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Vaccination contre l'hépatite B : succès et perspectives

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hepatitis B vaccines

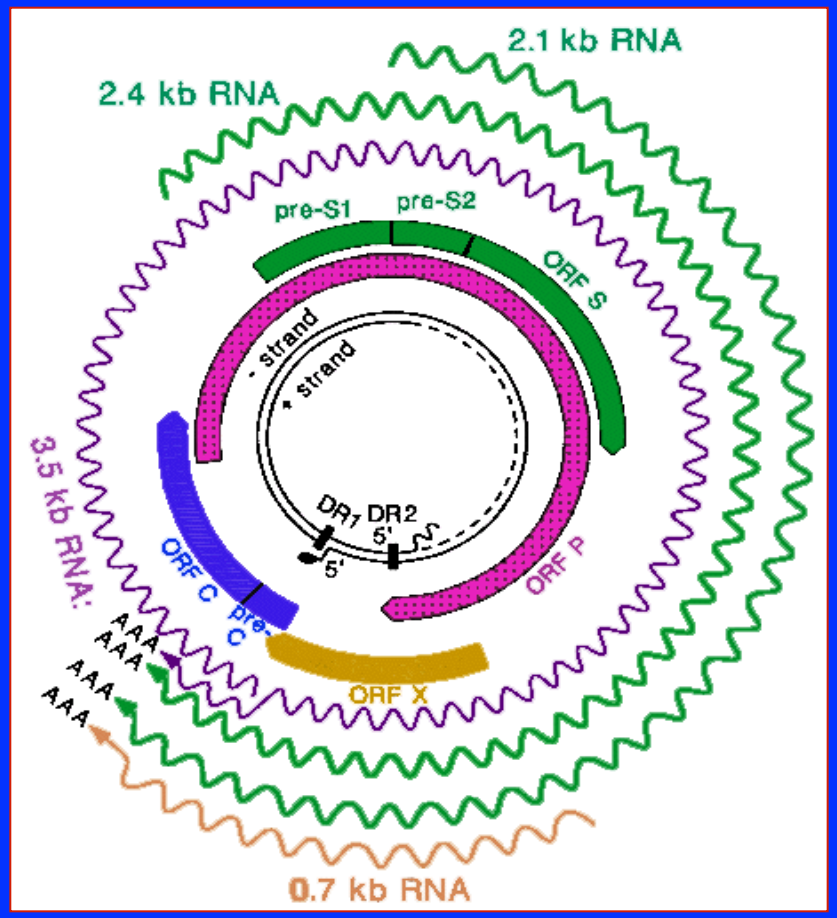
- HBV and the disease
- recombinant preventive vaccines
- chronic hepatitis B: toward an HBV cure

Global Burden of HBV

- > 2 billion individuals with markers of current or past infections
- 4 million acute cases of hepatitis B per year
- 200-300 million with chronic HBV disease
- Around one-third of persons with chronic HBV disease die from decompensated cirrhosis or hepatocellular carcinoma (HCC)
- 1 million deaths per year
- HBV causes 60% to 80% of all primary liver cancer
- HBV is second most important carcinogen behind tobacco

World Health Organization. Fact sheet. Available at http://www.who.int/hepatitis/en/. The Sixty-seventh session of the World Health Assembly (WHA) ,Geneva during 19–24 May 2014

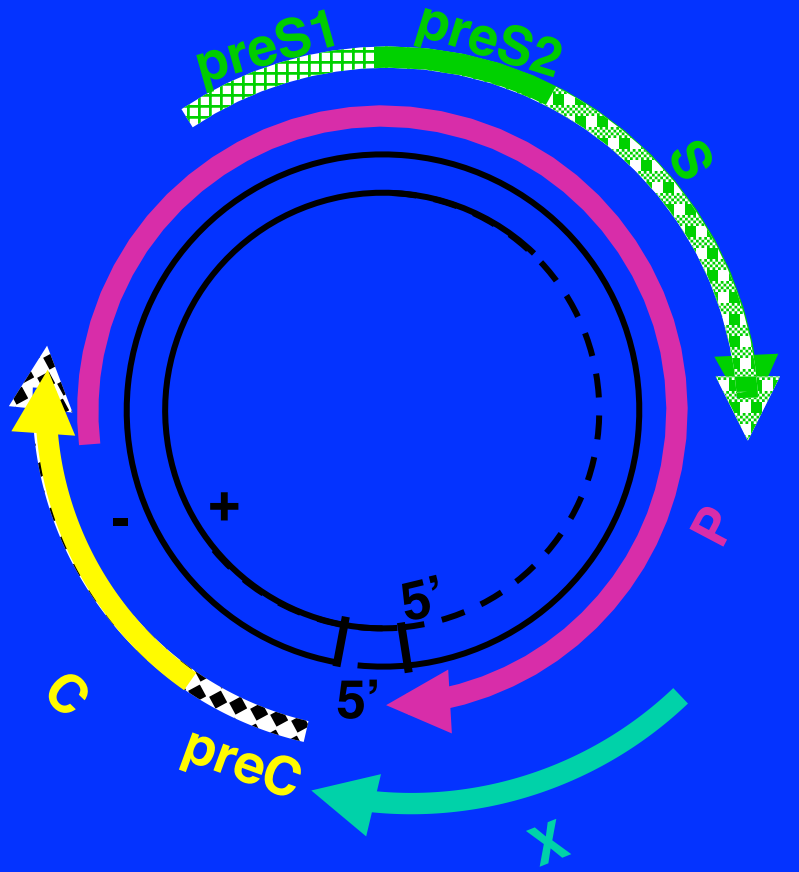
hepatitis B virus: HBV



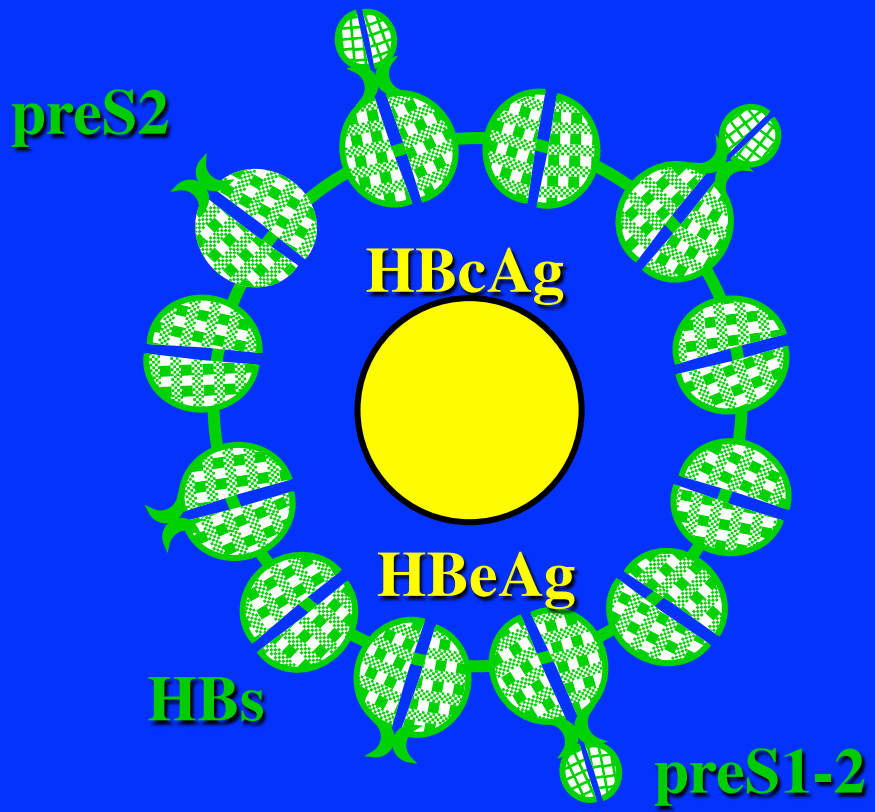
Seeger C & Mason WS; Virology 2015

- **Hepadnavirus**
  - partially double stranded DNA genome
  - 4 ORF
- **Viral proteins**
  - 3 envelope proteins (S, M, L)
  - viral polymerase (P)
  - HBx protein (X)
  - Capsid protein © and HBeAg (preC-C)
- **Viral cycle**
  - Host range: humans, chimpanzees
  - hepatocyte
  - Non cytopathic
- **Routes of transmission**
  - Perinatal (Mother-to-infant)
  - Infected blood (IVDU), sexual (30%in USA)
  - Horizontal (intra-familial)
  - Unknown (up to 30%)

Structure of HBV genome and viral antigens

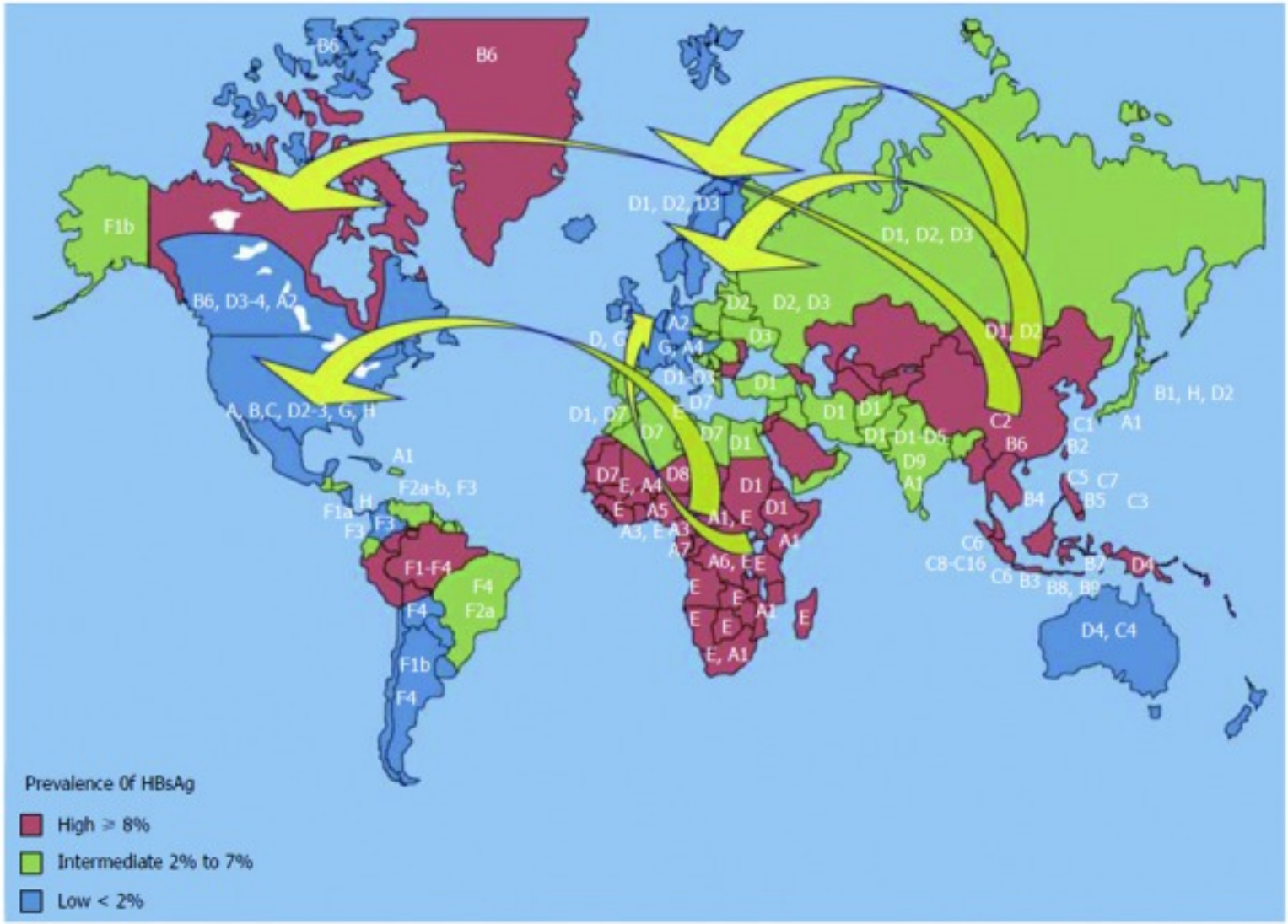


10 HBV genotypes



HBsAg: group "a"
Subtypes:"ayw, adr, adw"

Geographical distribution of hepatitis B virus genotypes and subgenotypes



Kramvis, A. Intervirolgy 2014

Pourkarim MR World J of Gastroenterology 2014

Outcome of hepatitis B virus infection

the younger the age of infection, the higher the HBV carrier rate!

Horizontal transmission (adult infection)

Vertical transmission neonatal, (childhood infection 2-4yo)

90%

HBV clearance

5-10%

>90% (25%)

HBV and HBsAg persistence

Full immune response (B+T +NK cells)

T cell ignorance Exhaustion

15-40%

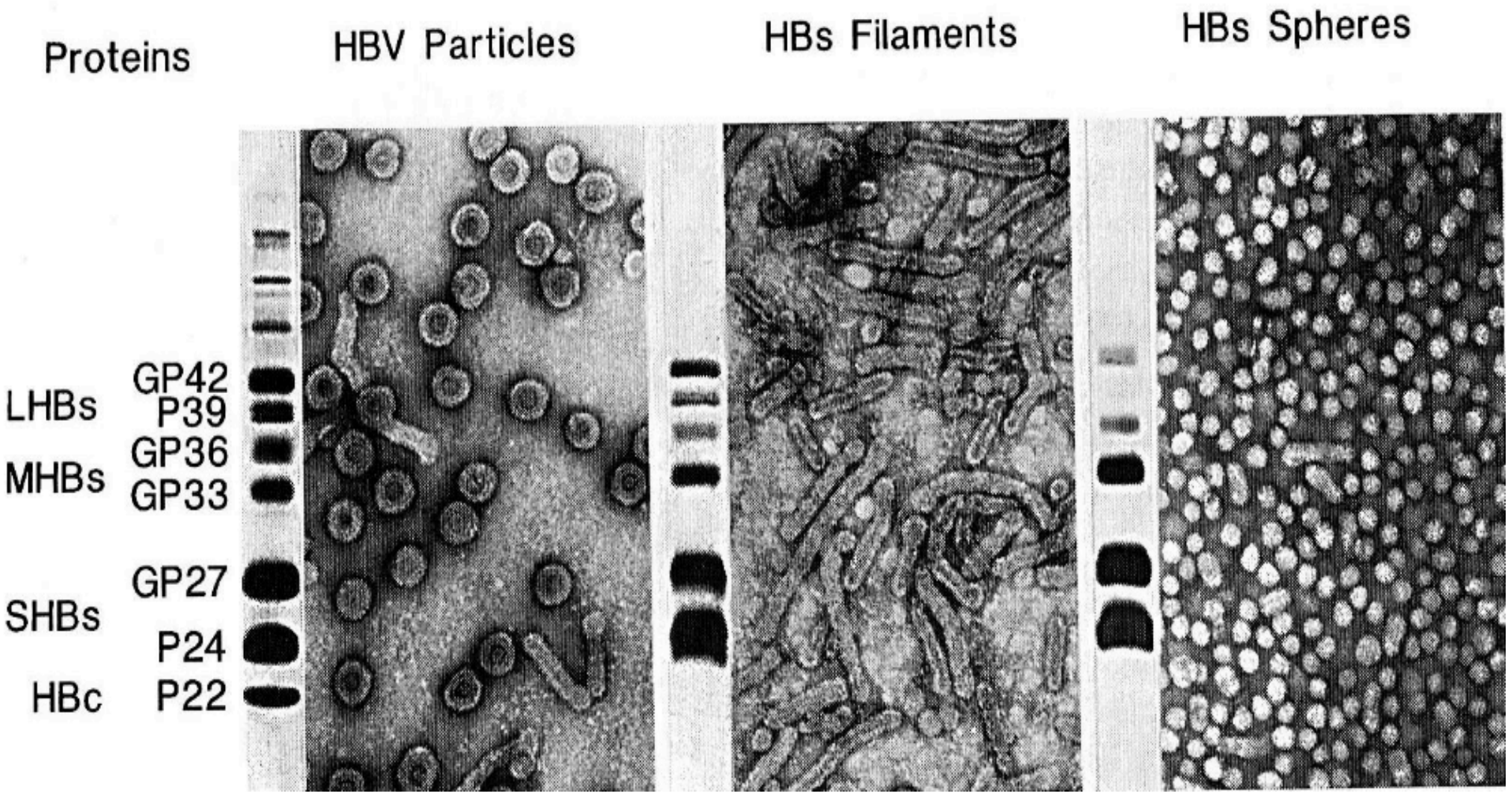
Activation of CD4/8+ T

asymptomatic or acute hepatitis B

asymptomatic chronic hepatitis B

liver injury: CAH Cirrhosis, HCC

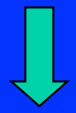
Plasma-derived vaccine :HBV envelope proteins from sera of HBV-carriers



From plasma-derived to recombinant hepatitis B vaccine

- 1964 *B. Blumberg* discovered the «Australia Ag». Nobel price 1976.
- 1968 *F. Prince*: Australia Ag = HBsAg on viral particles and on VLPs .
- The first hepatitis B vaccine derived from inactivated HBV or HBsAg particles purified from plasma of HBV chronic carriers

- HBsAg stimulates the production of protective anti-HBs antibodies in vaccinated children (*S. Krugman, 1970*), in chimps and in adults (*P. Maupas, 1976*)



- Lack of cell culture system susceptible to HBV infection in vitro (at that time…)

From the bench to recombinant hepatitis B vaccine

- HBV genome cloned and sequenced in 1976 *(Galibert F. & al. Nature 1979)*

- Localization on the viral genome of the gene coding for the major polypeptide of HBsAg *(Charnay P. & al. NAR 1979)*

- HBsAg expression toxic in E. coli & problems with purification *(Charnay P Nature 1980)*

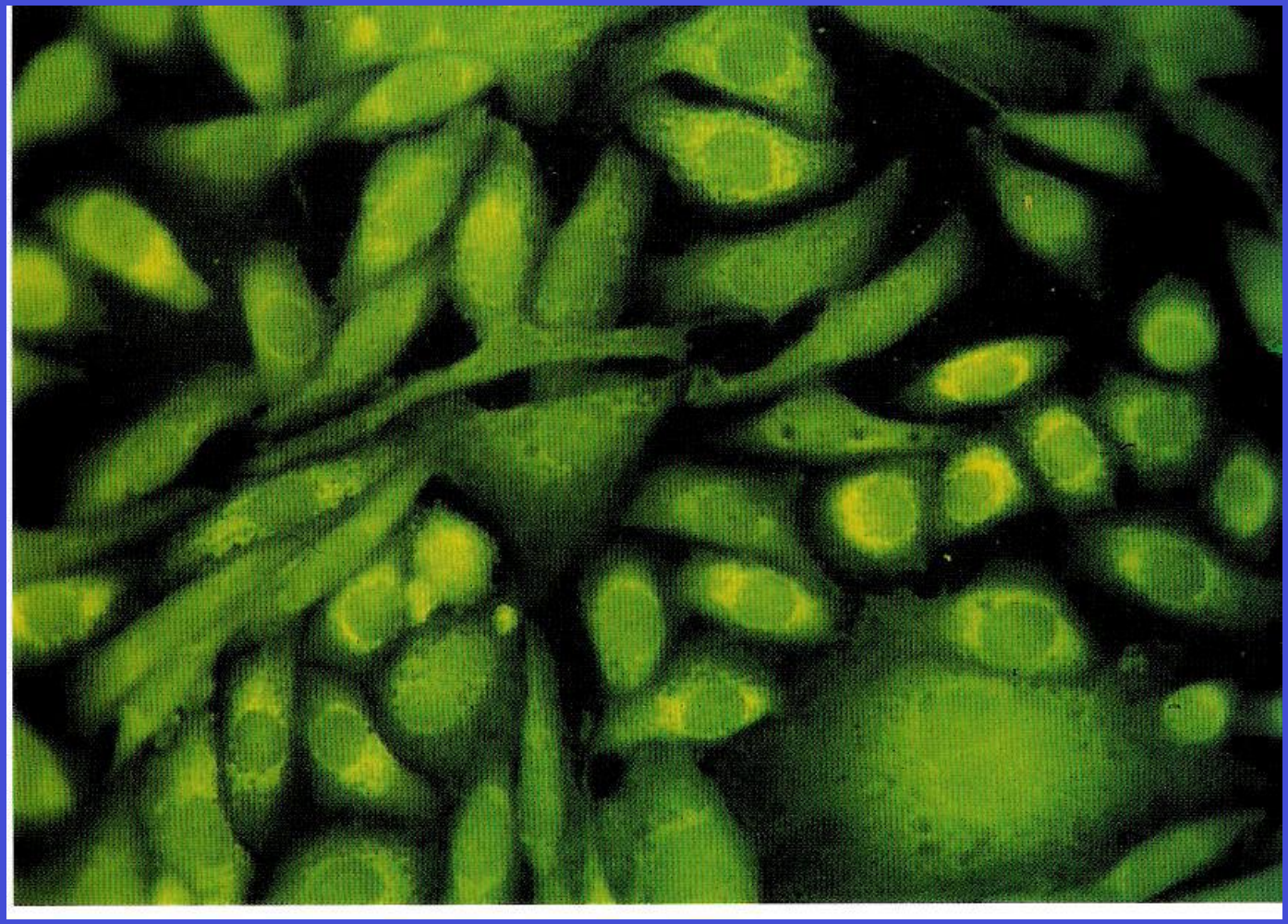
- Expression of HBV envelope proteins (HBsAg) in eucaryotic cells transfected with plasmids coding for HBV envelope proteins

  - Animal cells (*Dubois MF & al. PNAS, 1980*) mouse L cells. HBV endogenous promoter
  - yeast *(Valenzuela W et al. Nature, 1982)* yeast alcohol dehydrogenase I promoter

(Chinese hamster ovary) CHO cells and gene amplification system

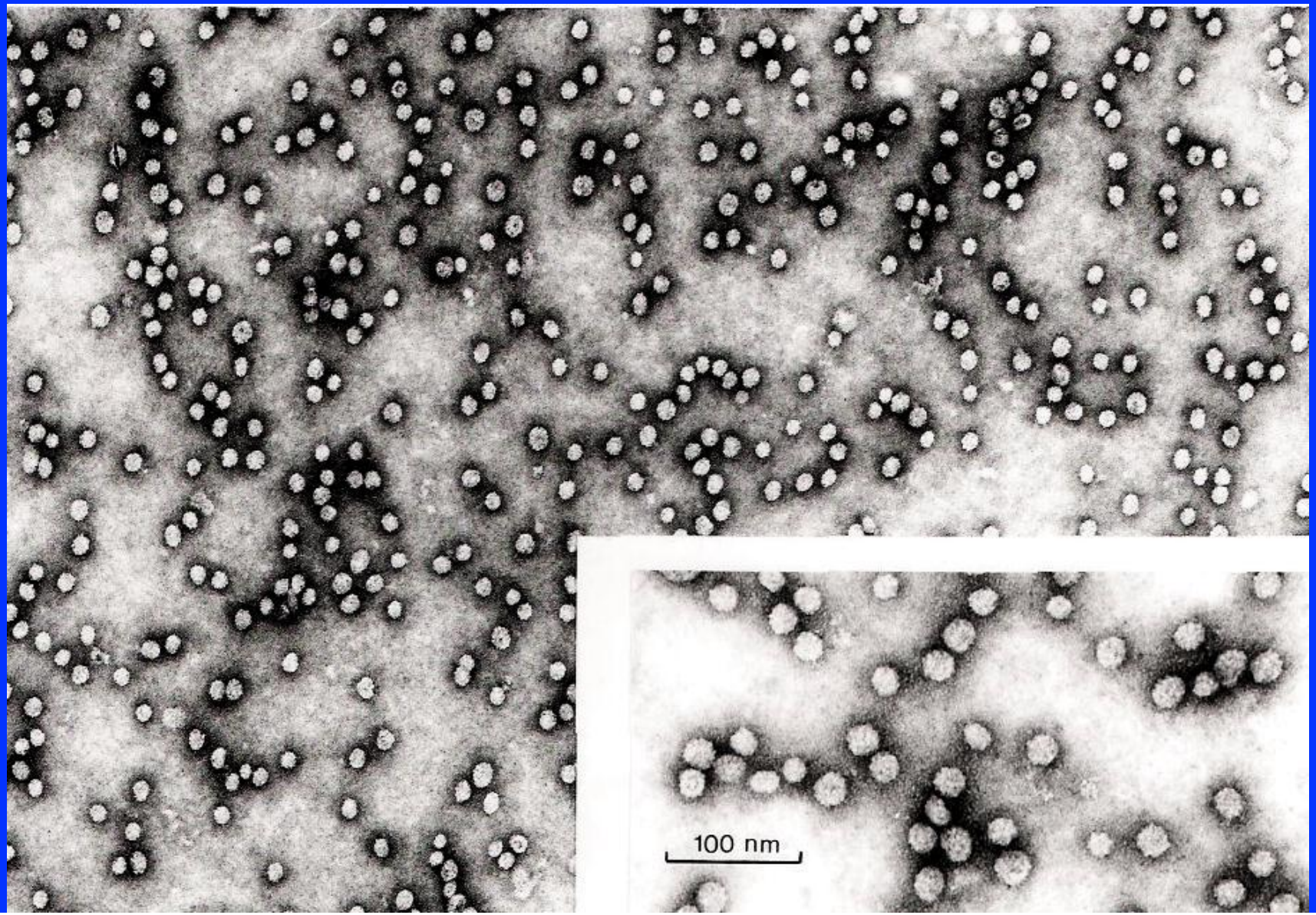
(HBsAg produced as secreted VLPs, glycosylation+)

Recombinant CHO cells expressing HBsAg



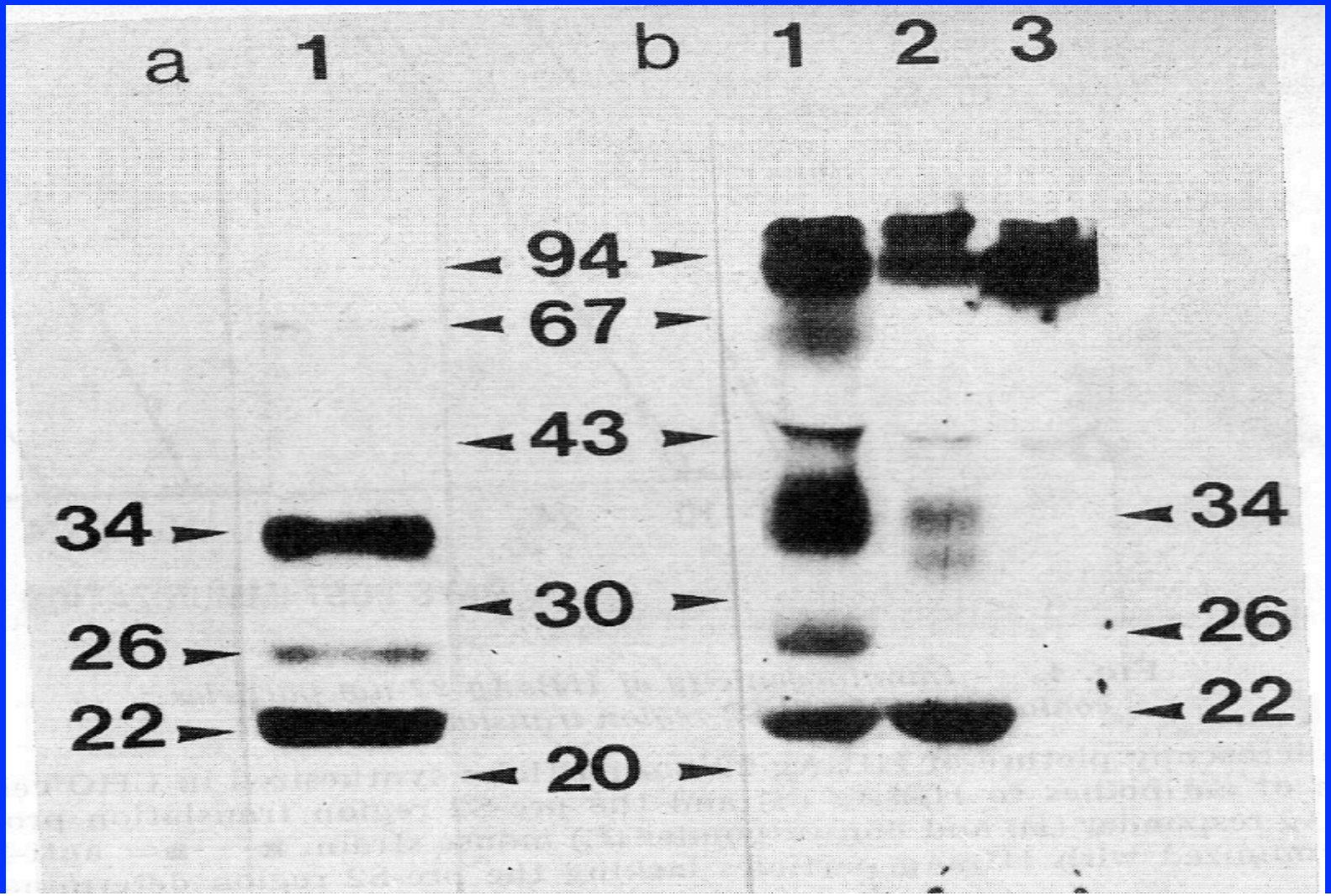
HBsAg particles produced from CHO cells

(Michel M-L & al. PNAS 1984)



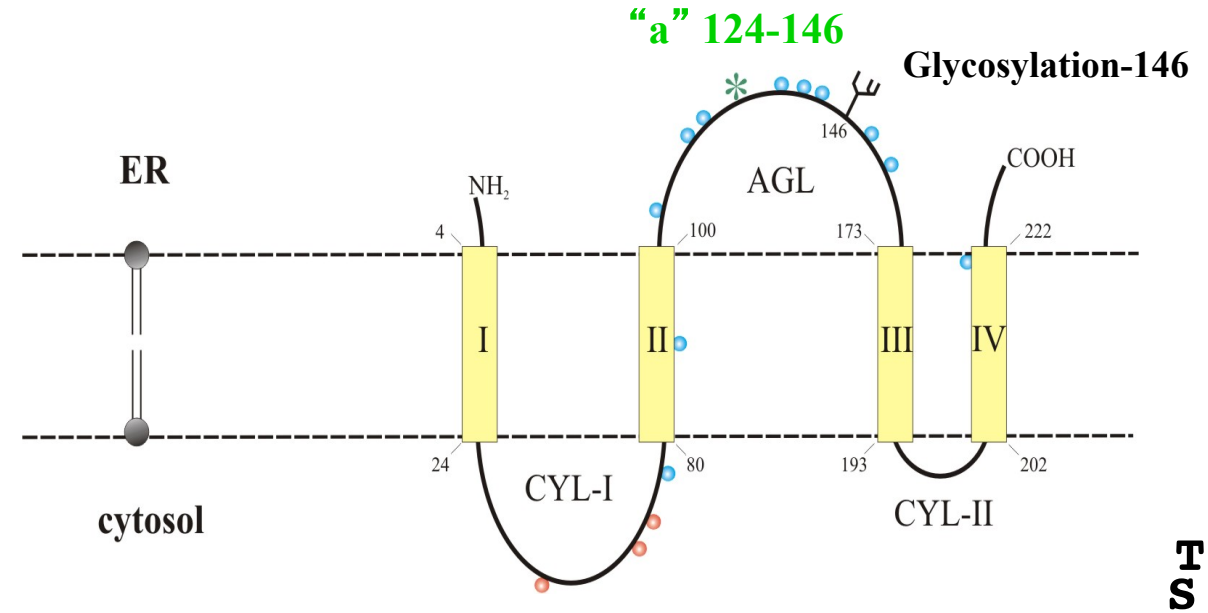
Protein composition of HBsAg particles secreted by rec. CHO cells:

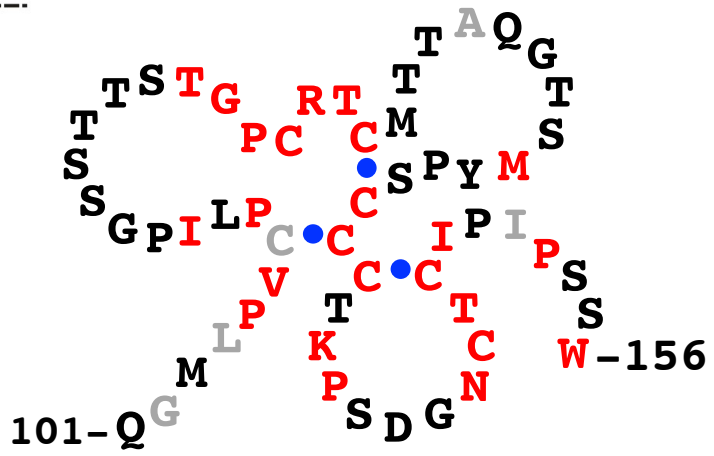
Envelope proteins are glycosylated



Structure of the small (S) HBV envelope protein

Antigenic loop: HBsAg: group « a », sub-types « d, y,w, r »





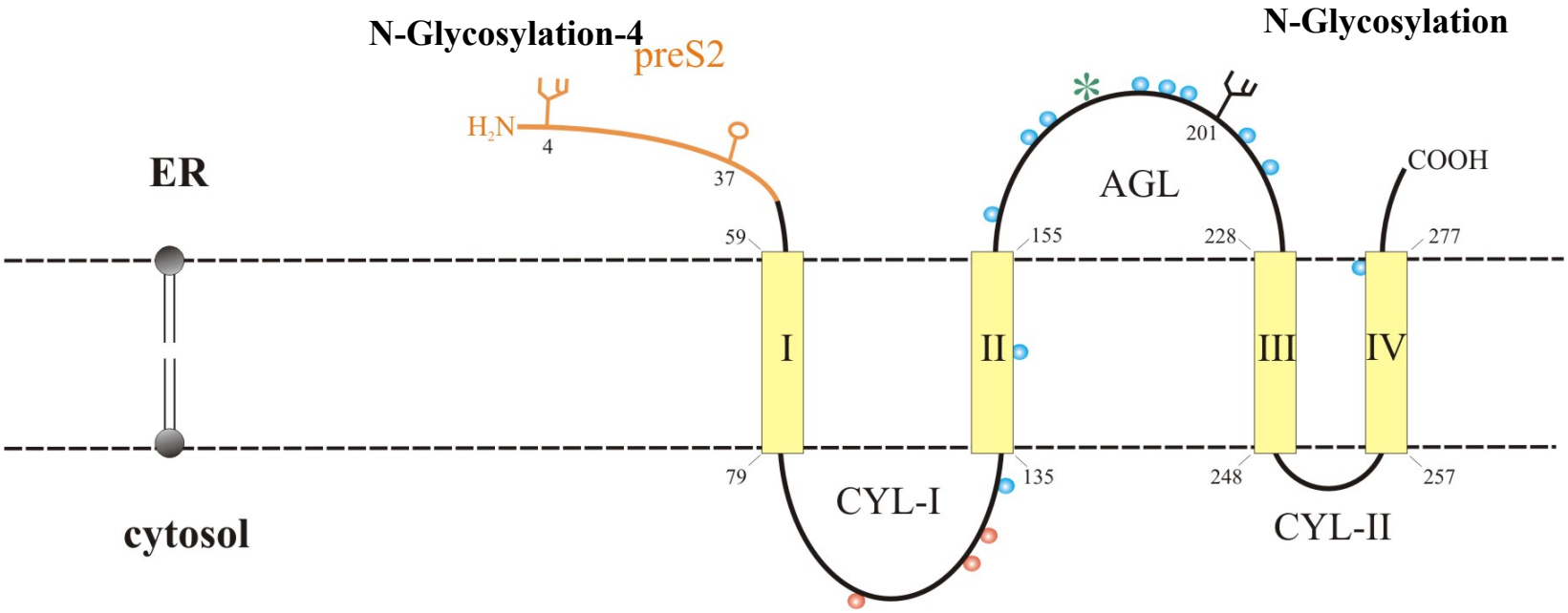
AGL: interact with heparan sulfates (infectiosity)
Intra/intermolecular disulfide bounds (antigenicity)
Targeted by vaccine-induced NT Ab

Slide courtesy of R. Patient/ P. Roingeard/ A. Desrames /C. Sureau

Structure of the middle (M) HBV envelope protein

preS2-antigenic domain

Antigenic loop: HBsAg



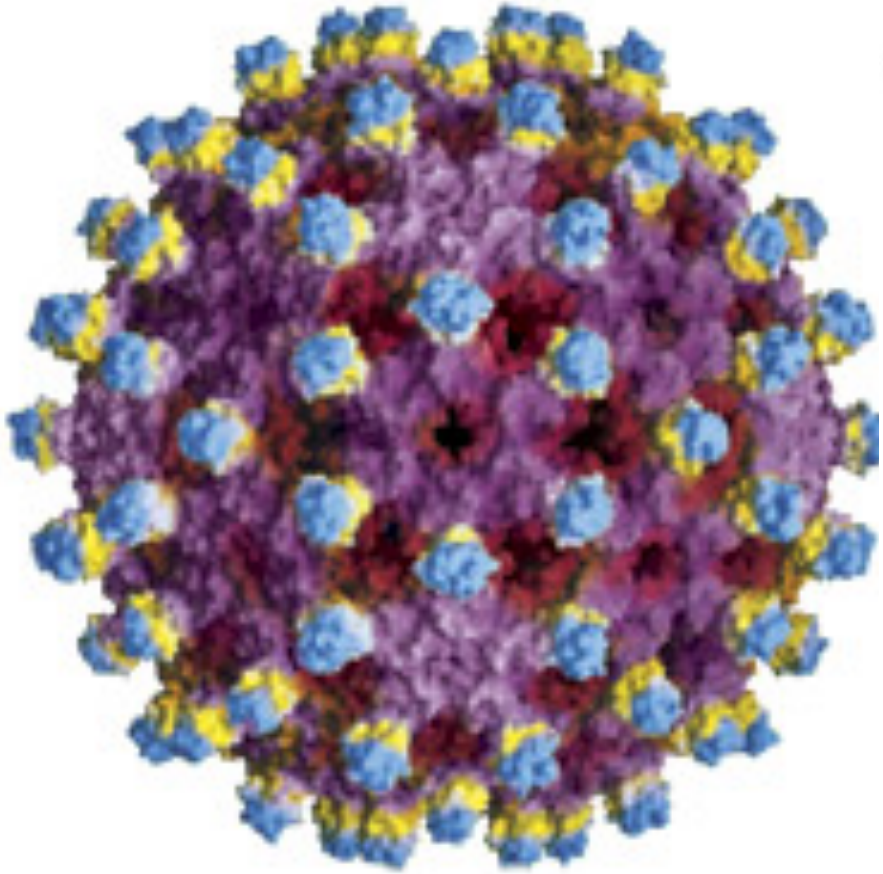
Role? Not implicated in viral cycle
preS2 Ab are neutralizing
Contain Th cell epitopes

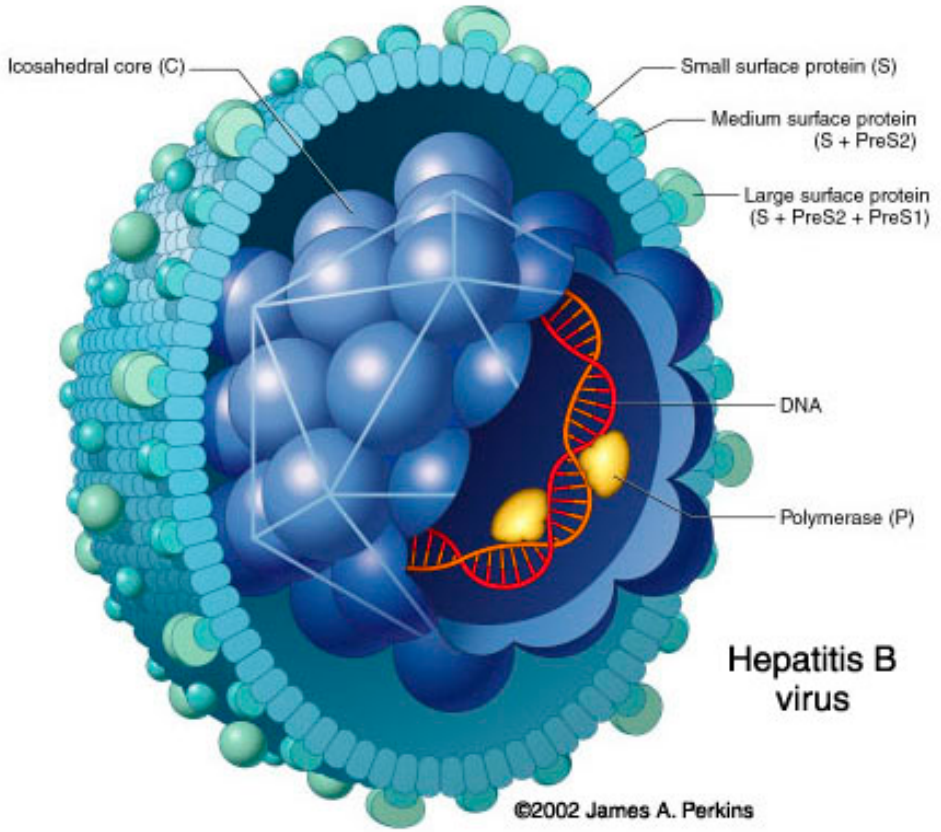
Slide courtesy of R. Patient/ P. Roingeard

Vaccin GenHevac B Pasteur (20μg)
HBsAg-producing CHO patented by I. Pasteur, INSERM & CNRS
Licenced to »Pasteur Mérieux sérums et vaccins»
now Sanofi Pasteur MSD

Yeast-derived recombinant vaccines
Engerix B (10 & 20μg) ,GSK
HBvaxPro (5&10μg), Merck)….

structure of HBV envelope/virus

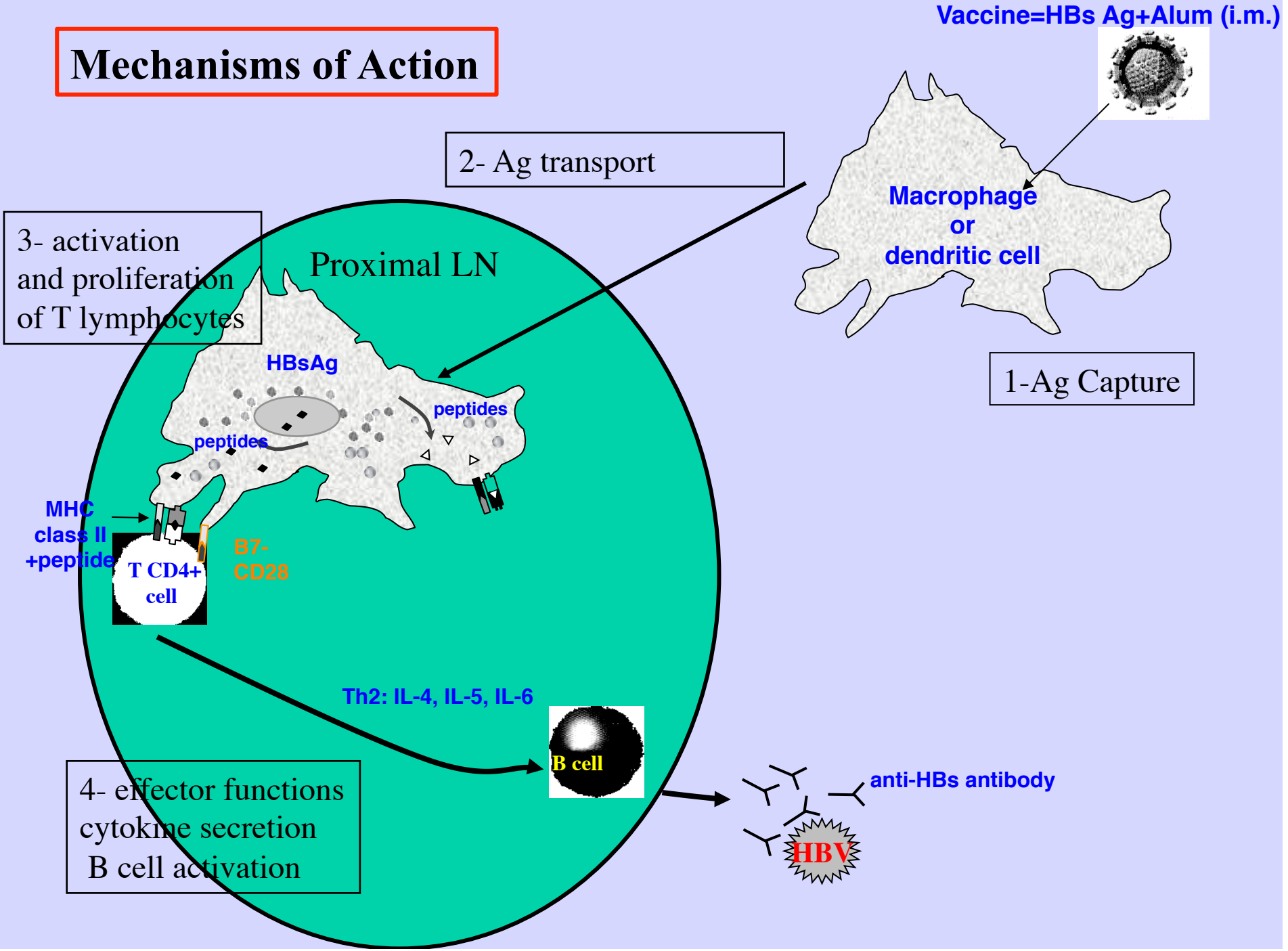




HBV vaccines contain only envelop proteins! No DNA

Hepatitis B small surface antigen particles are octahedral
Robert J. C. Gilbert et al.; PNAS, 102; 2005

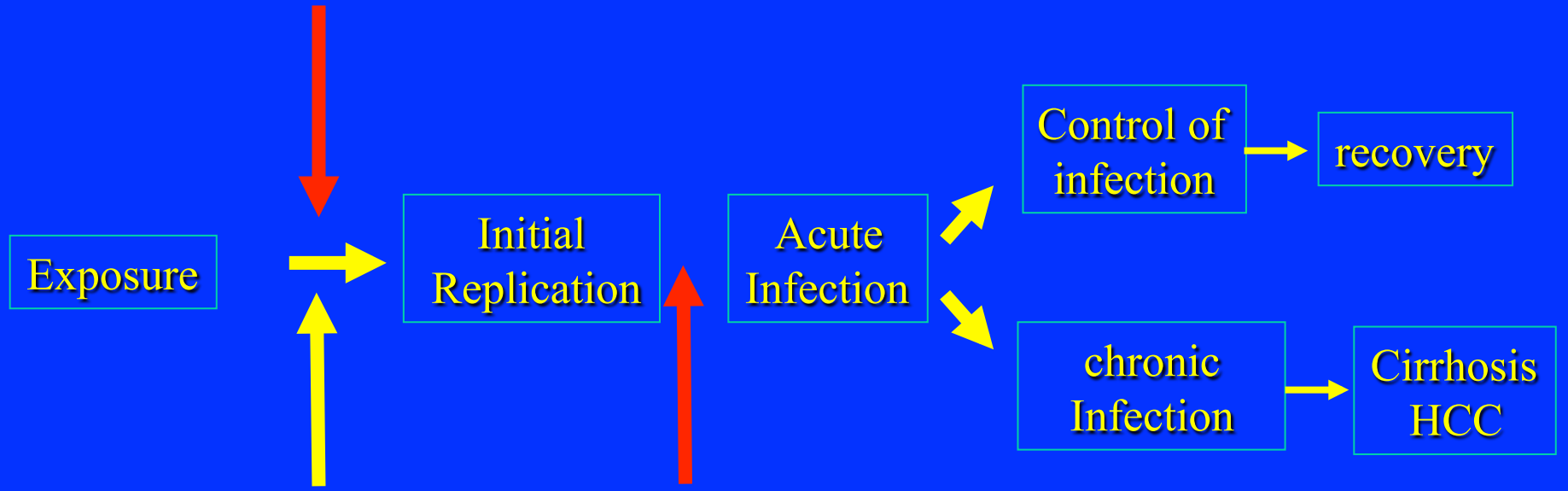
Mechanisms of Action



Vaccine protection against hepatitis B

1st mechanism : immediate viral neutralisation

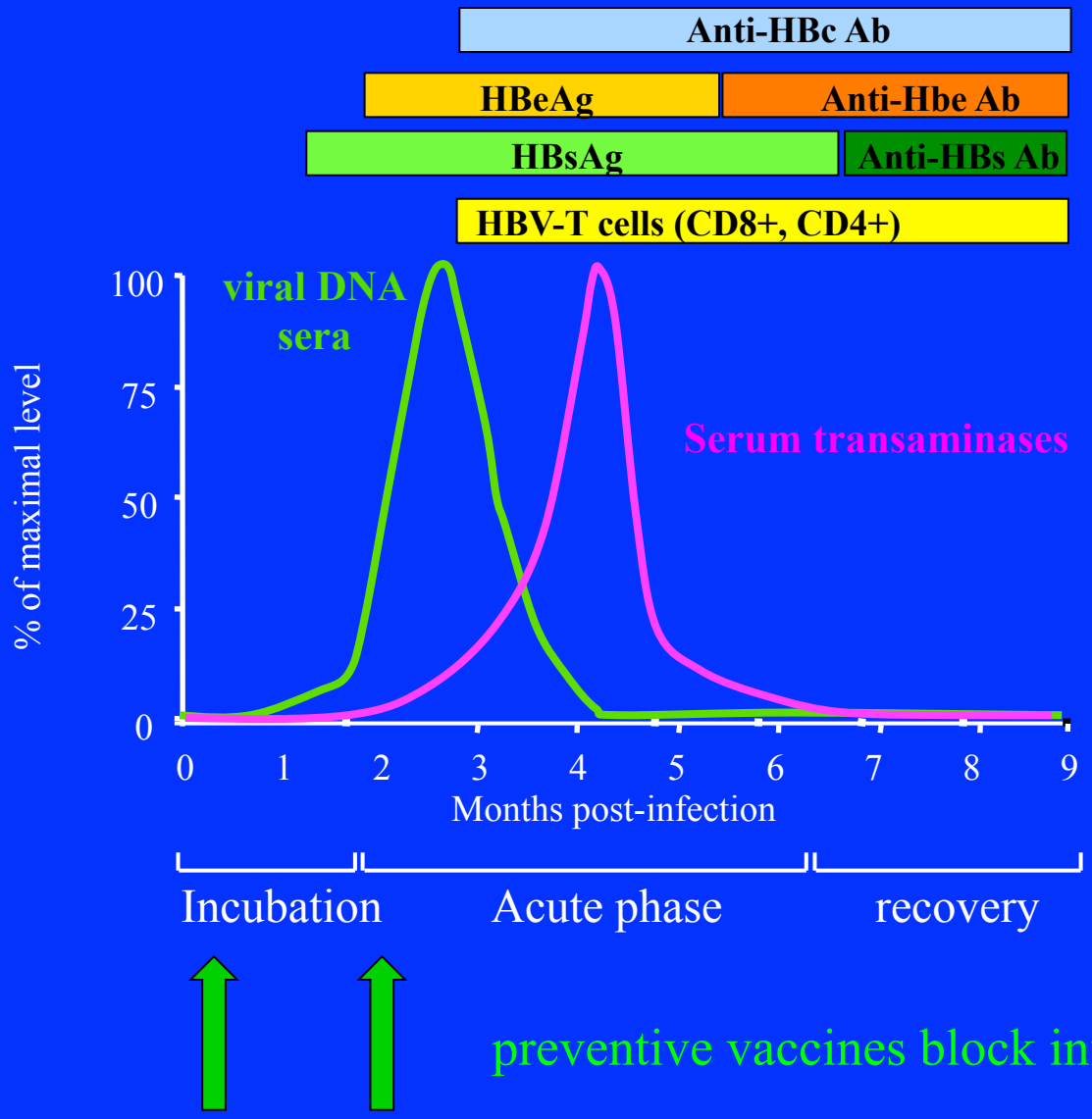
- Neutralizing antibodies anti-HBs "a" (> 10 mUI/ml) prevent initial infection
- Efficient if antibodies persist > 10 mUI/ml (chimp.)



2nd mechanism : Induction of CD4+ T helper response (HBs = T-cell dependent Ag)

- Activation of B lymphocytes secreting anti-HBs antibodies
- Activation or recall of memory B cell response

Serology of acute hepatitis B



preventive vaccines block infection at 2 steps

Factors Associated with Reduced Vaccine Responses

Patient-Related

- Older age (> 50 years)
- HLA DRB1*0301, *0701
- Male gender
- Smoking
- Obesity
- Immune deficiency
  - **HIV**
  - Transplant recipients
  - Dialysis
- Compliance

Vaccine-Related

- Schedule (accelerated < 0, 1, 2… 12 months)
- Double vs single dose
- Use of "adjuvants"
  MPL (TLR4), CpG ODN (TLR9), …
- IM > ID

Launay et al. JAMA 2011
Rey et al. Lancet Inf. Dis. 2015
Piroth et al. JID 2016
Launay et al. JAMA Intern. Med. 2016

Vaccination VHB et infection par le VIH: intérêt du schéma vaccinal alternatif

- **Essai multicentrique randomisé**
  437 adultes VIH+, CD4 > 200/mm3, vaccination VHB
  - 3 injections (20μg) IM (M0, M1, M6),
  - **4 injections (40μg) IM** (M0, M1, M2, M6),
  - **4 injections (4μg) ID** (M0, M1, M2, M6).

- **Critère d'évaluation principal**
  % de répondeurs 4 semaines après la dernière injection (S28)

- **Résultats**

  Supériorité des 2 schémas alternatifs par rapport au schéma standard :

  - répondeurs (Ac anti-HbS ≥ 10 mUI/ml) (65%, 82%, 77%),

  - forts répondeurs (Ac anti-HbS ≥ 100 mUI/ml (41%, 74%, 53%),

  GMT: 55, 795 et 104 mIU/mL.

  Pas d'effet sur CD4 et CV VIH

Launay O et al, JAMA 2011;305(14):1432-1440

Vaccination contre l'hépatite B des populations immunodéprimés : chez les patients VIH

- persistance de la réponse avec primo vaccination par 4 injections double dose

- perte des anticorps anti HBS chez 15% des patients:
  - **33,1 mois dans le bras IM40×4**
  - 8.7 mois dans le bras IM20×3
  - 6.8 mois dans le bras ID4×4

Research

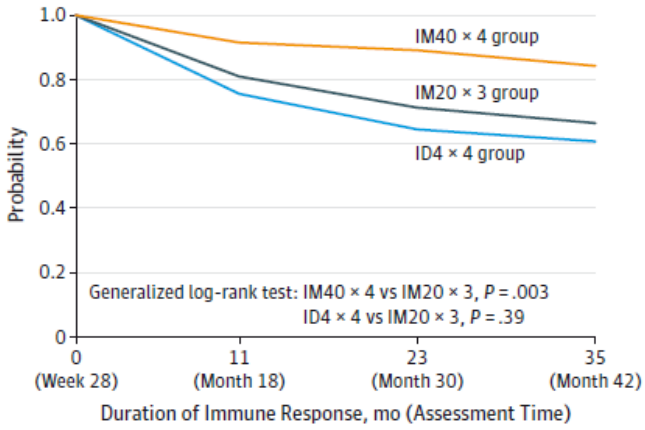
Original Investigation

Long-term Immune Response to Hepatitis B Virus Vaccination Regimens in Adults With Human Immunodeficiency Virus 1
Secondary Analysis of a Randomized Clinical Trial

Odile Launay, MD, PhD; Arielle R. Rosenberg, MD, PhD; David Rey, MD; Noelle Pouget, PhD; Marie-Louise Michel, PhD; Jacques Reynes, MD, PhD; Didier Neau, MD, PhD; Francois Raffi, MD, PhD; Lionel Piroth, MD, PhD; Fabrice Carrat, MD, PhD; for the ANRS HBO3 VIHVAC-B (Trial Comparing 3 Strategies of Vaccination Against the Virus of Hepatitis B in HIV-Infected Patients) Group

JAMA Intern Med. 2016 May 1;176(5):603-10

Figure 1. Duration of Immune Response



No. at risk

IM20 × 3 group	91	68	56	46
IM40 × 4 group	119	106	95	81
ID4 × 4 group	108	77	60	49

Vaccination contre l'hépatite B des populations immunodéprimées: intérêt de schémas intensifiés chez les patients vivant avec le VIH

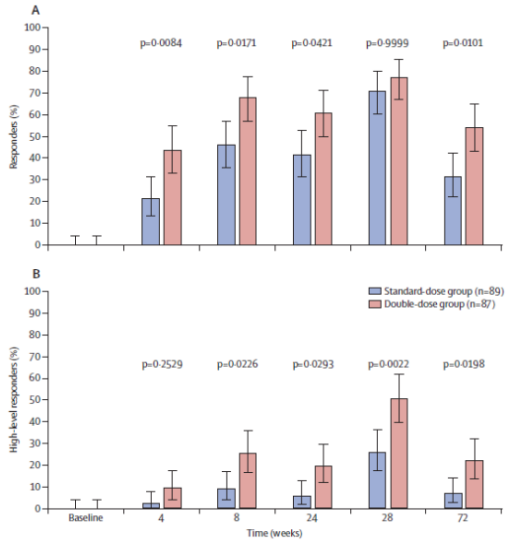
- **non répondeurs à une vaccination antérieure**: supériorité de la vaccination par 3 double doses en terme de réponse anticorps

- **Ac anti-HBc isolés:**
  - 46% de réponse après une dose de vaccin
  - en cas de non réponse : 89% sont répondeurs aux 3 double doses

Articles

Safety and immunogenicity of double-dose versus standard-dose hepatitis B revaccination in non-responding adults with HIV-1 (ANRS HB04 B-BOOST): a multicentre, open-label, randomised controlled trial

*David Rey, Lionel Piroth, Marie-Josée Wendling, Patrick Miailhes, Marie-Louise Michel, Cécilie Dufour, Georges Haour, Philippe Sogni, Alexandra Rohel, Faiza Ajana, Eric Billaud, Jean-Michel Molina, Odile Launay, Fabrice Carrat, and the ANRS HB04 B-BOOST study group**



The Journal of Infectious Diseases

MAJOR ARTICLE

Vaccination Against Hepatitis B Virus (HBV) in HIV-1–Infected Patients With Isolated Anti–HBV Core Antibody: The ANRS HB EP03 CISOVAC Prospective Study

Lionel Piroth,[1] Odile Launay,[2] Marie-Louise Michel,[3] Abderrahmane Bourredjem,[4] Patrick Miailhes,[5] Faiza Ajana,[6] Catherine Chirouze,[7] David Zucman,[8] Marie-Josee Wendling,[9] Dani Nazzal,[2] Fabrice Carrat,[10,11,12] David Rey,[13] and Christine Binquet[4]; the ANRS HB EP03 CISOVAC Study Group

Targets of anti-hepatitis B vaccine

- individuals at risk of infection
- babies born to HBV infected mothers

Since 1992 Hepatitis B vaccine is included in EPI

- as of 2012, 183 nations have this vaccine in their immunization program for infants (79% of children are protected worldwide)

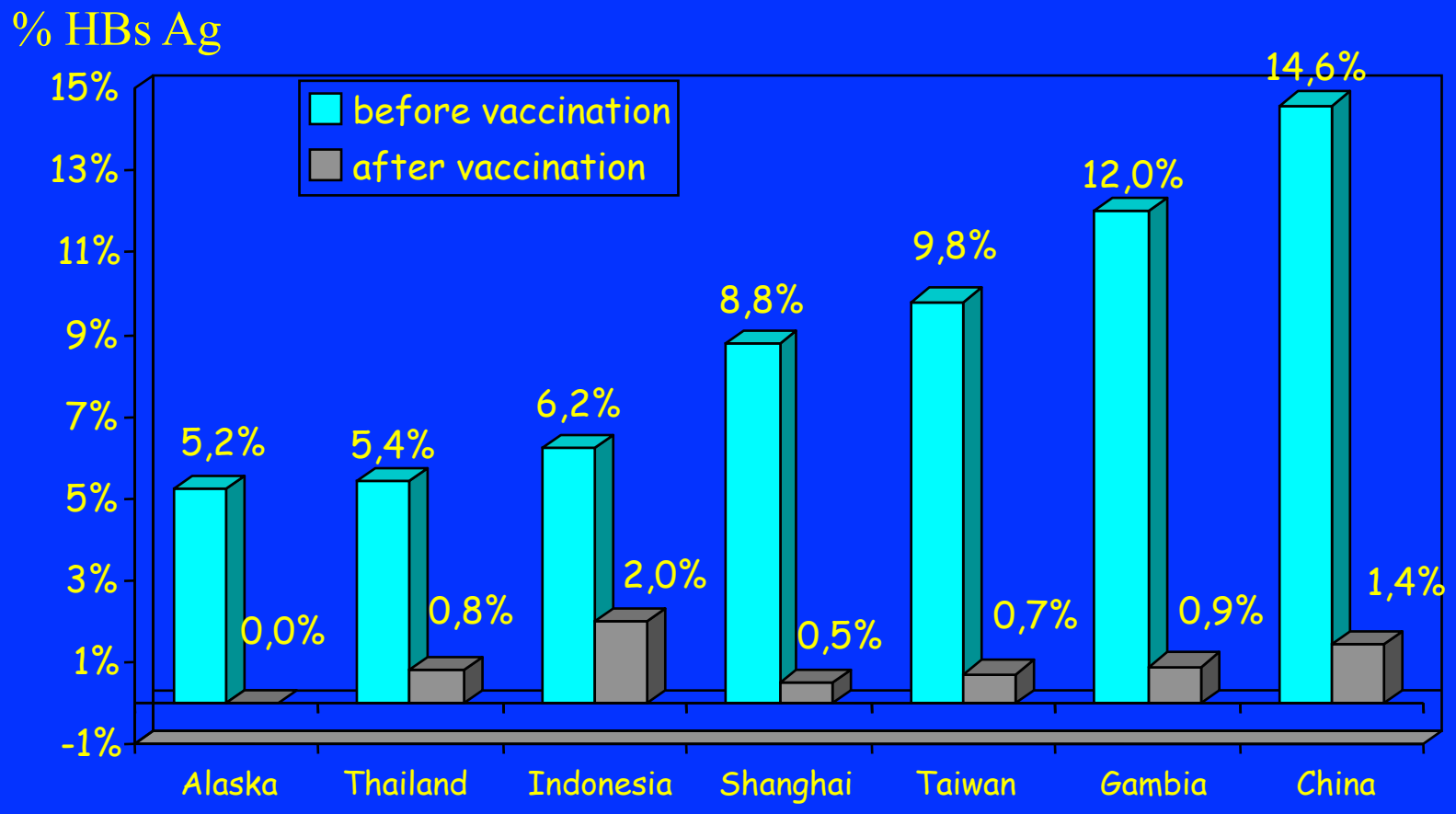
One billion of vaccinated individuals worldwide

Weintraub K, Nature 2014

Impact of anti-hepatitis B vaccination

- Decrease in the number of acute and fulminant hepatitis
  - $5.4/10^5$ (1975-1984)>> $1.7/10^5$ (1985-1998) = 68% decrease in fulminant hepatitis inTaiwan
- Decrease in mother-child transmission
- Decrease in HBsAg in serum and in HBV reservoir
- Decrease in hepatitis delta virus infections
- Decrease in the number of deaths related to cirrhosis and HCC

Efficacy of vaccination on the prevalence of HBsAg chronic carriers



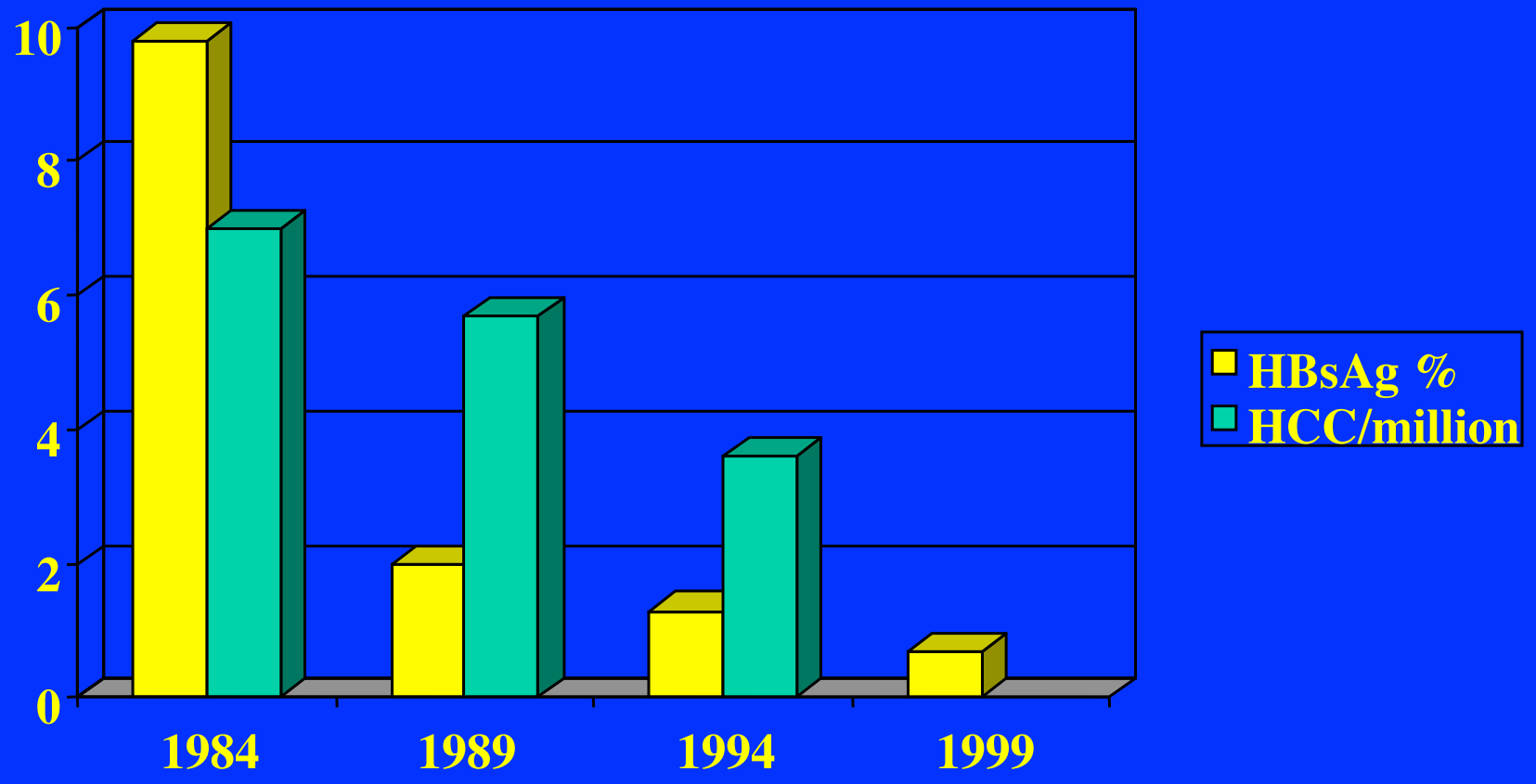
Global eradication of hepatitis B: feasible or fallacy?: Thursz M. Nature 2012

Active and passive hepatitis B vaccination:
post-exposure prophylaxis in infants

Maternal screening	Vaccine < 24h	HBIg < 24h	Efficacy	Cost	Countries
Yes HBsAg HBeAg	YES 0, 1, 6 mths	Infants/ HBeAg+ mothers only	Higher	Higher	Taiwan
Yes HBsAg only	YES 0, 1, 6 mths	Infants/ HBsAg+ mothers	Highest	Highest	USA
Yes HBeAg only	YES 0, 1, 6 mths	Infants / HBeAg+ mothers only	High	Highest	Japan
Yes HBsAg	YES 1, 2, 4, 6 mths	recommanded	high	highest	Thailand

hepatitis B vaccine : first anti-cancer vaccine

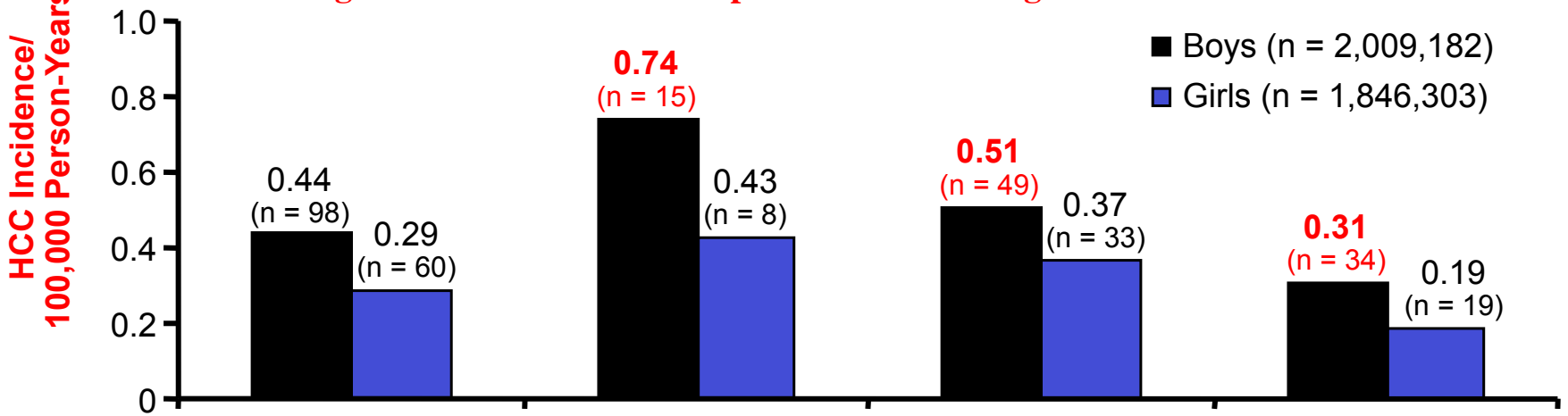
Prevalence of HBsAg and HCC children <12 yrs in Taiwan



Chang, MH, NEJM, 1997. Lin YC, JID, 2003

Relationship Between HBV Vaccination and HCC Incidence

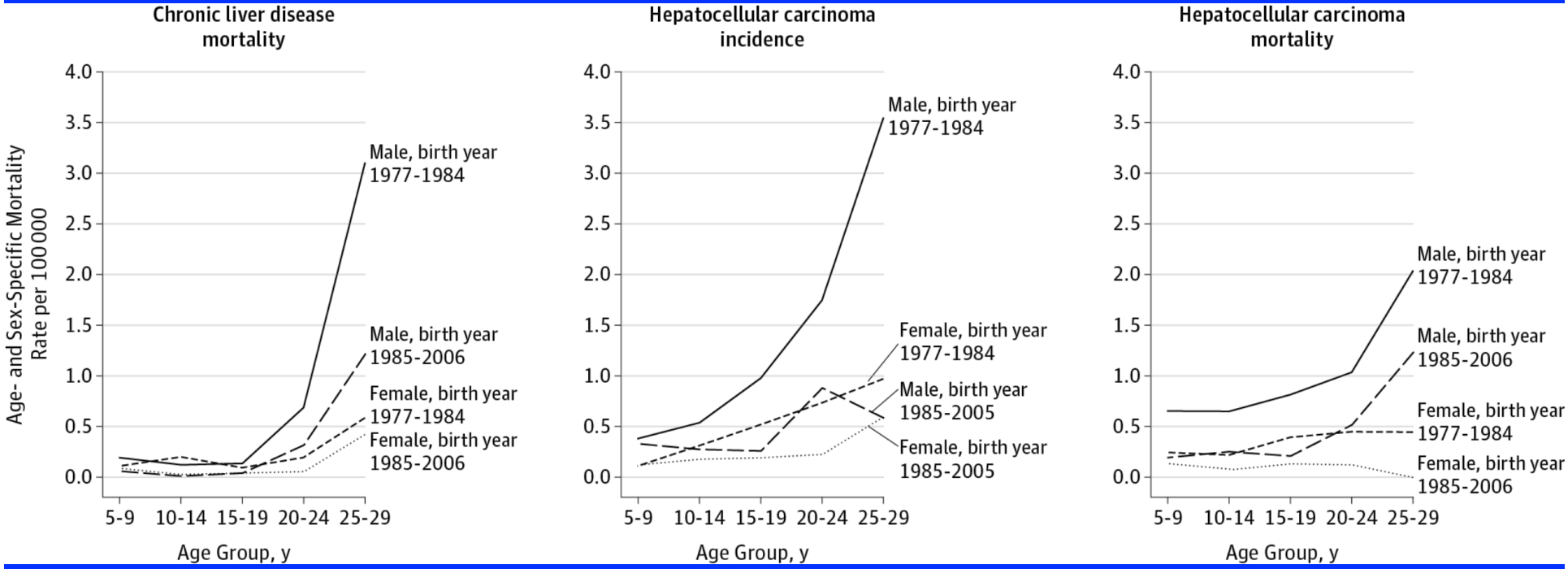
- 3,855,485 newborns vaccinated in Taiwan (1984-2000)
  - 43,134,217 person-years of follow-up
- 158 cases of newly diagnosed HCC during follow-up
  - **Rates higher in boys vs girls**
  - **Receiving 4 vs 1-2 doses increased preventive effects against HCC**



	All Participants, n	1-2 Vaccine Doses, n	3 Vaccine Doses, n	4 Vaccine Doses, n
Boys	2,009,182	217,768	1,061,759	729,655
Girls	1,846,303	197,921	979,213	669,169

Chang MH, JAMA 2000; J Natl Cancer Inst 2009;

Age- and Sex-Specific Mortality and Incidence Rates of Chronic Liver Disease and Hepatocellular Carcinoma for Birth Cohorts Born Before and After the Launch of the Hepatitis B Immunization Program in 1984 in Taiwan



Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan
Chiang CJ et al. JAMA. 2013;310(9):974-976.

Reduction of HCC in childhood by vaccination against HBV for infants born to HBV-carrier mothers (Japan)

Tajiri H et al. , 2011

2 doses of HBIg (1 at birth, 1at 2mths)+3 doses of vaccines (2, 3, 5mths)

- **Start 1986: 494 babies born to HBV-infected mothers vaccinated**
- **93.5% protection efficacy**
- **HBV carrier rate decreased from 0.8% (1985) to 0.005% (2005)**

incidence of HBV-HCC / hepatoblastoma (HB) among HCC (JCCR)

Period	HB cases	Total HCC	Ratio to HB	HBV+ HCC	Ratio to HB
1981-1985	124	20	0.161	11	0.089
1986-1990	119	25 (0-4yr)	0.210	10	0.084
1991-1995	147	22 (0-9yr)	0.150	9	0.061
1996-2000	133	15 (0-14yr)	0.113	7	0.053
2001-2005	133	8 (0-19yr)	0.060	1	0.008
2006-2008 (3years)	84	5 (0-22yr)	0.060	0	0.000 ($p<0.0001$)

hepatitis B vaccination: Unresolved issues

- **Decline in anti-HBs titers: Is a booster dose required ?**
  - **No (countries with low HBV endemicity, subjects with low infection risk)**
  - **Yes (immunocompromised subjects & subjects with high risk to HBV exposure)**

- **Anamnestic effect of booster dose on a-HBs Ab: stimulation of memory B cells**
  - Few significant breakthrough infections (*Ni YH et al. Gastroenterology 2007*)
  - unusual clinical courses of HBV infection in previously vaccinated subjects: transient viremia and no biochemical hepatitis after infection resulting from sexual contact or blood transfusion (*Stramer SL et al. NEJM 2011; Liu et al. J Hepatol 2006*)

- **Eliminating HBV through neonatal vaccination ?**
  - overall post-vaccination HBsAg carrier rate <1%
  - HBsAg carrier rate 7- 17% or occult HBV found in infants from mothers with high titer viremia (HBeAg+)

  –> administration of anti-viral agents (Lam, Tenofovir, Telbivudine) to pregnant mothers before vaccination of neonates

Vaccination and global elimination of hepatitis B

- Vaccination of infants and neonates:
  - has already prevented 210 million of new chronic infections by 2015
  - will prevent 1.1 million deaths by 2030
- Scaling up the coverage of infant vaccination

  to 90% of infants, 80% of neonates (birth dose)

  combined with the use of peripartum antivirals

  would prevent 7.3 million deaths between 2015-2030 and 63 million new chronic infections

Nayagam S et al. The Lancet Sept 2016

hepatitis B vaccines

- HBV and the disease
- recombinant preventive vaccines
- immuno-modulatory and anti-viral approaches to treat CHB

HBV INFECTIONS : STRONG NEED FOR DEVELOPMENT OF NEW THERAPEUTIC INTERVENTIONS

Existing vaccine

Worldwide HBV chronic carriers
300 Millions

"e" Ag mutants increase

Inactive carriers of HBsAg
HBV DNA< 2000 IU/ml
not treated

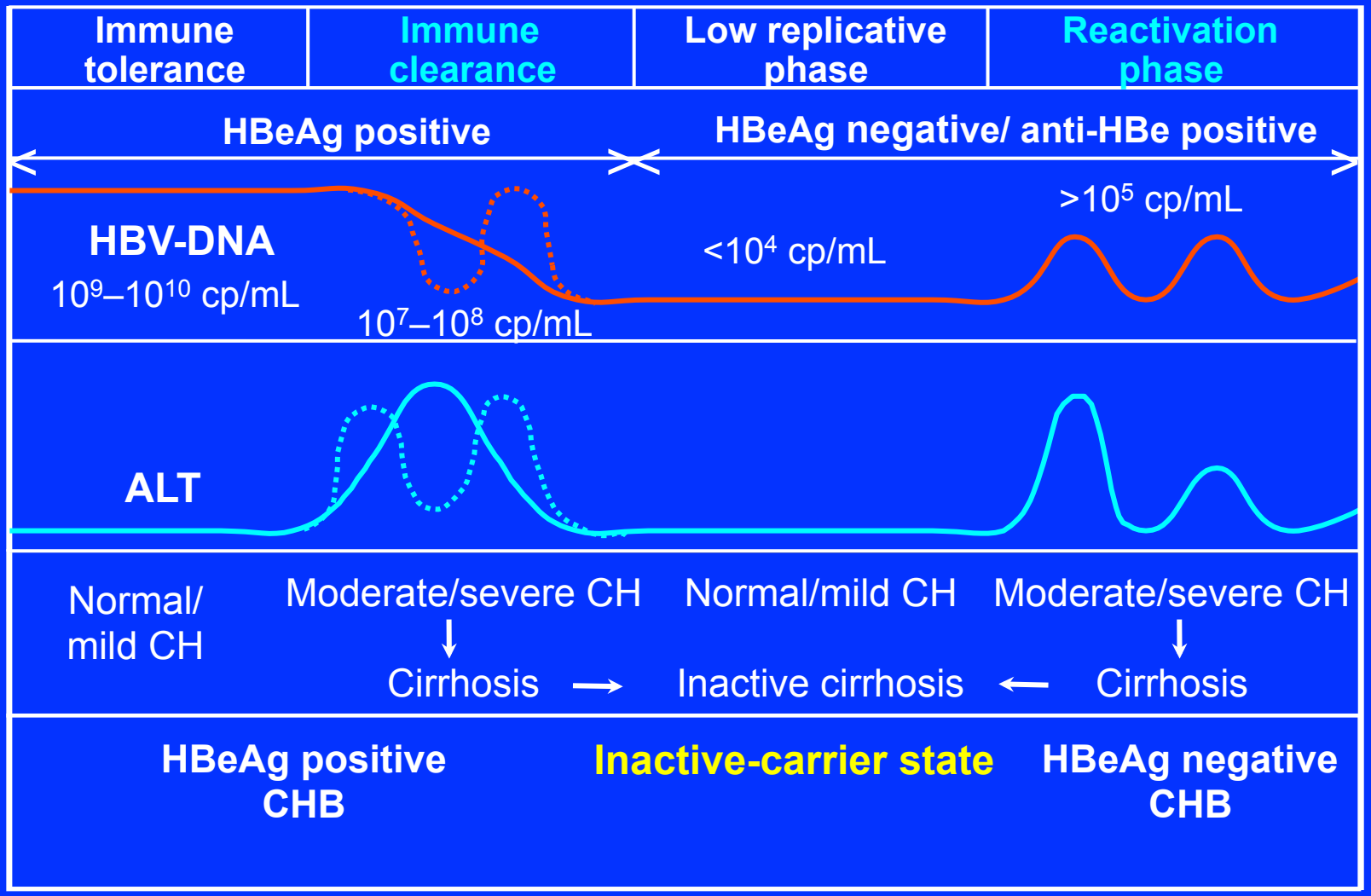
IFN-alpha
successful in 30%
Side effects

Antiviral treatments

Lamivudine /Adefovir therapy
emergence of resistant virus
Annual resistance rate 15-20%

Entecavir/ tenofovir therapy
Low rate of anti-HBe+ , cccDNA+
long term treatment

Stages of Chronic Hepatitis B (CHB) Infection



<10^4cp/ml =2 000 IU/ml

Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet. 2014

Medical needs in chronic HBV infection

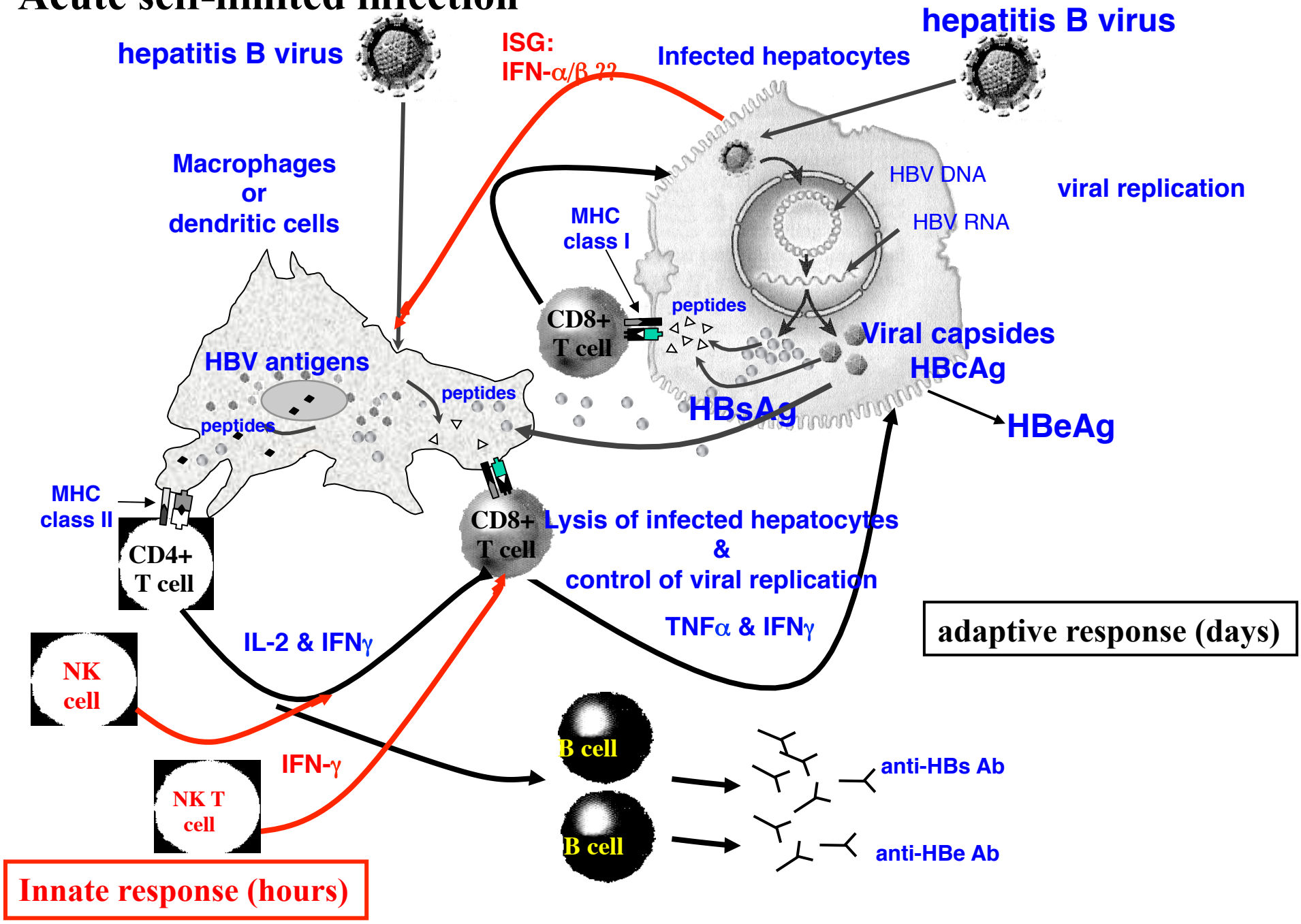
- **Inhibition of viral replication**
- **Normalization of ALT**
- **Improvement in liver necroinflammation**
- **Improvement in fibrosis**

Fulfilled by nucleos/tide analogs (NUC) treatments

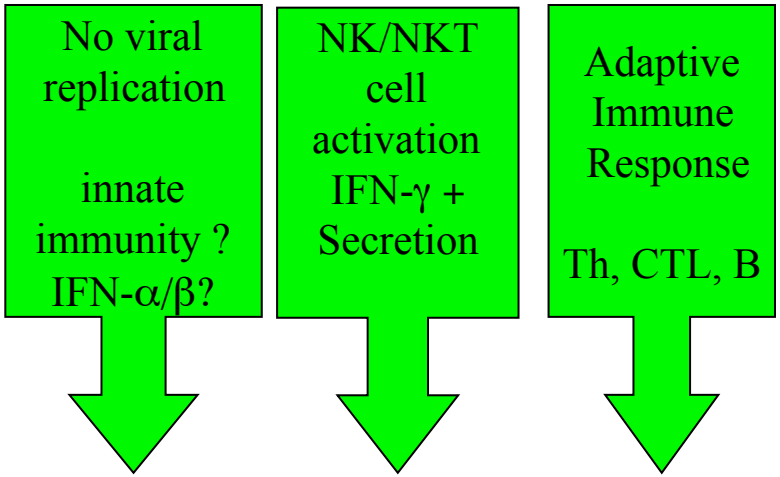
- **HBeAg negativation and a-HBe seroconversion**
- **Elimination of cccDNA and HBV-infected hepatocytes**
- **HBsAg loss and seroconversion to anti-HBs Ab**

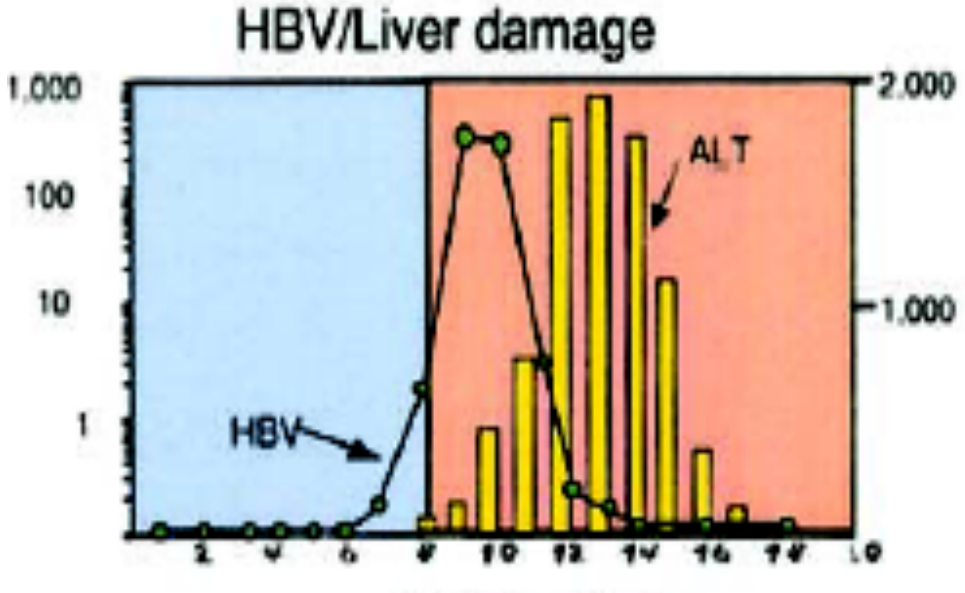
HBV cure: an achievable goal by using immune stimulation ??
(IFN-α, vaccine therapy, cytokines, TLR agonists…)

Acute self-limited infection



Acute self-limited HBV infection: Co-ordinated immune responses



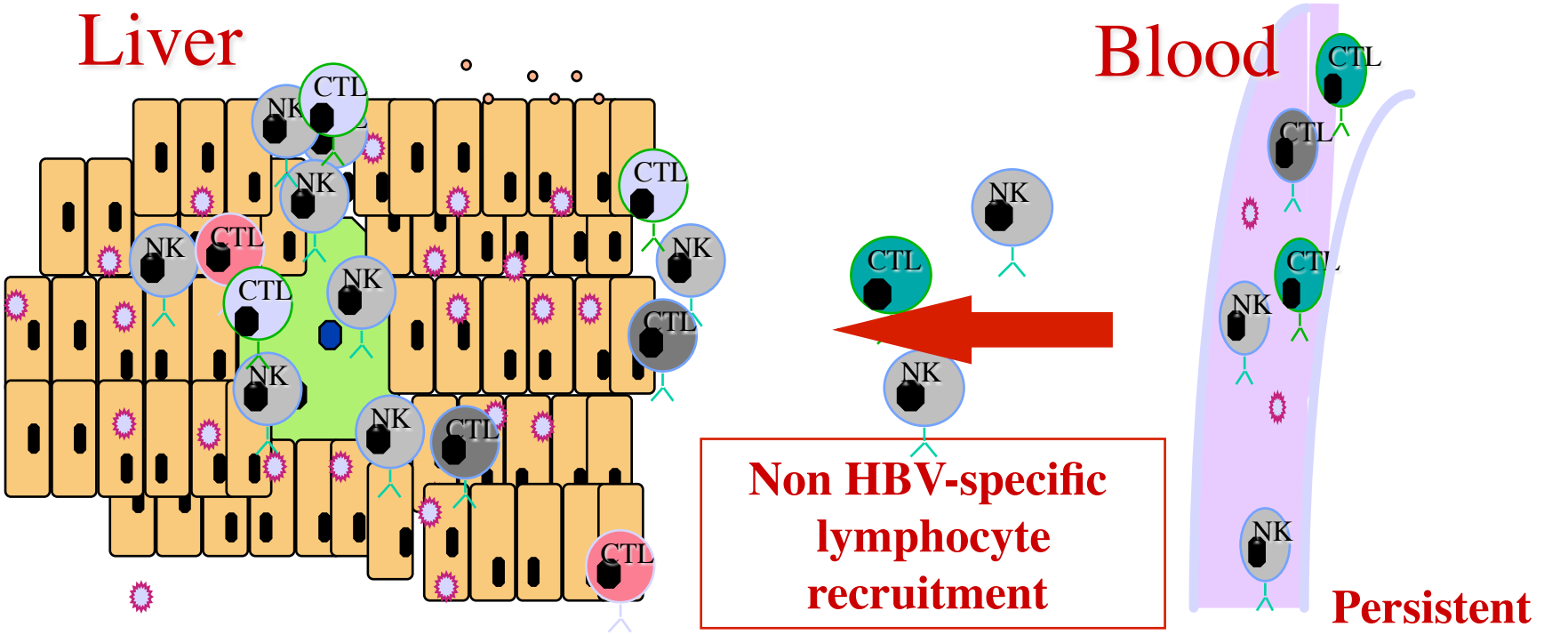


- **IR delayed by 4-6 wks post infection**
- **HBV Infection = high viral replication (>10^8 copies /ml) all hepatocytes are infected**
- **IFN-γ production by NK, NK T & MAIT cells**
- **non cytolytic control of viral replication (IFN-γ / TNF-α; LTβ)**
  Strong multi-specific CD8 T cells
  Strong proliferation of CD4+ T cells
  HBV-specific CD8+ T recruited in liver
  Hepatic lysis = >ALT

Rehermann Nat. Rev. Immunol., 2005)

Chronic HBV infection:

uncontrolled viral replication and ongoing liver damage or persistent episomal form of HBVcccDNA, resistant to antivirals



Low frequency HBV-specific CD8 T-cell responses

- with exhausted phenotype (PD-1, CTLA-4, CD244, Tim3…)

Impaired IL-2 production /proliferation of T cells

Impaired production of anti-viral cytokines (IFN-γ, TNF-α)

-increase in Tregs and IL-10-secreting T cells

Impaired NK cell responses

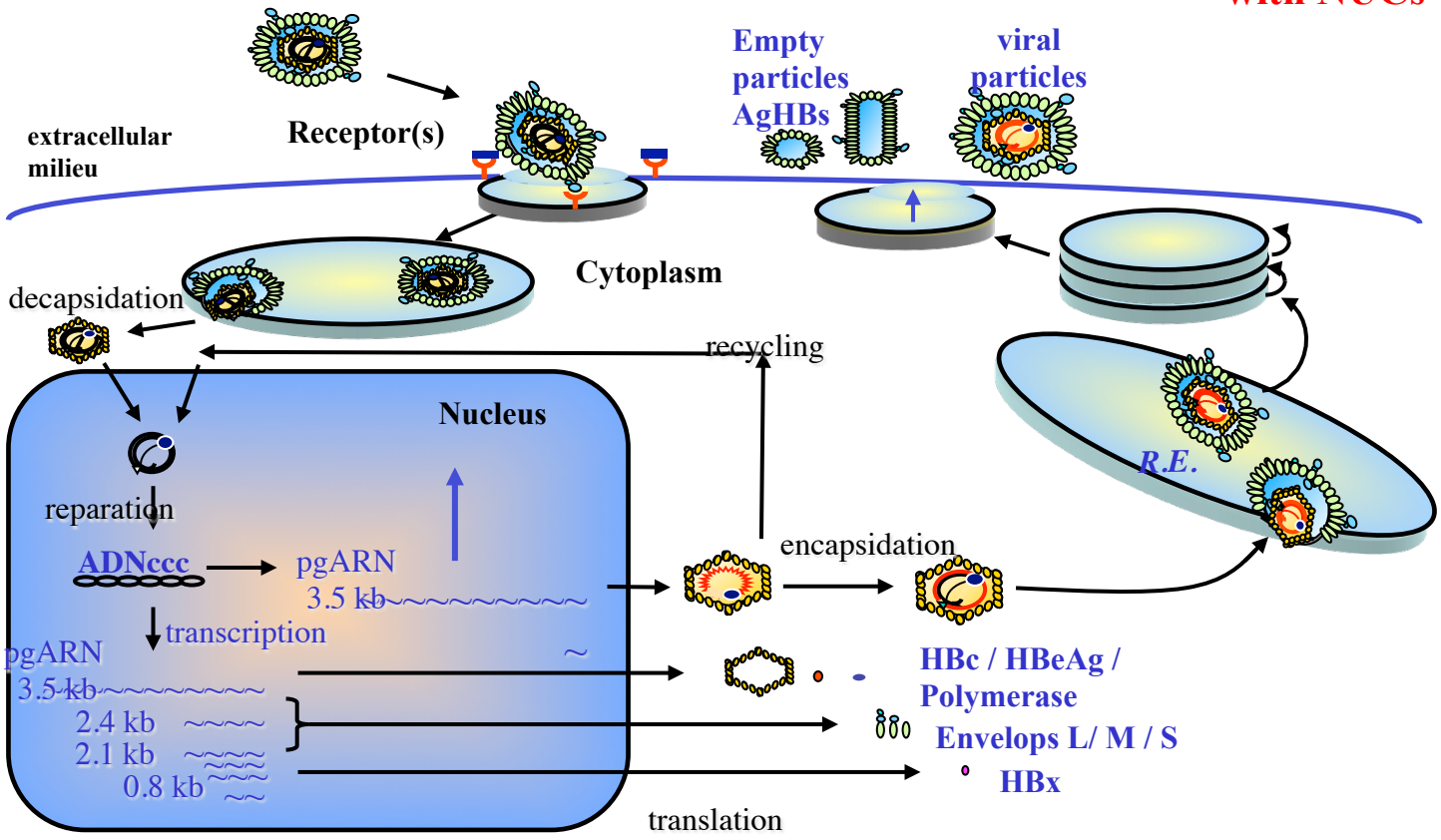
(Bertoletti &Maini, Antiviral. Ther., 2010).

Therapeutic options : towards an HBV cure….

Stimulation of innate immunity TLR agonists

Stimulation of HBV-specific T cells: Therapeutic vaccines

Restoration of functional T cells: Combined therapy with NUCs

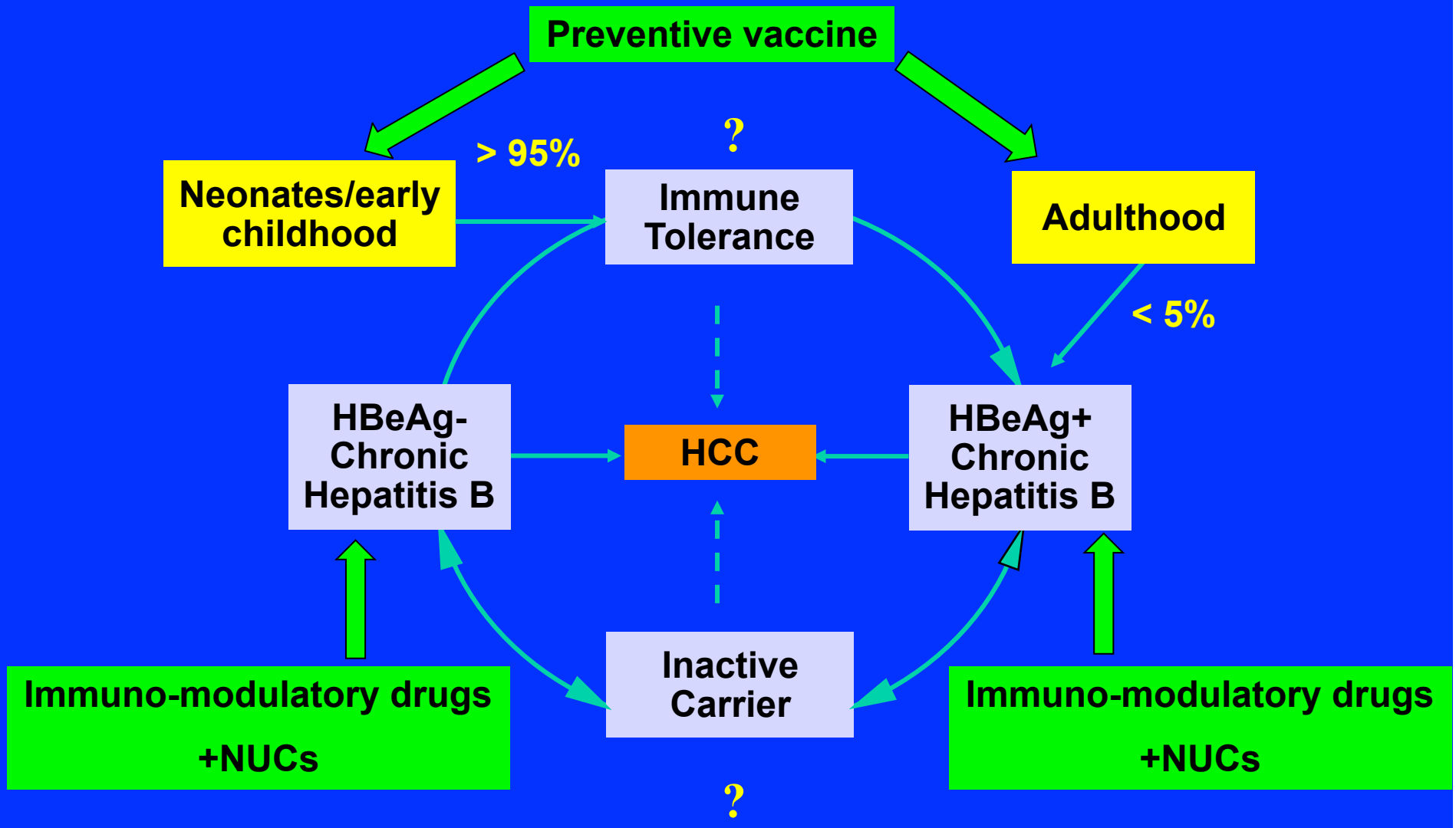


Targeting the virus: Direct Acting Agents
Inhibitors of cccDNA
inhibitors of transcription (RNAi)
Inhibitors of capsid assembly

Blocking inhibitory mechanisms in liver: Host Targeting Agents
Therapeutic antibodies
Blocking HBV entry

(Michel M-L Virologie, 2014, vaccine 2017)

hepatitis B vaccination combined with anti-viral treatments would avert 1.5 million of cancer deaths (2015-2030)



Acknowledgments

Maryline Bourgine
Ophélie Godon
Sarah Dion
Delphine Loirat
Ren Zhu
Qiang Deng
Marie-Louise Michel

Institut Pasteur

-**Laboratoire de Pathogenèse des virus de l'hépatite B /INSERM U994**

Daniel Scott-Algara

Laboratoire F. Barré-Sinoussi

Pierre Tiollais

Institut Pasteur

Hélène Fontaine
Stanislas Pol
Christian Bréchot
…..

Assistance Publique Hôpitaux de Paris, Service d' Hépatologie
Institut Cochin, CNRS (UMR 8104) and INSERM U-1016,
Hôpital Cochin, Service d'hépatologie, Paris France

Mala Maini

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anRS
French National Agency for Research on AIDS and Viral Hepatitis
An autonomous agency at Inserm

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