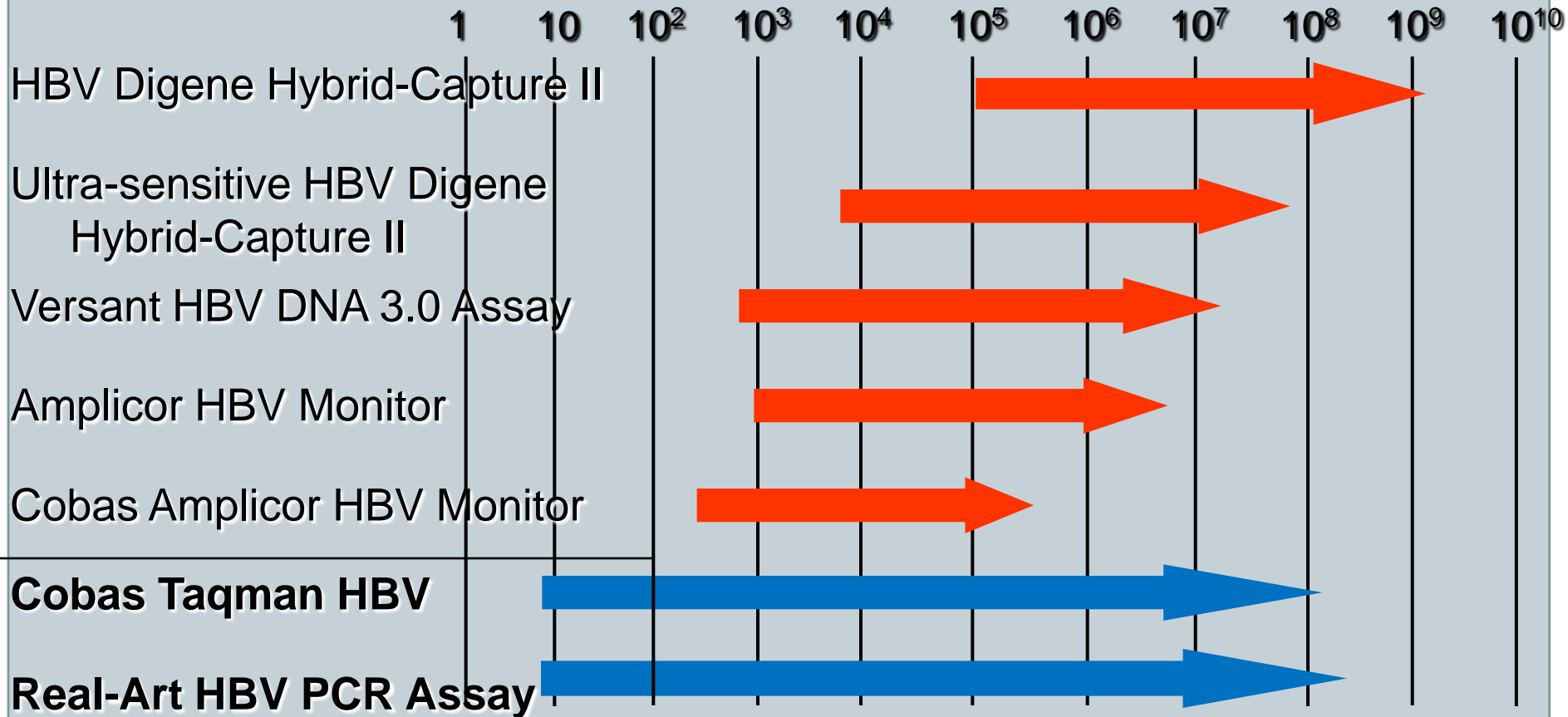
SEROLOGICAL AND VIROLOGICAL PROFILES FOR STATES OF INFECTION

Table 1 Characteristics of four dynamic phases of chronic hepatitis B virus infection

	Immune tolerance (minimally active)	Immune clearance (HBeAg-positive CHB)	Low replication (inactive carrier state)	Reactivation (HBeAg-negative CHB)
HBeAg	Positive	Positive	Negative	Negative
Precore/core promoter	Wild-type	Most wild-type	Most mutants	Most mutants
HBV DNA Level (copies/ml) ^a	Very High ($>10^8$)	High ($>10^5$)	Low ($<10^4$)	Moderate ($>10^4$)
ALT level	Normal	Elevated	Normal	Elevated
Liver histology	Normal or minimal change	Chronic inflammation and fibrosis	Normal or minimal change	Chronic inflammation and fibrosis
Candidate for approved therapy	No	Yes	No	Yes

👉 Importance of DNA quantification
Real-time PCR+++

QUANTIFICATION OF HBV DNA



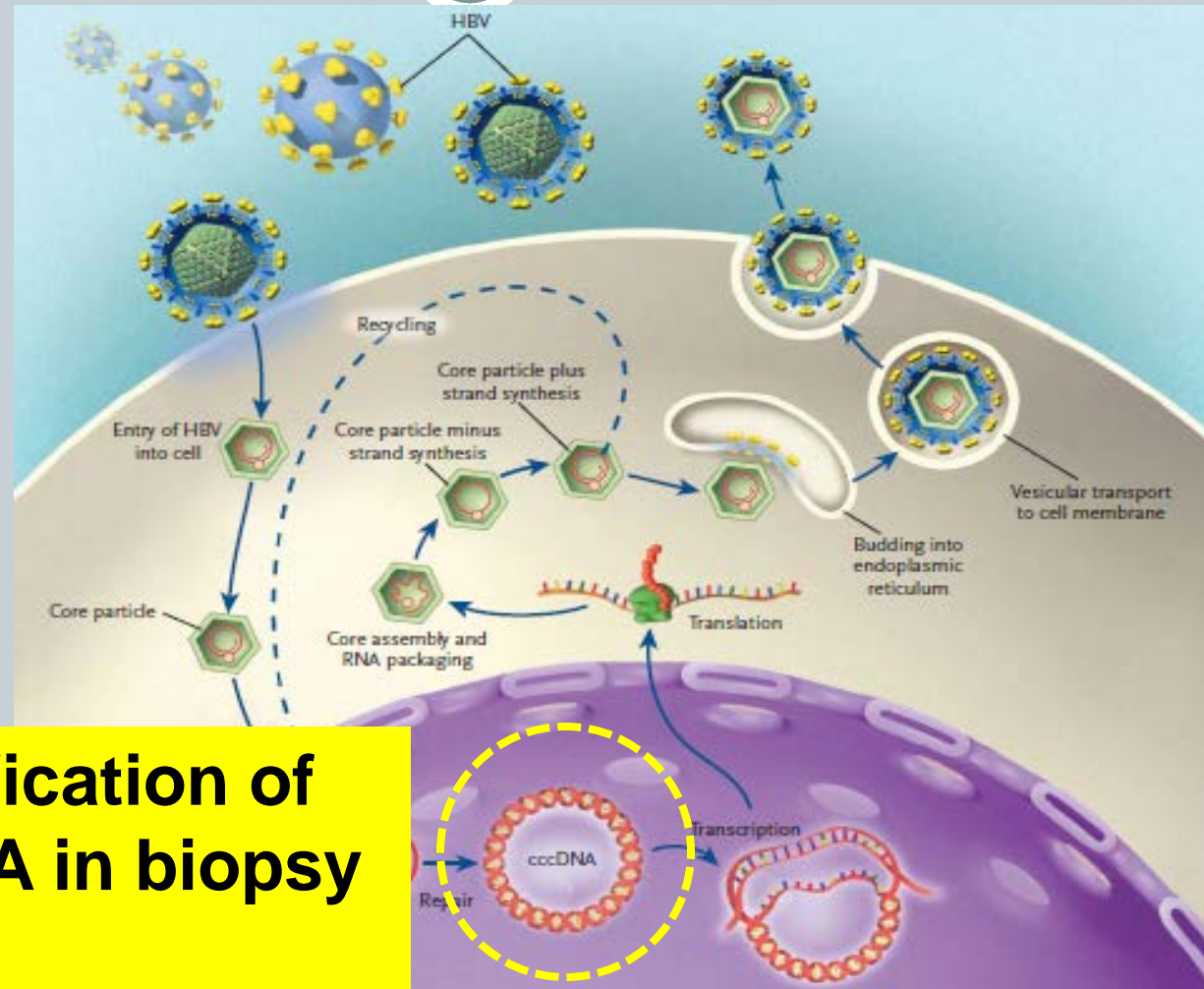
QUANTIFICATION OF HBV DNA



Objectives:

- Determine the state of chronic infection
- Survey evolution of chronic hepatitis B
- Explore viral reactivation
- Indicate and monitor treatment
- Detect an emergence of resistant mutants to treatment

NEW DIAGNOSTIC TOOLS



Quantification of cccDNA in biopsy

NEW DIAGNOSTIC TOOLS

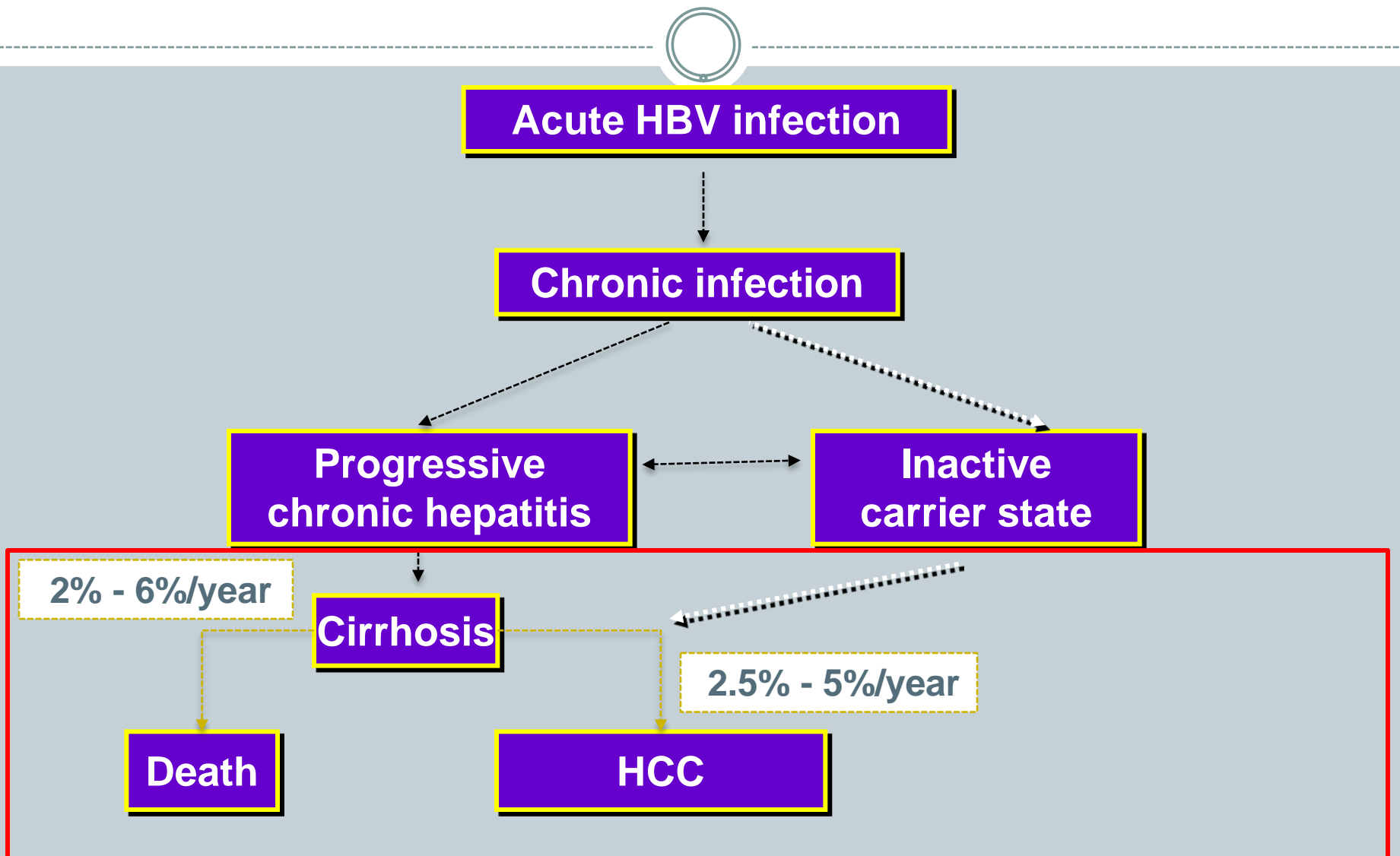
QUANTIFICATION OF HBsAg



A useful new tool for monitoring and optimization of hepatitis B treatments

- Levels of serum HBsAg and intrahepatic cccDNA are closely correlated
- HBsAg quantification = indirect reflect of the number of infected hepatocytes.
- The decline of HBsAg levels in serum = A predictive marker for sustained virological response, and clearance of HBsAg.

NATURAL HISTORY OF HEPATITIS B



RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS



1- Host factors

2- Host-viral interaction

3- Viral factors

RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS

HOST FACTORS

	Strength of association
<i>Male</i>	++
<i>Age > 40y</i>	++
<i>Genetic susceptibility</i> <i>(polymorphism of IL10, IL18...)</i>	? (under evaluation)
<i>Family history of HCC</i>	+
<i>Regular alcohol consumption</i>	+/-

RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS



HOST-VIRAL INTERACTIONS

Risk Factors	Strength of association
<i>Cirrhosis</i>	++
<i>ALT levels</i>	+

ALT levels = poor predictor for progression to severe forms especially the reactivation phase (fluctuation of ALT)

RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS

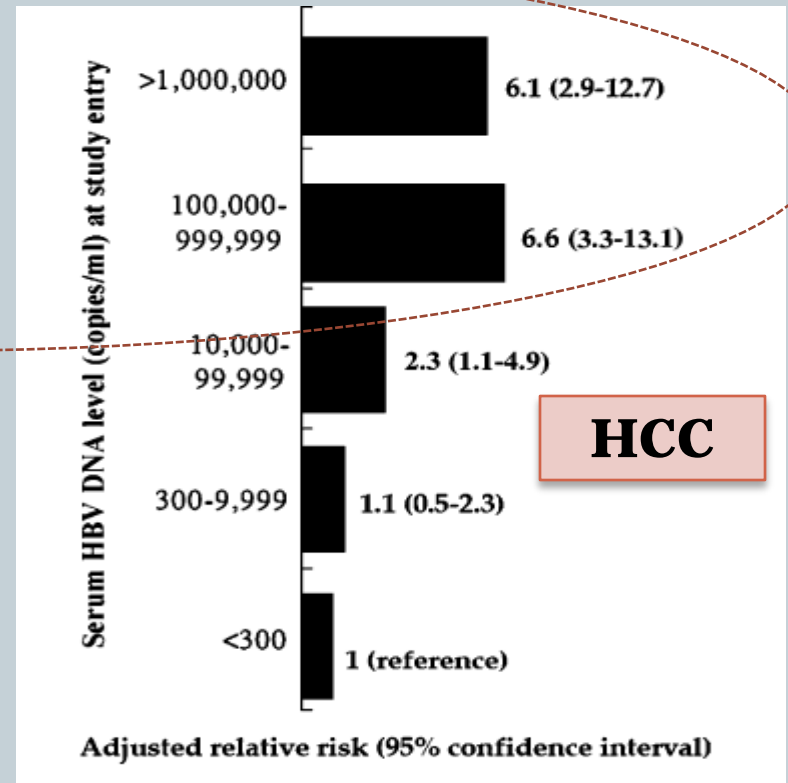
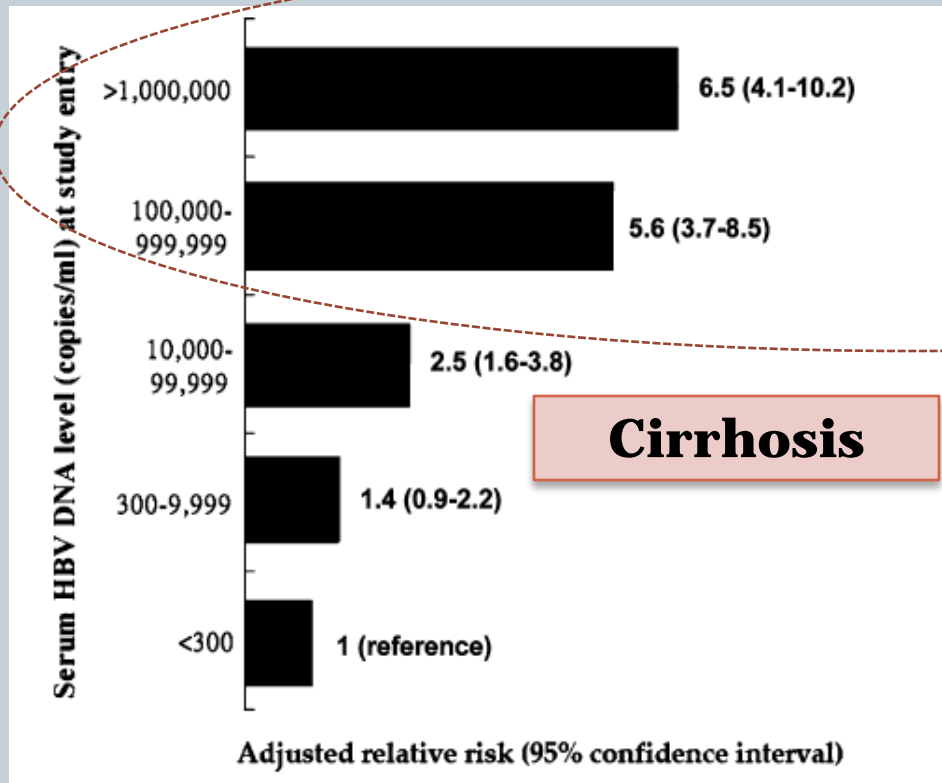
VIRAL FACTORS

Risk Factors	Strength of association
<i>High HBV DNA levels</i>	++
<i>Genotype C</i>	+
<i>Mutations</i>	
<i>Precore mutation</i>	-
<i>Core Promoter mutation</i>	++
<i>Pre-S</i>	+
<i>HBx</i>	+

RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS

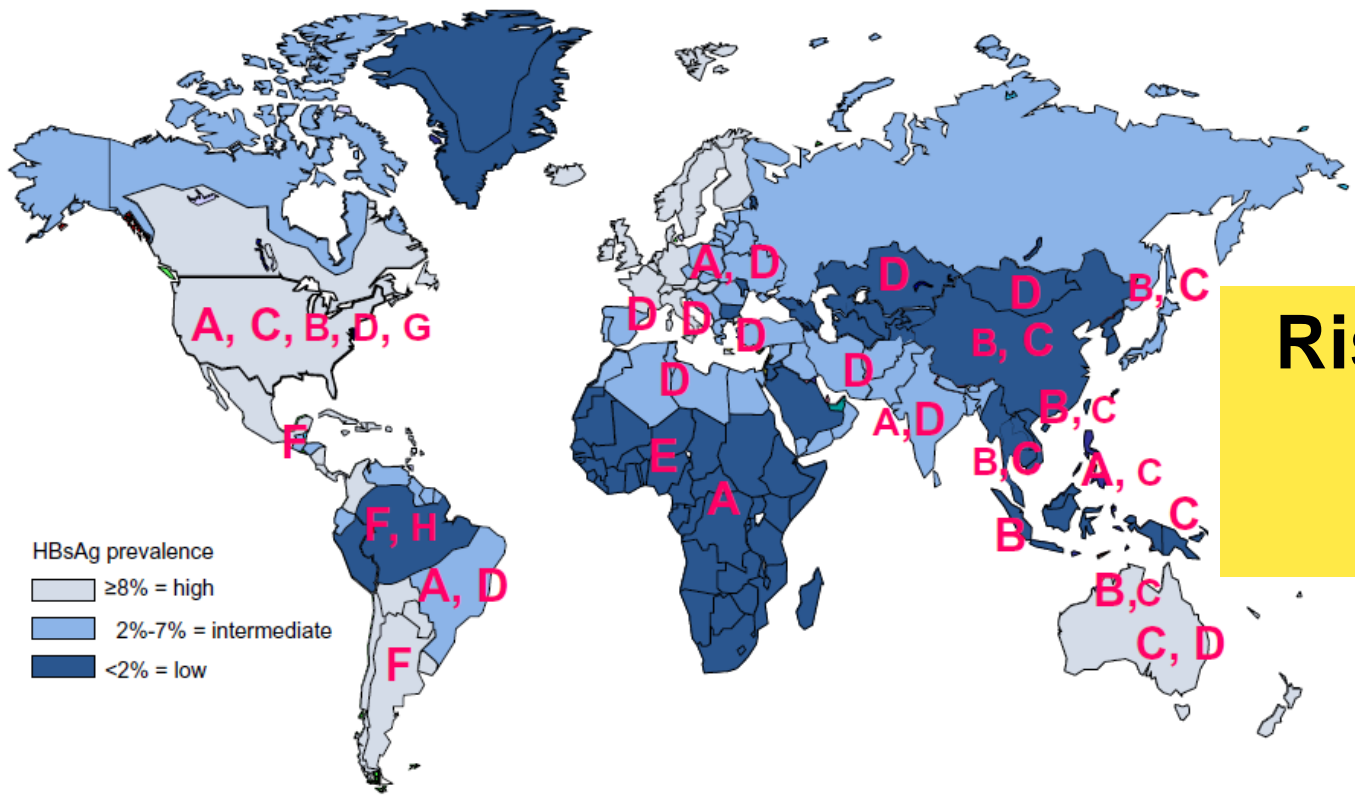
HBV DNA LEVELS

REVEAL –HBV study: Population-based prospective cohort in Taiwan (3582 HBV carriers)



RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS

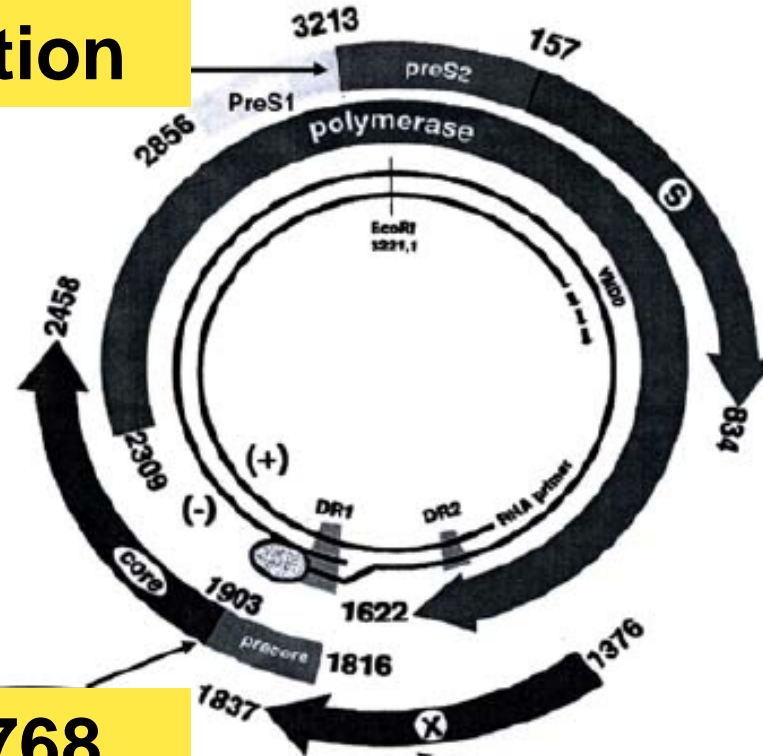
VIRAL GENOTYPES



RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS

VIRAL MUTATIONS

Pre-S deletion



Nt 1766/1768

Nt 1653/1753

RISK FACTORS FOR SEVERE EVOLUTION OF CHRONIC HEPATITIS



OTHER RISK FACTORS

Virus	Host	Environment
Persistently high HBV replication	Male gender	Concurrent HCV, HDV or HIV infection Alcohol drinking Cigarette smoking
Genotype (C > B; D > A)	Advanced age or longer duration of infection	Aflatoxin exposure Diabetes mellitus Obesity Hepatic steatosis
Specific HBV mutants (core promoter mutant, pre-S deletion)	Family history of HCC Ethnicity (Asian, African > Caucasian) Genetic alteration	
X gene transactivation	Repeated hepatitis flare	

RISK FACTORS AND PREDICTIVE SCORES



Some authors proposed predictive scores

☛ To monitor treatment and to survey HCC

RISK FACTORS AND PREDICTIVE SCORES



	Studied population	Parameters used
<i>Yuen MF et al. 2009</i>	820 untreated-patients with CHB	Age – Gender – HBV DNA level – Core/BCP mutations – Cirrhosis
<i>Yang et al. 2010</i>	3600 HBV infected patients	Sex – Age – Family history of HCC – Alcohol – HBeAg – HBV DNA level – HBV genotype
<i>Wong et al. 2010</i>	1000 HBV infected patients	Age – Albumin – Bilirubin – HBV DNA level – Cirrhosis

Predictive scores must be evaluated before introduction in routine

CONCLUSION



- Characteristics of chronic hepatitis B
 - Complexity
 - High variability
 - Implication of several risk factors
- Cohort studies in different parts of the world are needed to best:
 - Understanding of the evolution for HBV infection
 - Monitoring of chronic infection