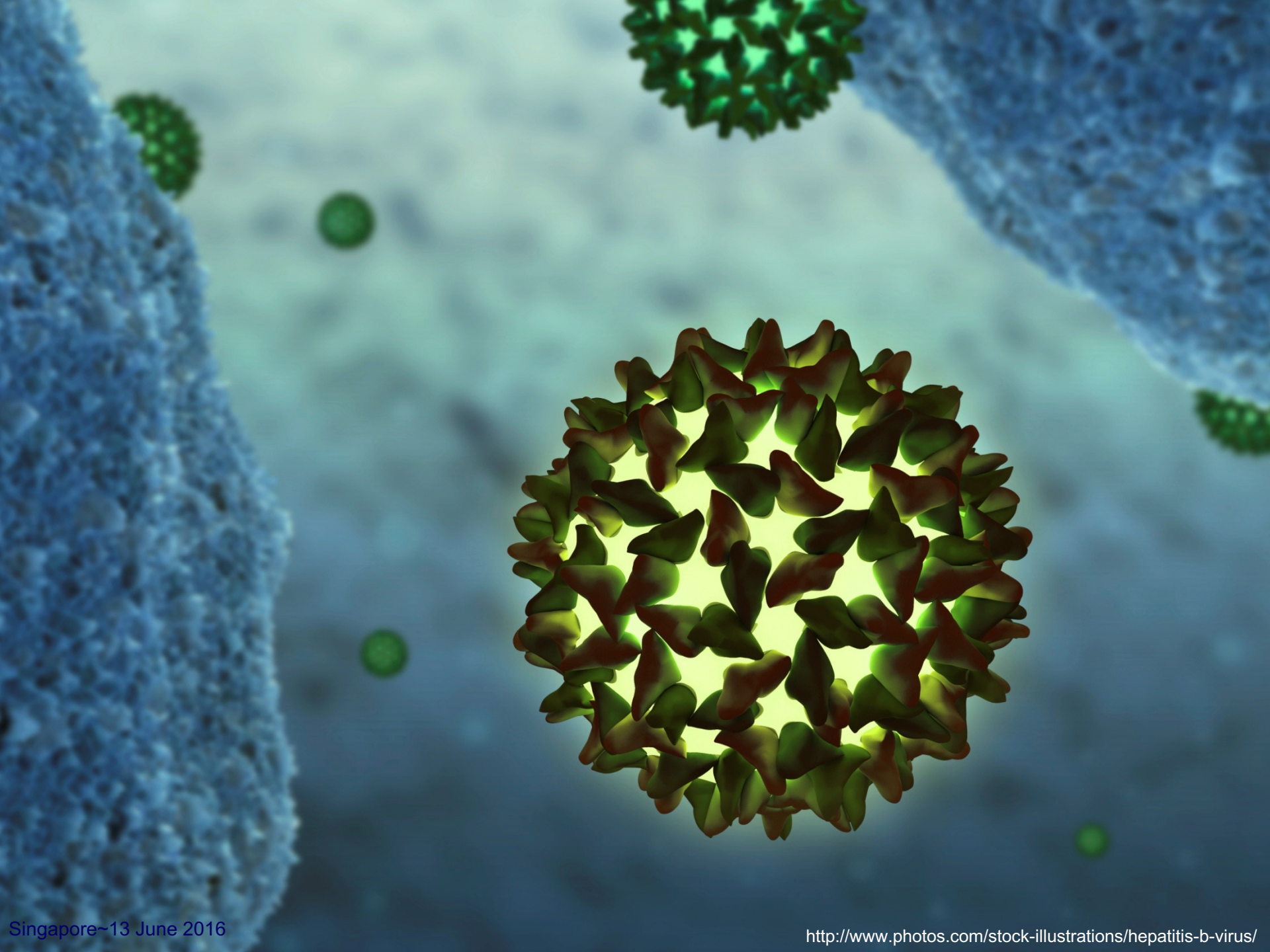
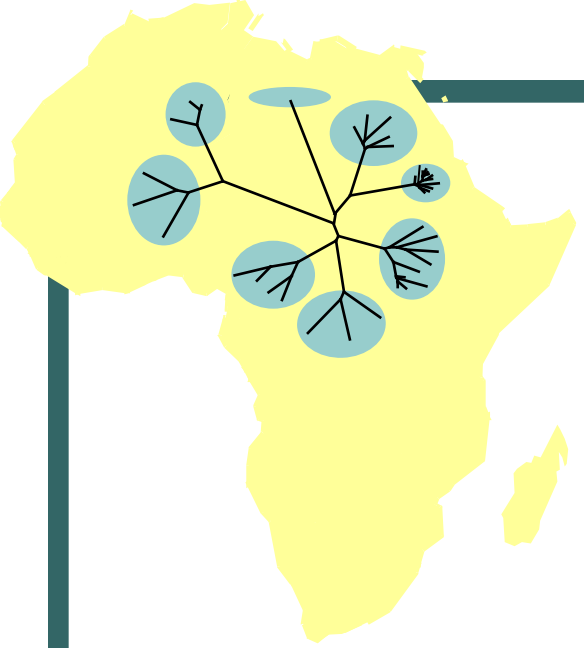


Singapore~13 June 2016

http://www.photos.com/stock-illustrations/hepatitis-b-virus/



The clinical implications of hepatitis B virus genotypes HBeAg in paediatrics

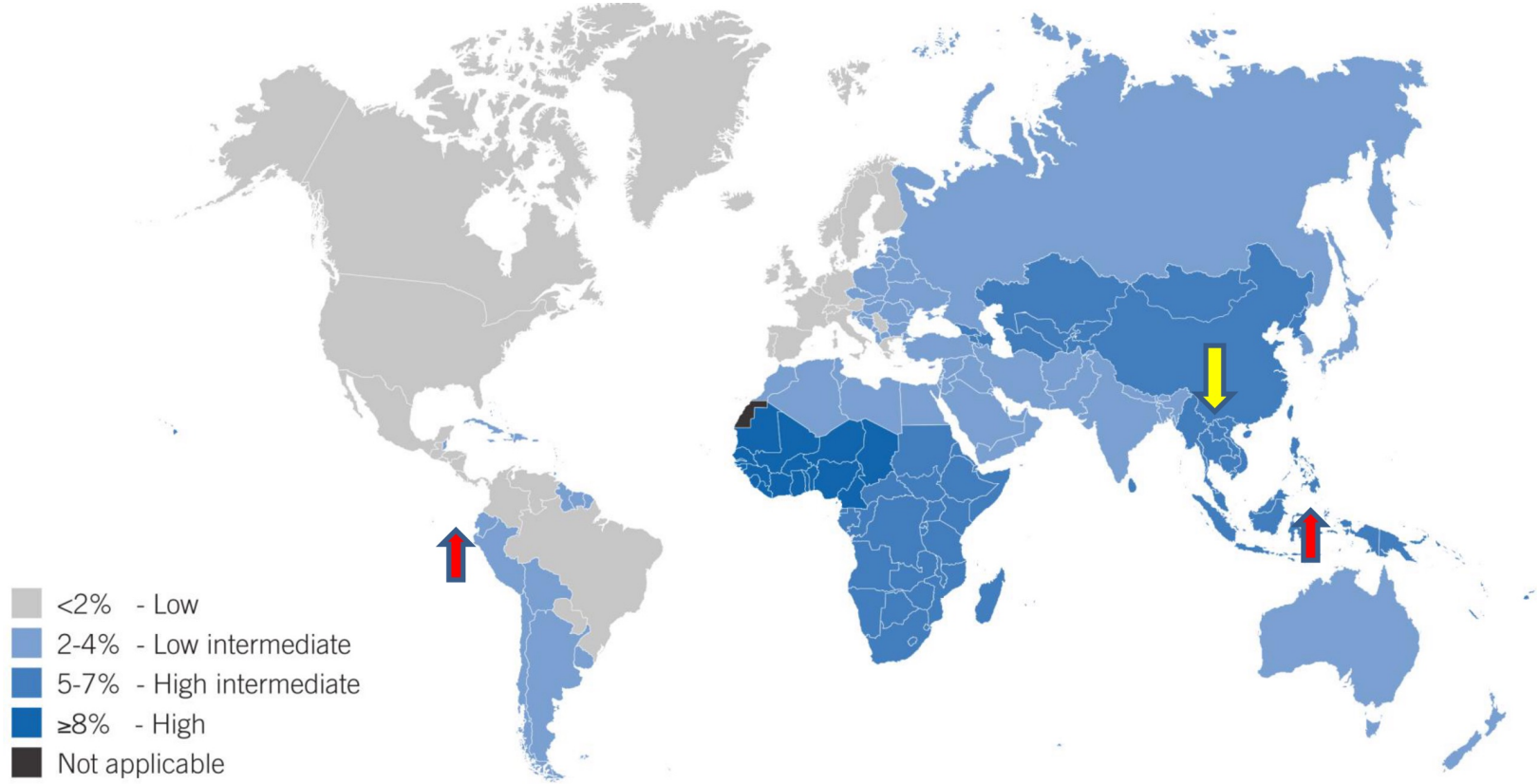
Professor Emerita Anna Kramvis
Hepatitis Virus Diversity Research Unit
University of the Witwatersrand
Johannesburg, South Africa

Overview

- Global HBV prevalence in children
- Transmission of HBV in children
- HBeAg
- Natural history of HBV infection in children
- Genotypes and subgenotypes of HBV
- Effect of (sub)genotypes on HBeAg expression and natural history of HBV infection

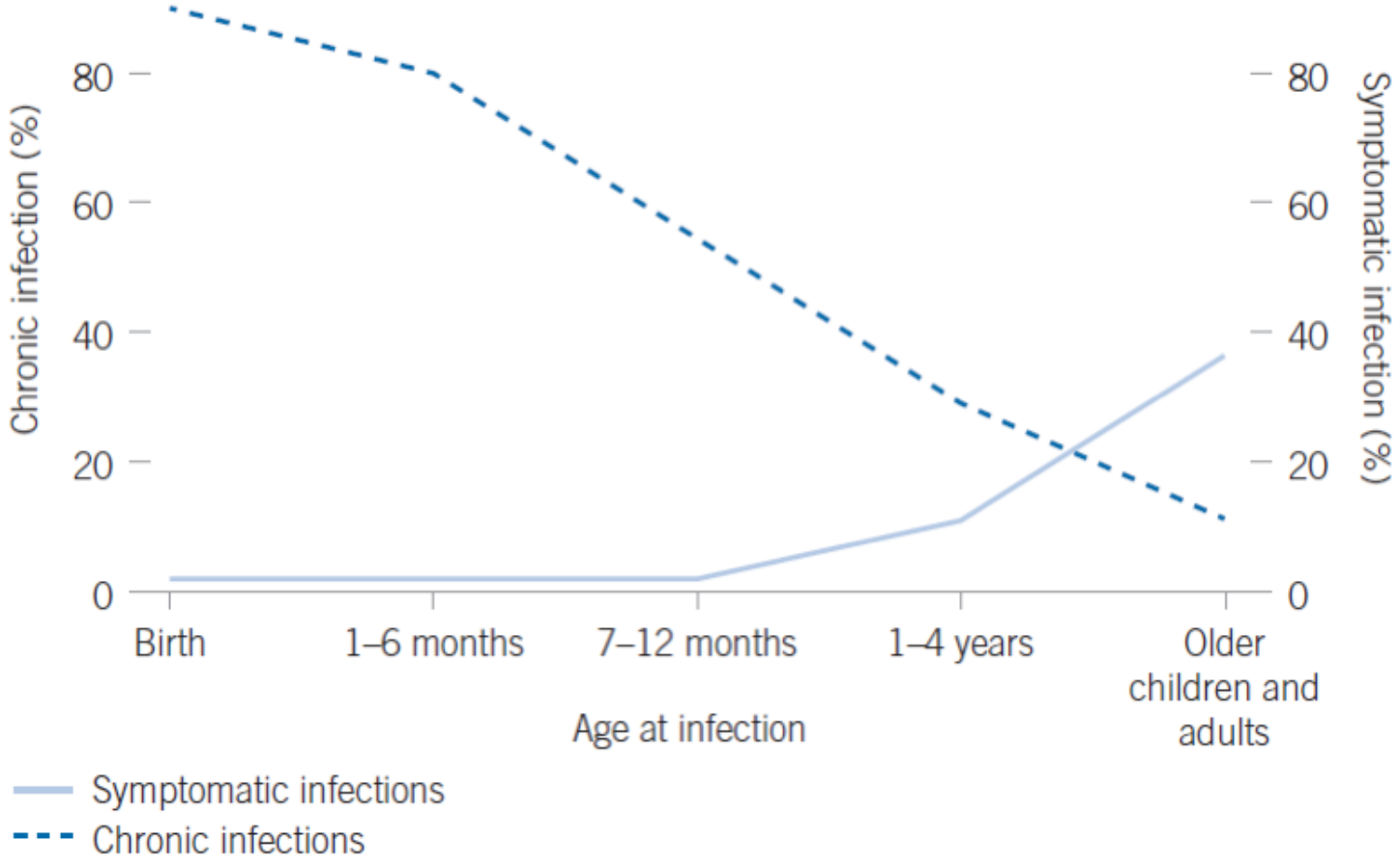
http://www.nature.com/nrgastro/journal/v12/n4/images/nrgastro.2015.28-i1.jpg

Prevalence of HBV in Children



Kramvis 2016; Rev Med 2016 26(4):285-303

Outcomes of HBV Infection by Age of Infection



http://www.who.int/hiv/topics/hepatitis/en/

Liver Disease in Children

- Liver damage is minimal in the majority of children, some can manifest mild inflammation and acute hepatitis, as well serious complications of HBV infection, including cirrhosis and HCC, 2 to 7 years after infection.

SAMJ 2018; 108:389-392

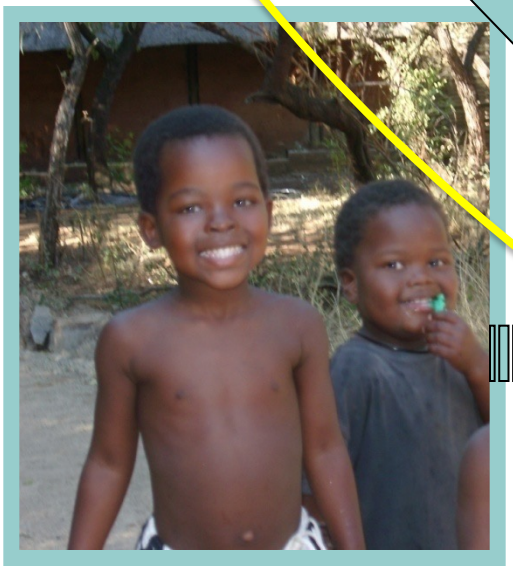
CASE REPORT

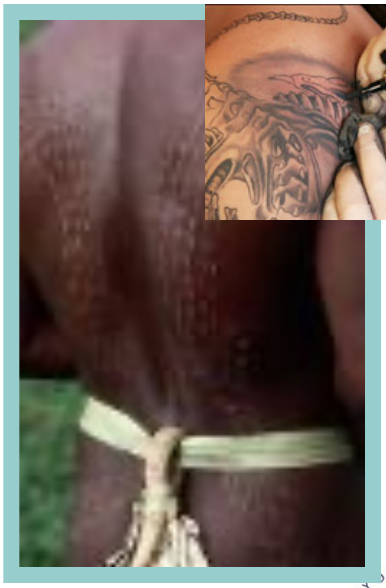
Fulminant hepatitis B virus (HBV) infection in an infant following mother-to-child transmission of an e-minus HBV mutant: Time to relook at HBV prophylaxis in South African infants

O Babatunde,[1] MBBS, MSCI, FMCPaed; H Smuts,[2,3] PhD; B Eley,[1] MB ChB, FCP (SA) (Paed), BSc Hons;
S Korsman,[2,3] MB ChB, FC Path (SA) Viro, MMed; R de Lacy,[4] MB ChB, FCP (SA) (Paed); D R Hardie,[2,3] MB ChB, MMed

Wen et al Journal of Pediatrics 2004; 144: 397–399.
Boxall et al Archives of Disease in Childhood—Fetal and Neonatal Edition 2004; 89: F456–460.

Transmission of HBV





Cape Town – 2 December 2023

Iatrogenic Transmission in Children

Pediatr Blood Cancer 2015;62:1914–1919

Nosocomial Outbreak of Hepatitis B Virus Infection in a Pediatric Hematology and Oncology Unit in South Africa: Epidemiological Investigation and Measures to Prevent Further Transmission

Ané Büchner, MBChB, DCH, FCPaed(SA), MMed(Paed), Cert. Medical Oncology(Paed),[1]* Nicolette M. Du Plessis, MBChB, DipAllerg(SA), FCPaed (SA), MMed(Paed), Dip HIV Man(SA), Cert ID Paed(SA),[2] David T. Reynders, MBChB, FCPaed(SA), MRCPCH, Cert. Medical Oncology(Paed), Fareed E. Omar, MBChB, FCPaed(SA), Cert. Medical Oncology(Paed),[1] Simnikiwe H. Mayaphi, MBChB, FCPath(SA)Viro,[3] Ahmad F. Haeri Mazanderani, MBChB, Dip HIV Man(SA),[3] and Theunis Avenant, MBChB, MMed(Paed), FCPaed(SA)[2]

BMC Pediatrics 2022; 22:168

CASE REPORT Open Access

Molecular characterization of hepatitis B virus (HBV) isolated from a pediatric case of acute lymphoid leukemia, with a delayed response to antiviral treatment: a case report

Chien-Yu Chen[1], Christina Hajinicolaou[2,3,4], Priya Walabh[3], Luicer Anne Olubayo Ingasia[1], Ernest Song[5] and Anna Kramvis[1*]

HBeAg Expression and Mother-to-Child Transmission

746 THE NEW ENGLAND JOURNAL OF MEDICINE April 1, 1976

e ANTIGEN AND ANTI-e IN THE SERUM OF ASYMPTOMATIC CARRIER MOTHERS AS INDICATORS OF POSITIVE AND NEGATIVE TRANSMISSION OF HEPATITIS B VIRUS TO THEIR INFANTS

KIYOSHI OKADA, M.D., ICHIRO KAMIYAMA, M.D., MINAKO INOMATA, B.S., MITSUNOBU IMAI, B.S., YUZO MIYAKAWA, M.D., AND MAKOTO MAYUMI, M.D.

1976

AMERICAN JOURNAL OF EPIDEMIOLOGY Vol. 105, No. 2

Printed in U.S.A.

THE e ANTIGEN AND VERTICAL TRANSMISSION OF HEPATITIS B SURFACE ANTIGEN

R. PALMER BEASLEY,[1,2] CHRISTIAN TREPO,[3] CLADD E. STEVENS,[3] AND WOLF SZMUNESS[3]

1977

HBeAg and Anti-HBe Detection by Radioimmunoassay: Correlation With Vertical Transmission of Hepatitis B Virus in Taiwan

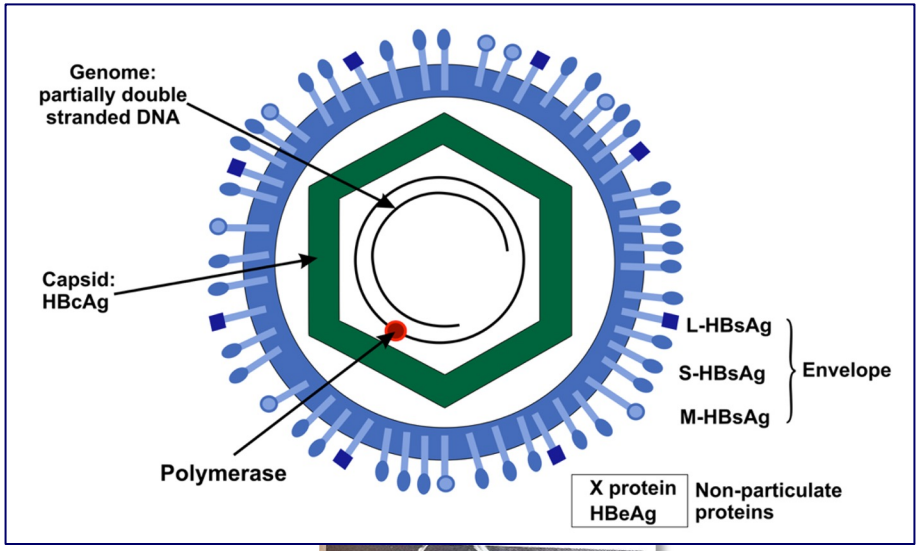
Cladd E. Stevens, Robert A. Neurath, R. Palmer Beasley, and Wolf Szmuness

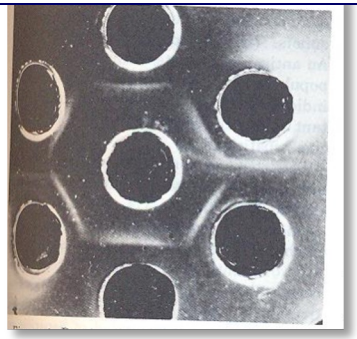
1979

HBeAg+ve vs HBeAg-ve
9.26% vs. 0.23%, p <0.001

Chen et al Gastorenterology 2012; 142e772

HBeAg



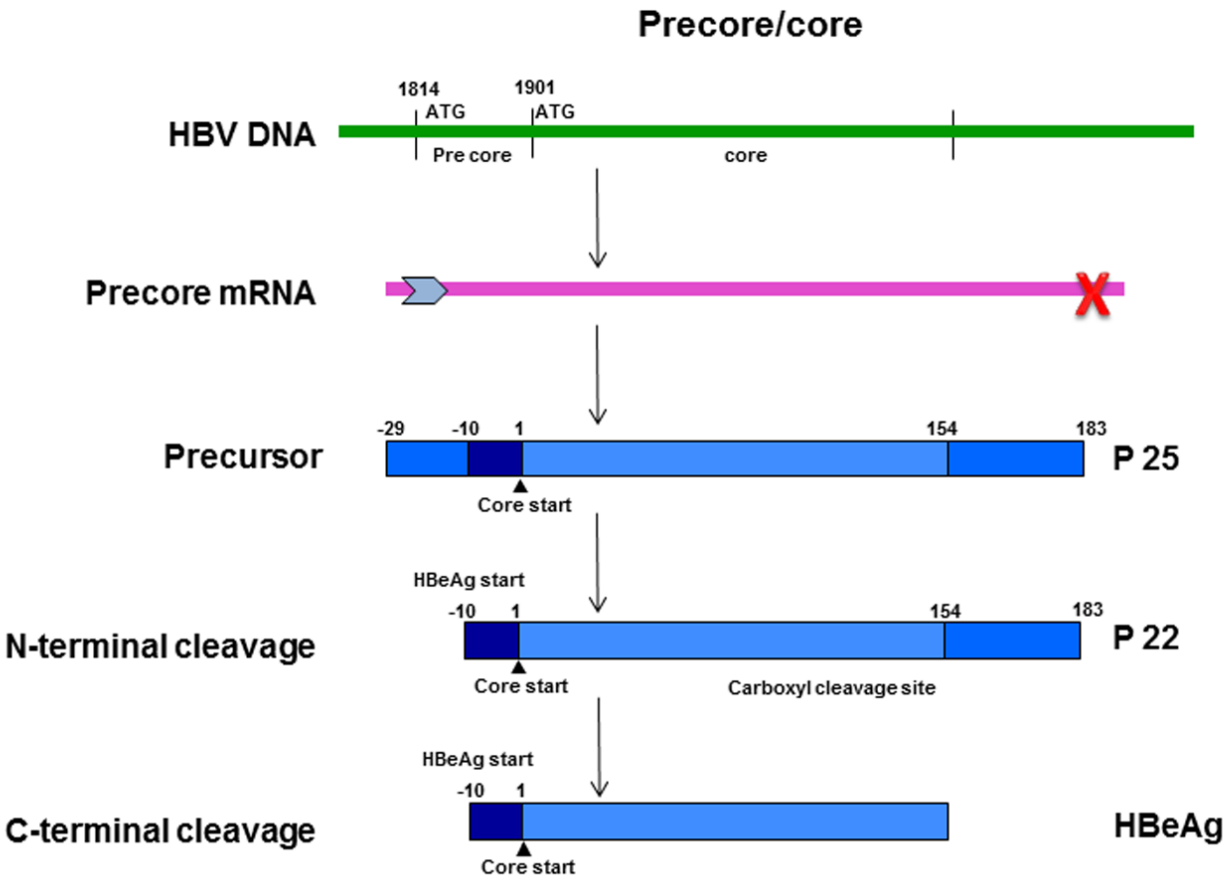


Ouchterlony plate

Gerlich, Glebe, Kramvis, Magnius Virus Genes 2020; 56:109-119

Magnius & Espmark Immunology 1972; 109: 1017 – 1021
Kramvis 2016; Rev Med 2016 26(4):285-303

Expression of HBeAg

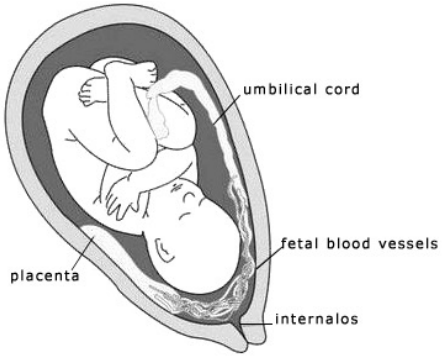


Revill….Kramvis J Med Virol 2010;82: 104-115
Kramvis; Rev Med 2016 26(4):285-303

Function of HBeAg

- Not required for viral assembly or replication but is important for natural infection *in vivo.*
- Required for the development of CHB
- Clinically
  - Index of viral replication
  - Infectivity
  - Severity of disease
  - Response to antiviral treatment

- **Immunoregulatory protein**
  - **Immunogen**
  - **Tolerogen**
  - **↓ Innate IR**



Milich, D & Liang (2003) Hepatology 38: 1075 – 1086Yang, CY et al (2006) J Biol Chem 281:34525 – 34536
1. Visvanathan, K et al (2007) Hepatology 45: 102 -110
https://classconnection.s3.amazonaws.com/129/flashcards/475129/gif/vasa_previa1352911684347.gif

HBeAg as an oncoprotein?

viruses

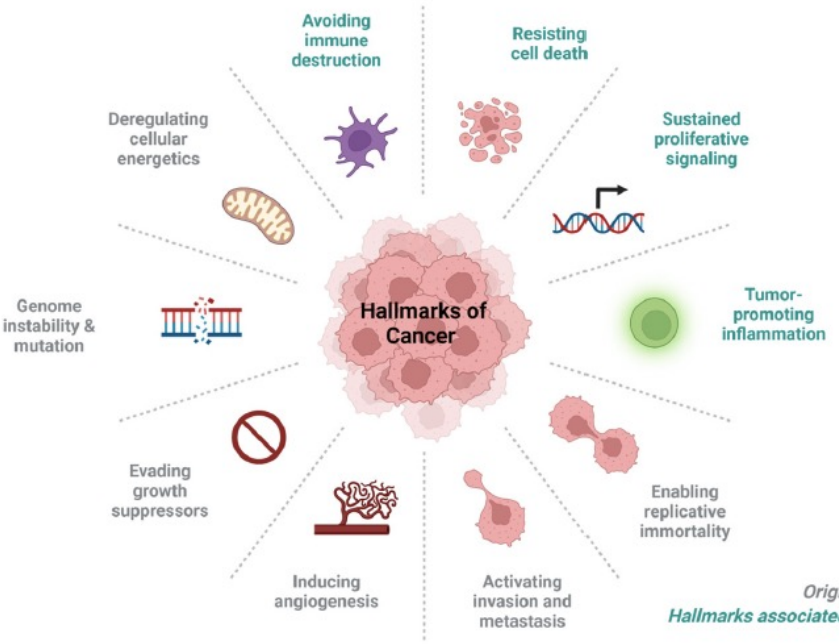
MDPI

Review

The Complex Role of HBeAg and Its Precursors in the Pathway to Hepatocellular Carcinoma

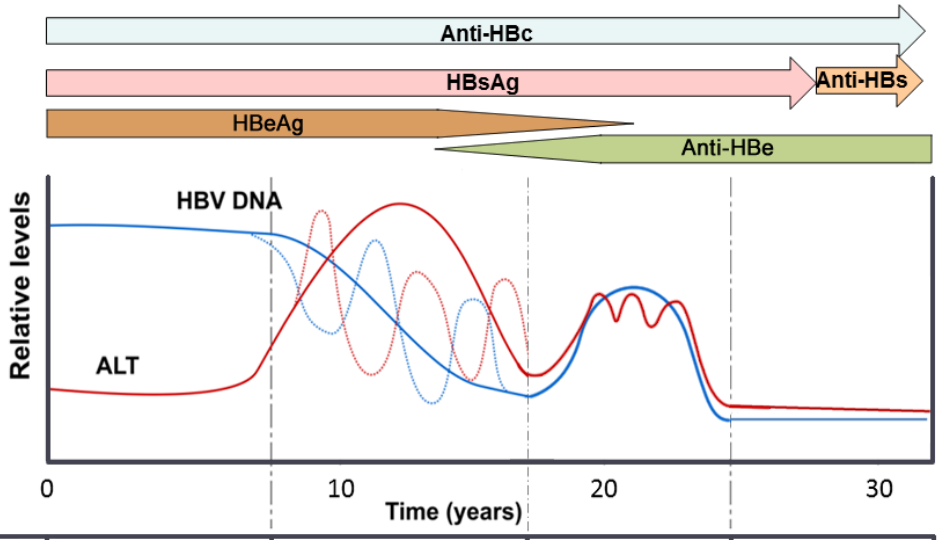
Kiyasha Padarath [1], Aurélie Deroubaix [1,2,*] and Anna Kramvis [1,*]

1. Immune evasion, leading to persistence
2. Resisting cell death
3. Tumor-promoting inflammation
4. Promote sustained proliferative signalling



Viruses 2023, 15, 857.

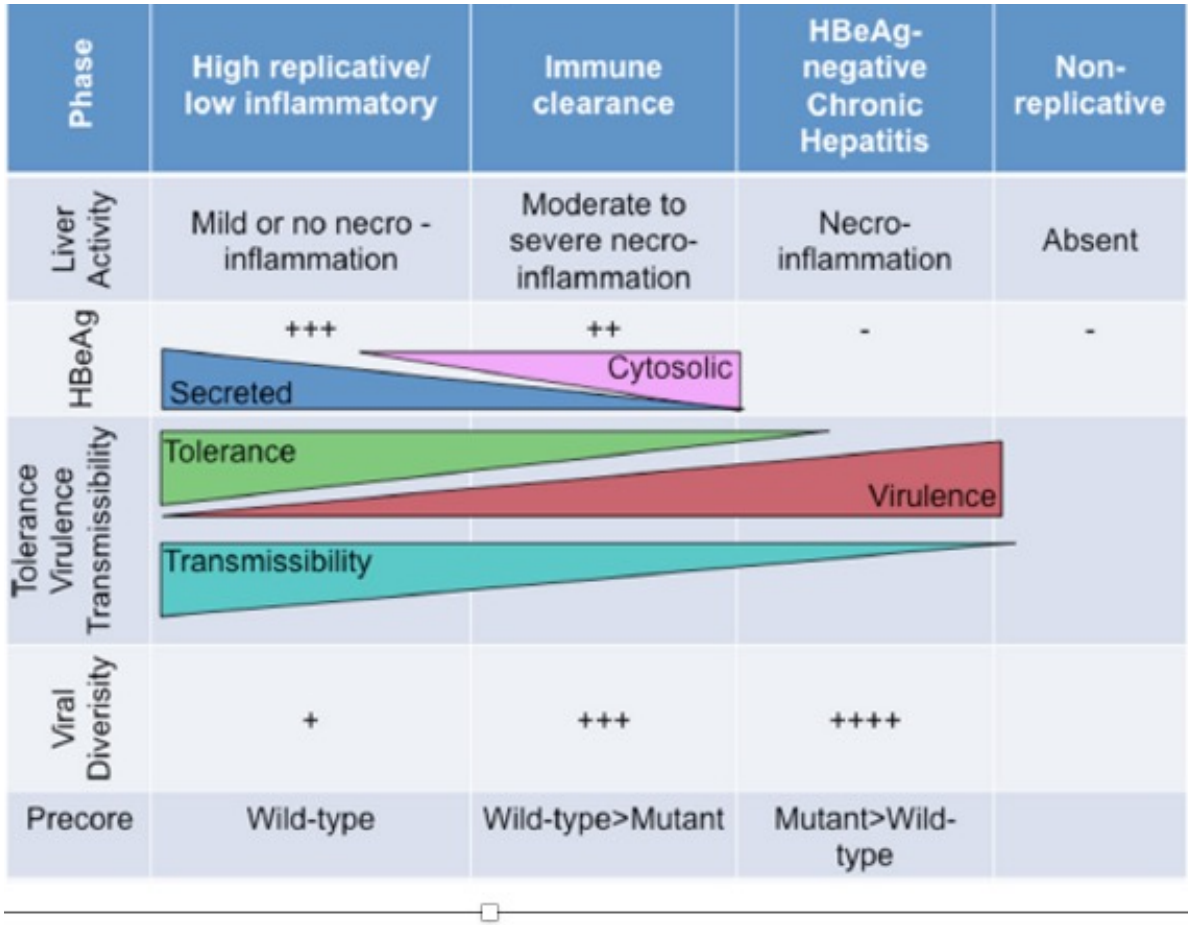
Natural history of infection of hepatitis B virus (HBV) in children



Liver activity	Mild or no necroinflammation	Moderate to severe necroinflammation	Necro-inflammation	Absent
Phase	High replicative/ low inflammatory	Immune clearance	HBeAg-negative Chronic Hepatitis	Non-replicative

Kramvis 2016; Rev Med 2016 26(4):285-303

Relationship of HBeAg Expression on the Natural History of HBV Infection



Kramvis Rev Med Virol 2016; 26:285-303
Kramvis Frontiers in Microbiol 2018; ; 9:2521

HBeAg and Liver Disease in Children

- Risk factors for early HCC development include cirrhosis and HBeAg seroconversion before 3 years
- It is possible that there are different mechanisms for the development of HCC in adults and children.
- The former require higher viral loads and liver inflammation, whereas integration of HBV in the human genome may trigger HCC in children.

Hepatology 1991; 13:316-320

Hepatitis B Virus Integration in Hepatitis B Virus–related Hepatocellular Carcinoma in Childhood

MEI-HWEI CHANG,[1] PEI-JER CHEN,[2] JEN-YANG CHEN,[3] MING-YANG LAI,[2] HEY-CHI HSU,[4] DER-CHENG LIAN,[1] YUEH-GIAO LIU[1] AND DING-SHINN CHEN[2]

[1]Department of Pediatrics, [2]Graduate Institute of Clinical Medicine, [3]Department of Microbiology, and [4]Department of Pathology, College of Medicine, National Taiwan University, Taipei 10016, Taiwan, Republic of China

Wen et al Journal of Pediatrics 2004; 144: 397–399.
Boxall et al Archives of Disease in Childhood—Fetal and Neonatal Edition 2004; 89: F456–460.

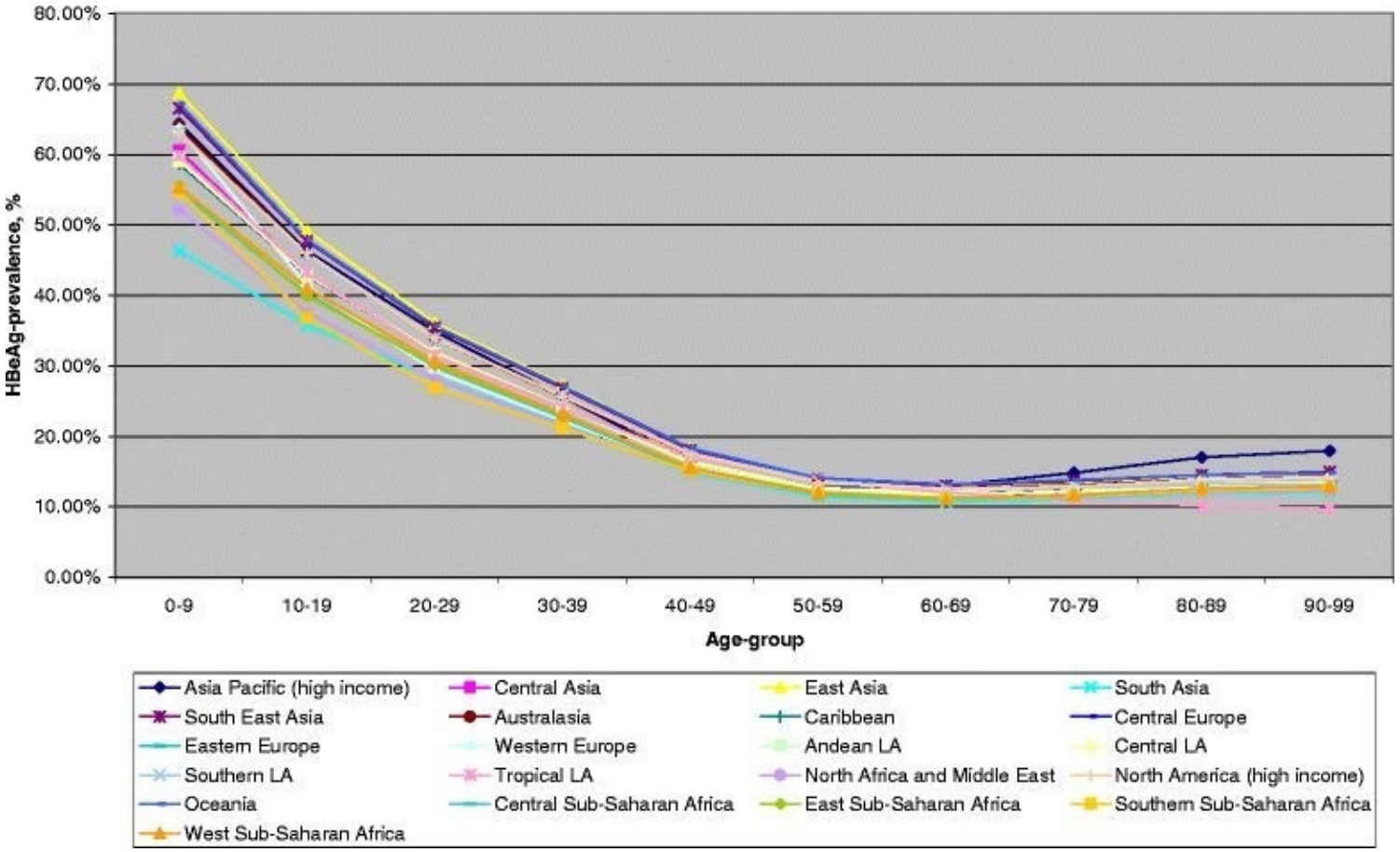
Duration of HBeAg Expression

- In south east Asia, the annual HBeAg seroconversion rate is 4%–5% in children older than 3 years, but only 2% in those younger than 3 years[1].

- In contrast, in Euro-Mediterranean and African countries, HBeAg seroconversion is more frequent, occurring at an annual rate of 14%–16%[2,3].

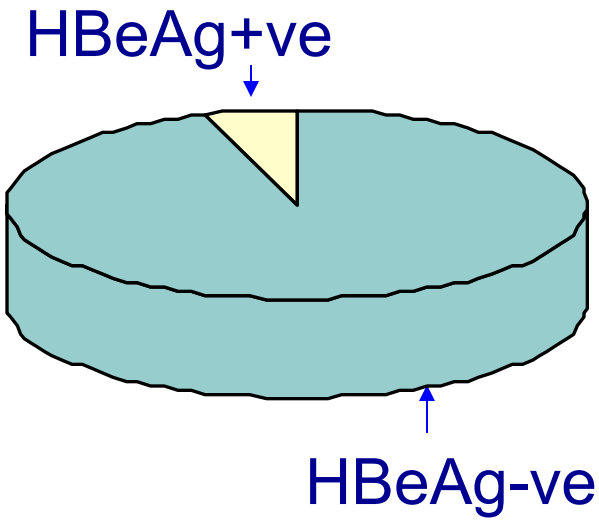
1. Chang et al Hepatology 1995; 22 1387–1392
2. Hadjiyannis et al Journal of Hepatology 2011; 55: 183–191.
3. Iorio et al Clinical Infectious Diseases 2007; 45: 943–949.

HBeAg Prevalence in HBsAg-positive Females: 2005

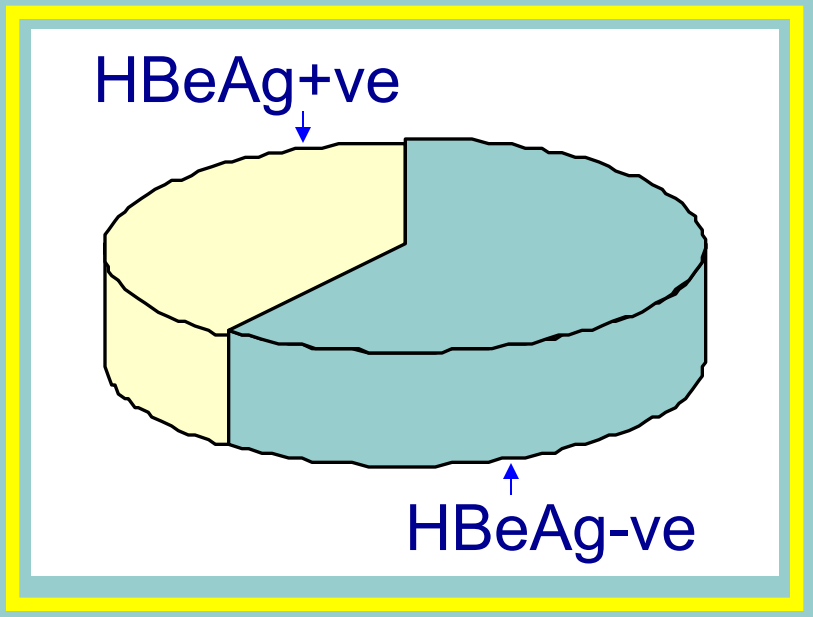


Ott et al BMC Infect Dis 2012; 12:131

Regional Differences in HBeAg-positivity



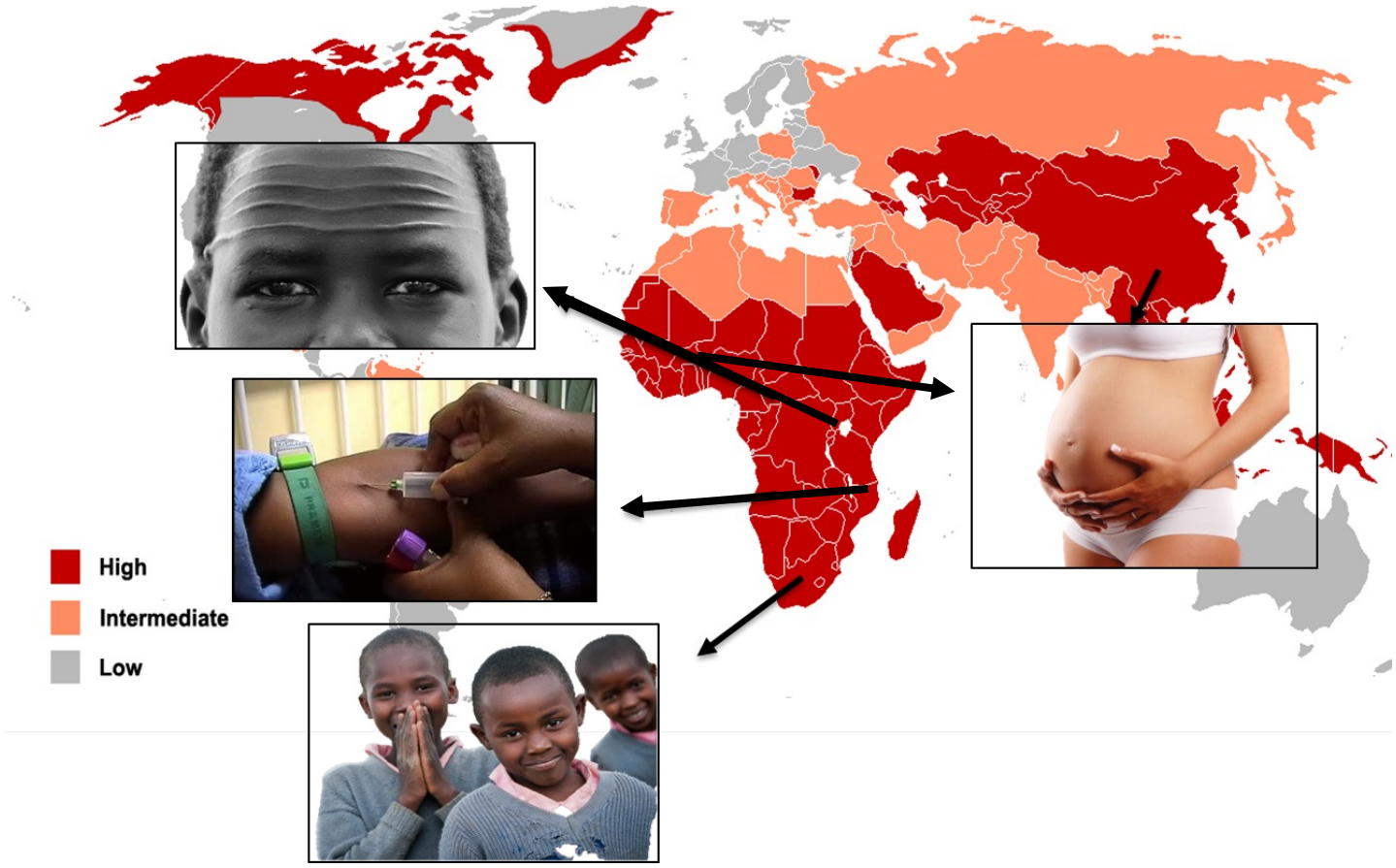
Sub-Saharan Africa



South East Asia

Botha et al, Lancet 1984; 1(8388):1210-1212

Effect of HBeAg expression on Mode of Transmission of HBV



Kramvis Rev Med Virol 2016; 26:285-303

Kramvis Frontiers in Microbiol 2018; ; 9:2521

HBeAg-positivity and Genetic Factors?

1987

Perinatal transmission of hepatitis B virus in high-incidence countries

Y. Ghendon

World Health Organization, Geneva, Switzerland

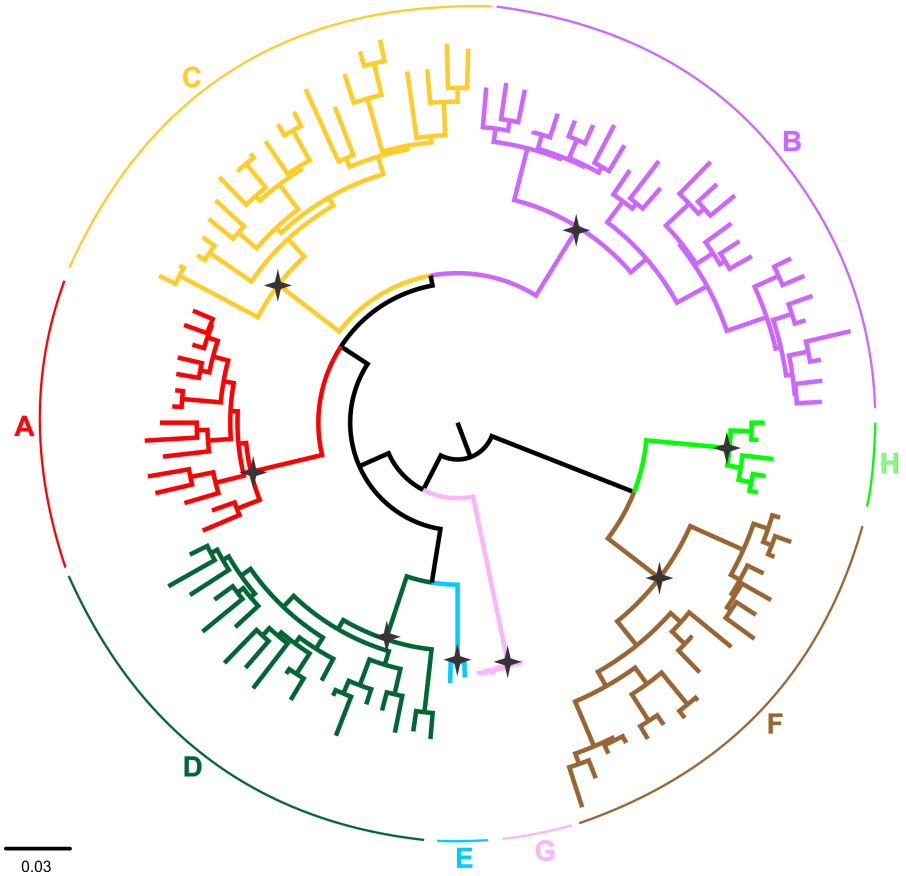
(Accepted 27 March 1987)

Genetic factors in perinatal transmission of HBV

The expression of HBeAg seems to be determined genetically: most Chinese carrier women but rather fewer African carrier women are HBeAg-positive and throughout children born to Chinese carrier mothers, 40–70% become carriers; to African mothers about 30%; to Asian mothers about 6–8% and to European mothers almost none (Derso et al., 1978; Stevens et al., 1975; Wong et al., 1980).

Ghendon, Y 1987; J Virol Methods 17: 69-79

Genotypes and Subgenotypes of HBV



- 9 Genotypes: A to I
  >7.5%
- > 35 subgenotypes
  ~4% to 8%

⇩

A–D, F, H, and I

Kramvis et al Vaccine 2005;23:2407-2421

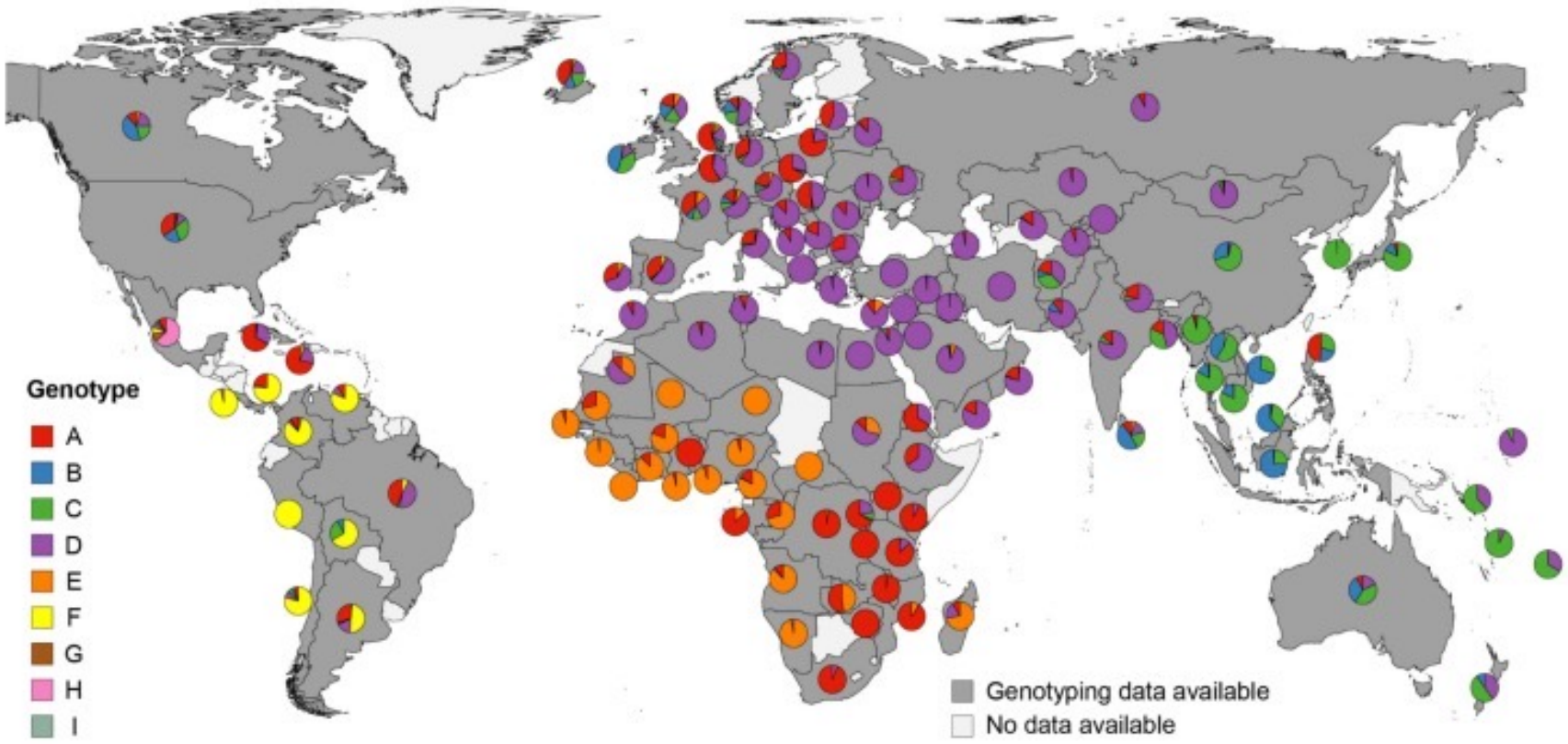
Kramvis Frontiers et al in Microbiology 2018; 9:2521

Velkov et al Genes 2018, 9, 495

Kramvis Intervirology. 2014;57:141-50

Kramvis Rev Med Virol 2016;26:285-303

Geographical Distribution of Genotypes

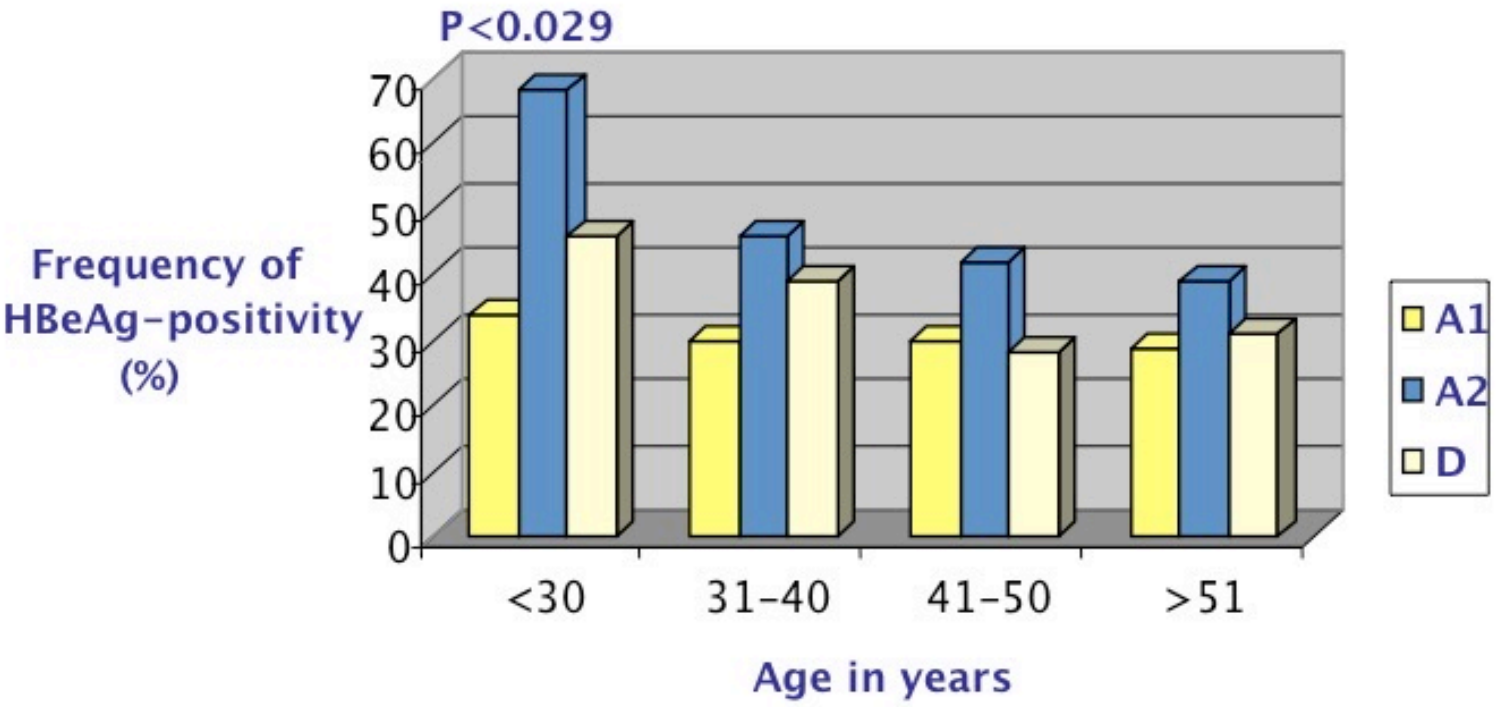


Velkov et al Genes 2018, 9, 495

Kramvis et al Vaccine 2005;23:2407-2421

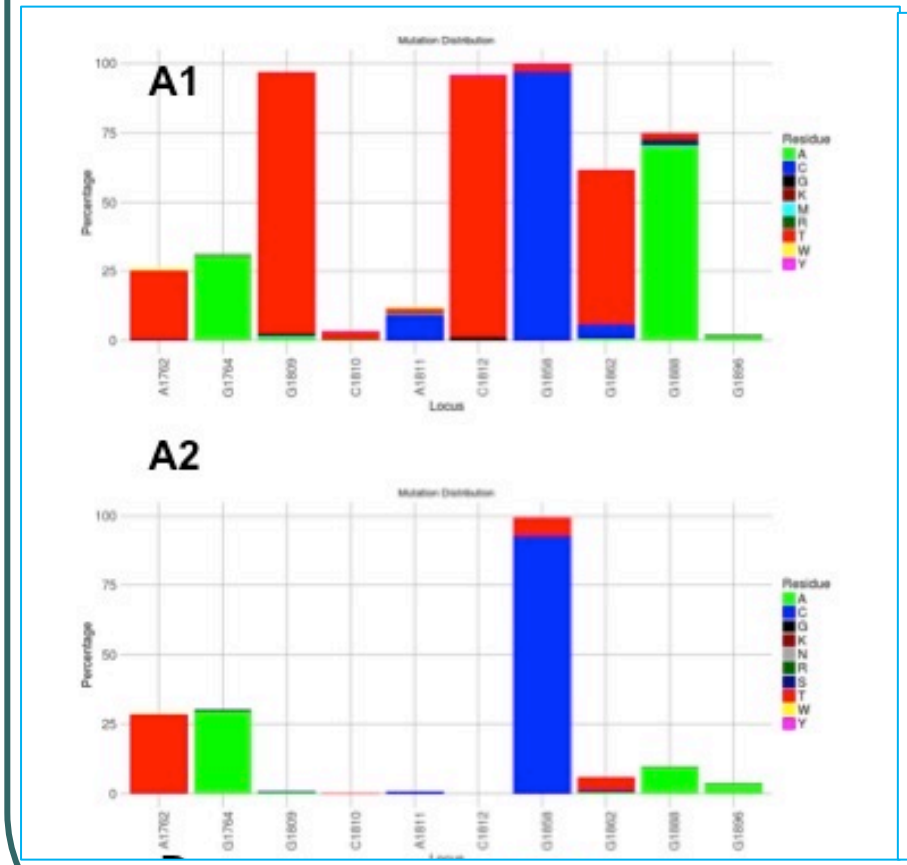
Kramvis Intervirology. 2014;57:141-50

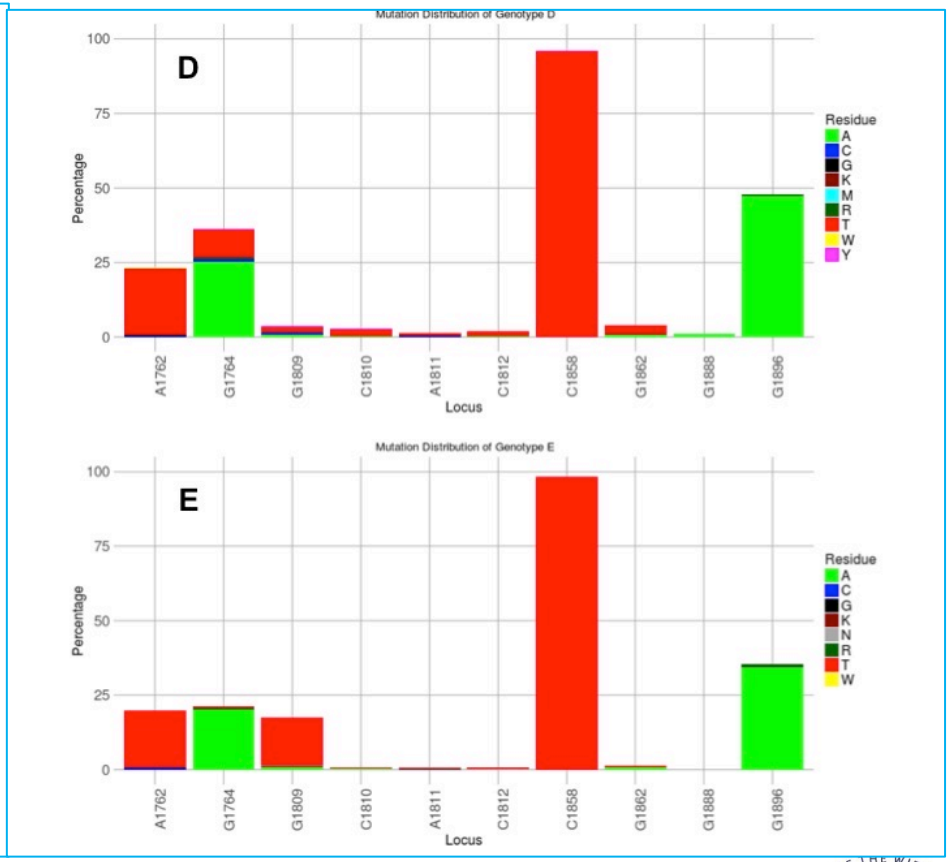
The Effect of Genotype/Subgenotype on HBeAg Expression



Tanaka et al Hepatology 2004; 40: 747-755

Basic Core Promoter/Precore Mutants

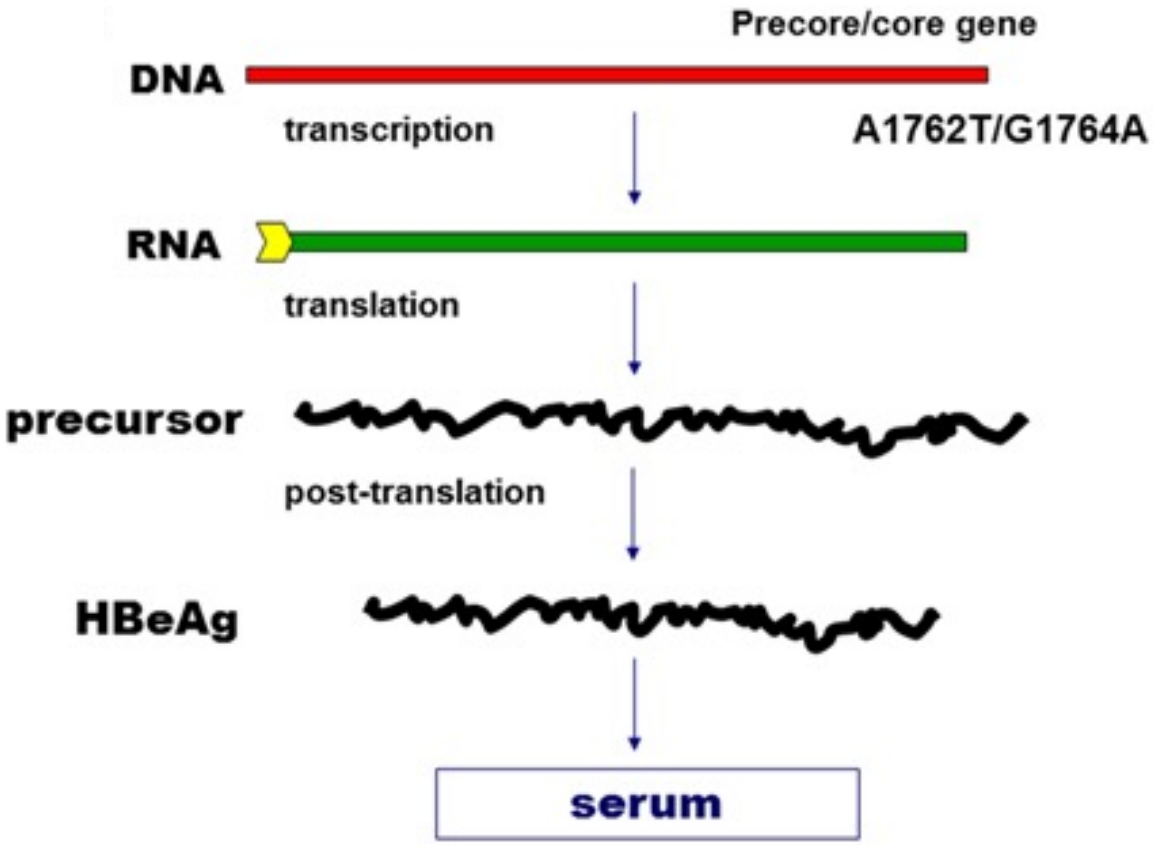




Mutation Reporter Tool: Bell & Kramvis Virol. J 2013; . 10:62. 10.1186/1743-422X-10-62

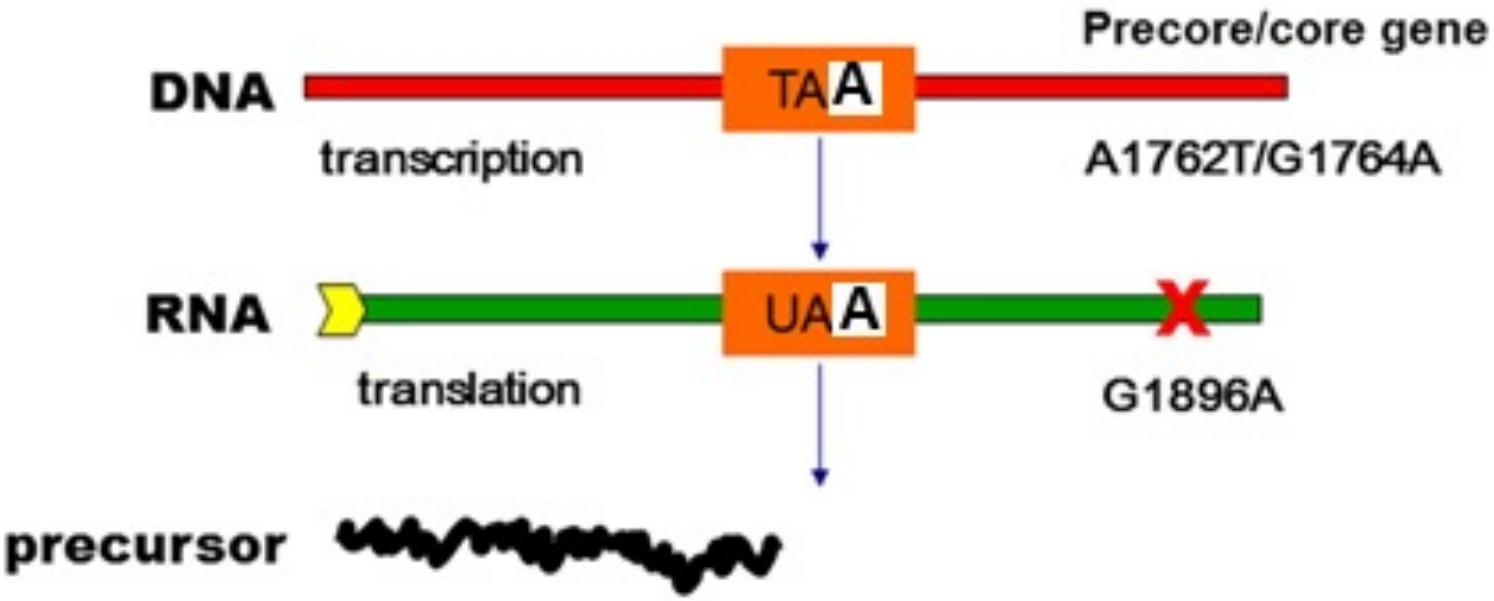
Kramvis J Med Virol 2008; 80: 27 -46
Kramvis Rev Med Virol 2016; 26:285-303
Kramvis Frontiers in Microbiol 2018; ; 9:2521

Subgenotype A2



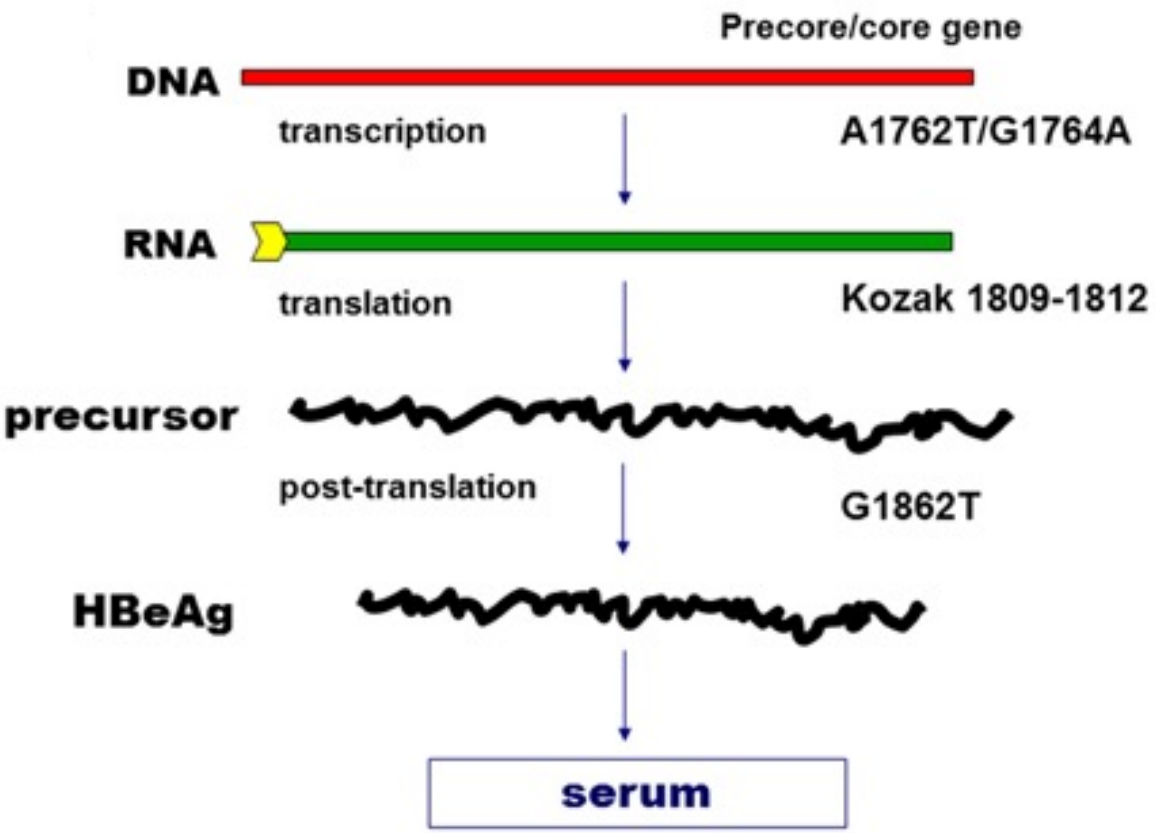
Kramvis 2016; Rev Med 2016 26(4):285-303

G1896A Mutation in Genotype D/E



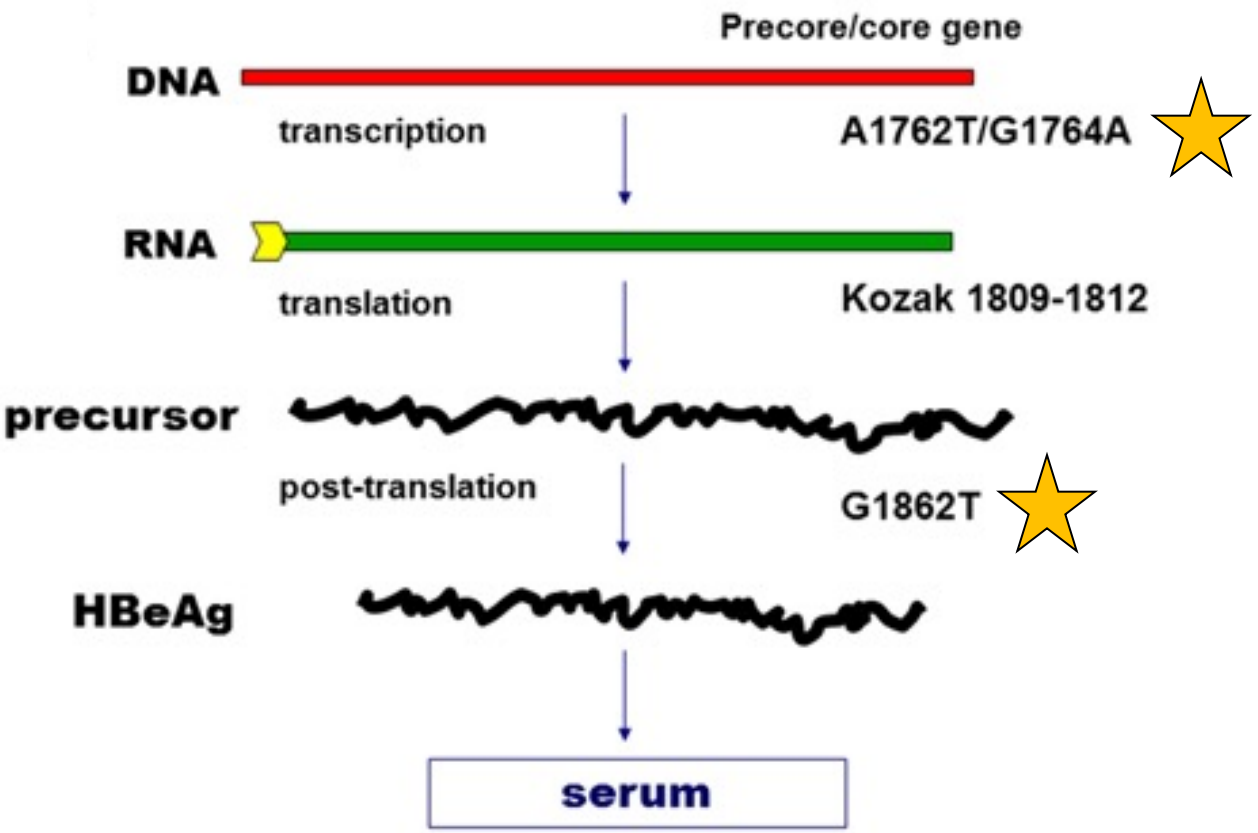
Carman et al Lancet 1989; **2**(8663): 588-591.

Subgenotype A1



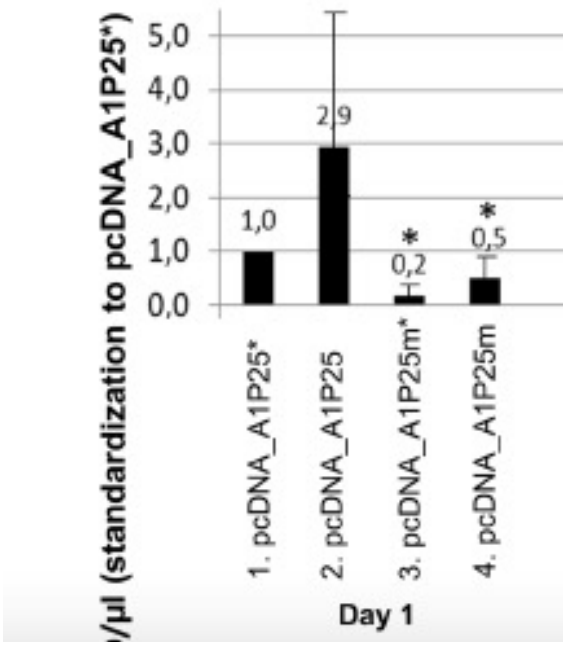
Kramvis 2016; Rev Med 2016 26(4):285-303

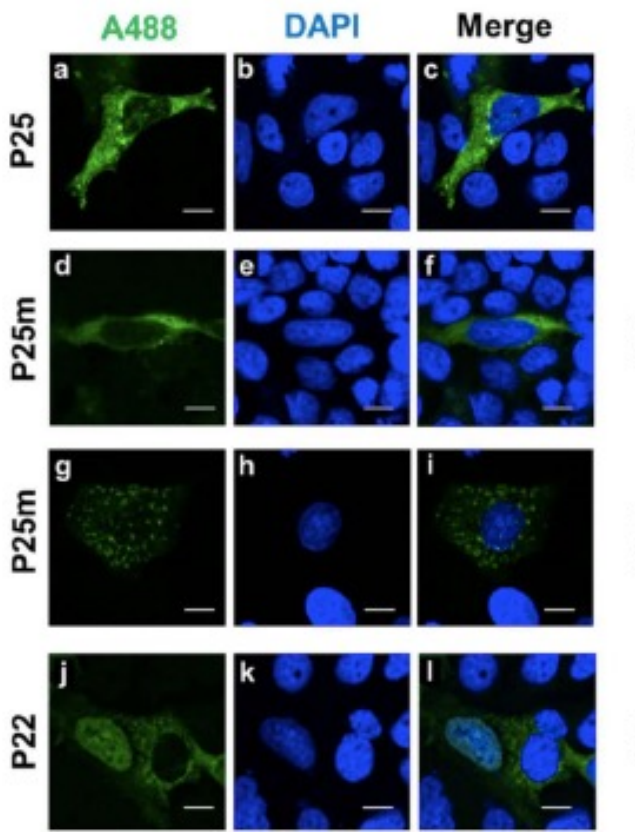
Subgenotype A1



Kramvis 2016; Rev Med 2016 26(4):285-303

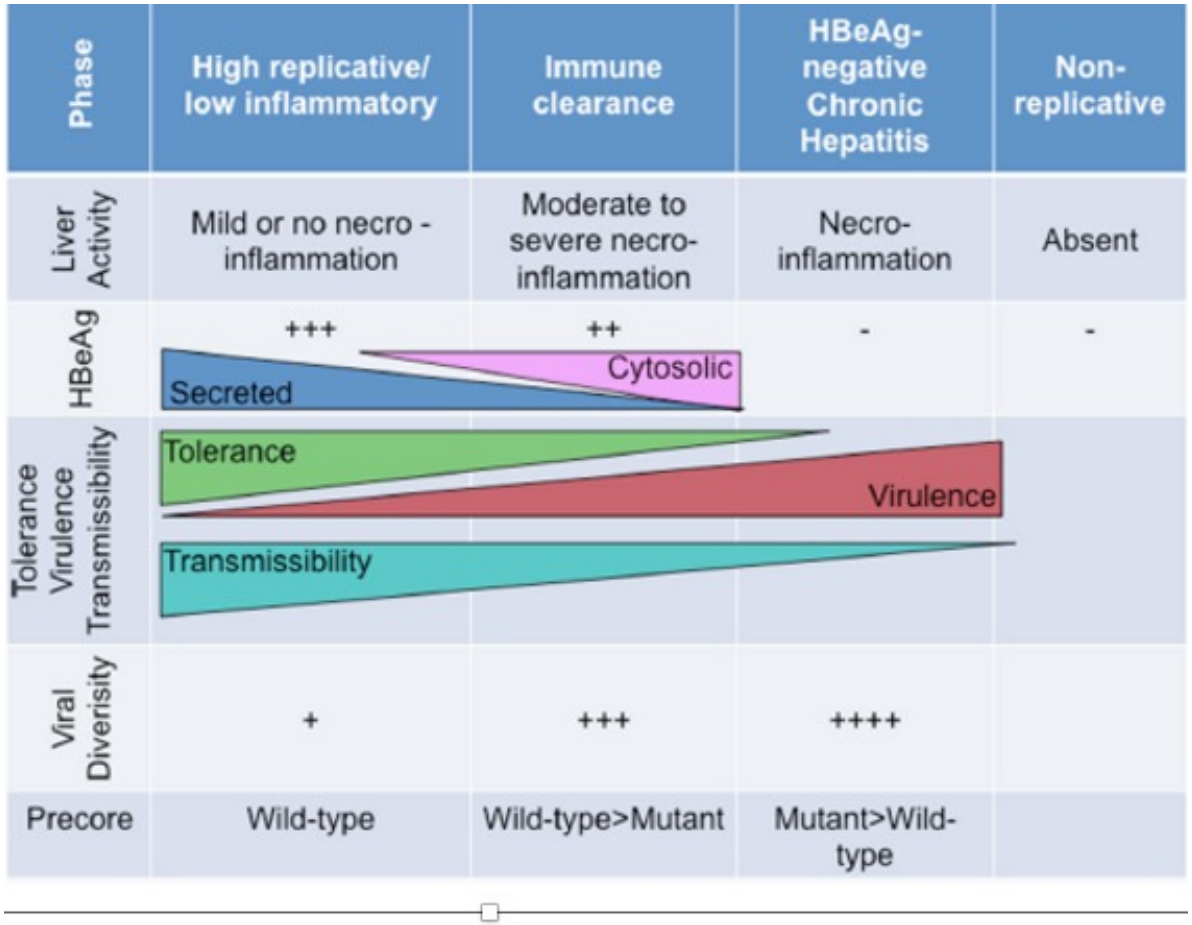
Expression of G1862T mutant versus wild-type





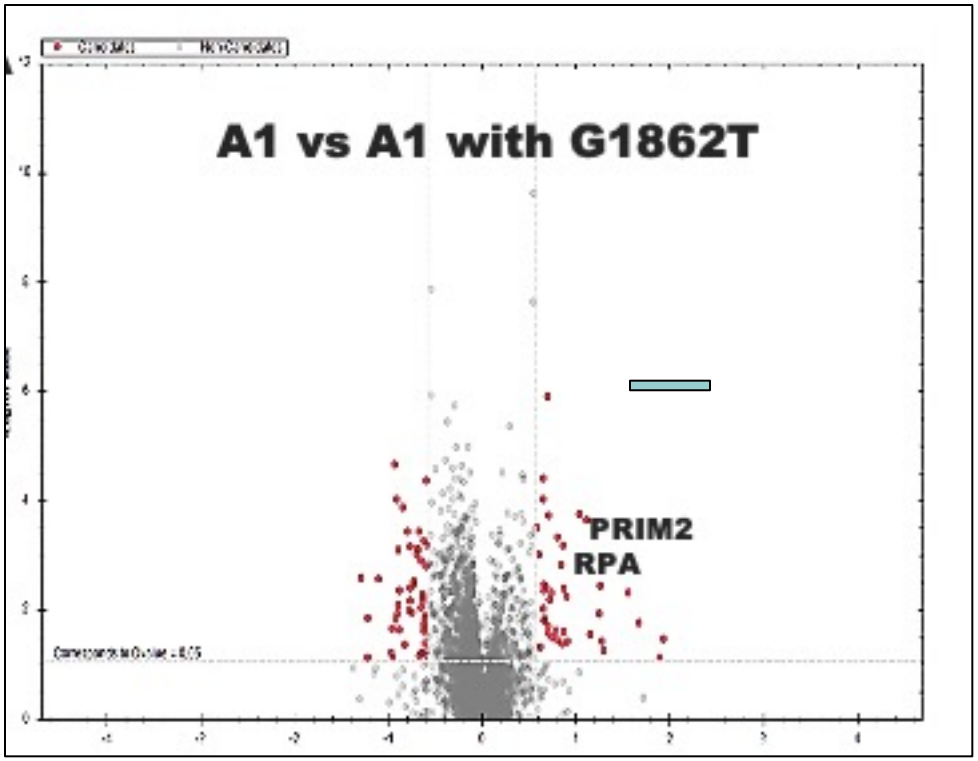
Deroubaix & Kramvis Scientific Reports 2021; 11:8167

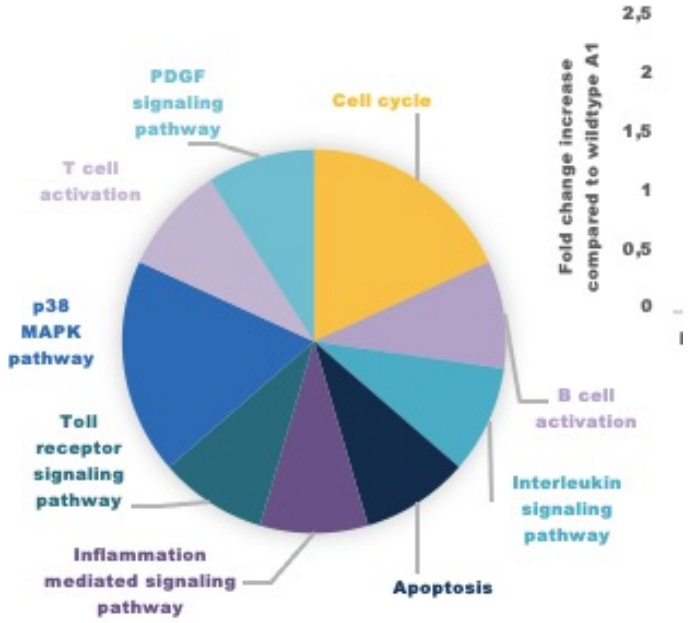
Short-sighted evolution of subgenotype A1



Kramvis Rev Med Virol 2016; 26:285-303
Kramvis Frontiers in Microbiol 2018; ; 9:2521

Mass Spectrometry & Proteomic Analysis





Padarath, PhD unpublished

Subgenotype A1 has high hepatocarcinogenic potential

Journal of Medical Virology 75:513–521 (2005)

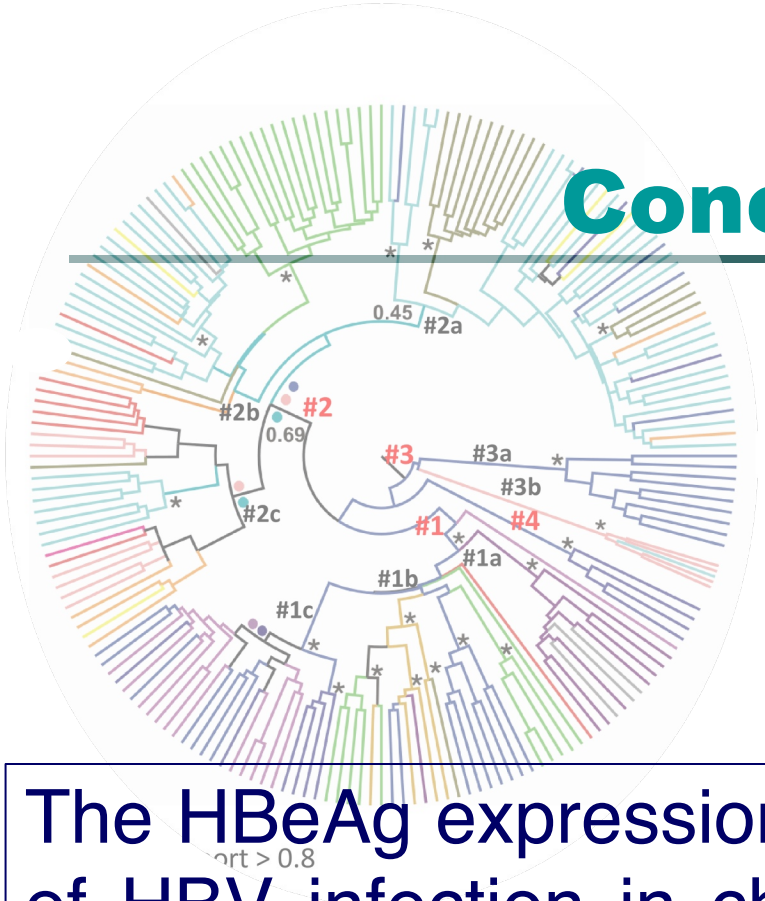
Increased Hepatocarcinogenic Potential of Hepatitis B Virus Genotype A in Bantu-Speaking Sub-Saharan Africans

Michael C. Kew,[1]* Anna Kramvis,[1] Mimi C. Yu,[2] Kazuka Arakawa,[2] and John Hodkinson[1]

Hepatitis B virus subgenotype A1 predominates in liver disease patients from Kerala, India

World J Gastroenterol 2013 December 28; 19(48): 9294-9306

Conclusion



The HBeAg expression and thus the natural history of HBV infection in children can be influenced by the genetic heterogeneity of the genotypes and/or subgenotypes, which develop different mutations.

Take Home Message

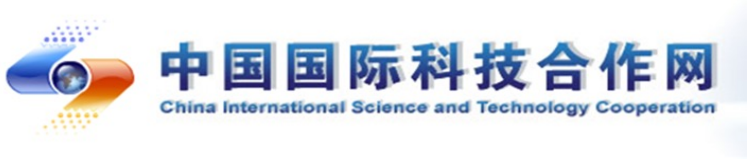
Subgenotype A1 circulating in sub-Saharan Africa has unique characteristics including

- Early HBeAg seroconversion
- Higher hepatocarcinogenic potential

therefore it is important that

birth dose vaccination is implemented strictly and widely, without further delays, to prevent the establishment of chronic hepatitis B in infants and therefore the development of HCC later in life.

BWTS Programme "Bilateral (International) scientific and technologica cooperation (BSTC)"



Effect of Changing HBV Genotype Distribution on Natural History

Journal of Medical Virology 89:639–646 (2017)

First Epidemiological and Phylogenetic Analysis of Hepatitis B Virus Infection in Migrants From Mali

J Gastroenterol
DOI 10.1007/s00535-017-1315-4

The Japanese Society of Gastroenterology

CrossMark

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Natural history of chronic hepatitis B virus infection in children in Japan: a comparison of mother-to-child transmission with horizontal transmission

American Journal of Epidemiology

DOI: 10.1093/aje/kwx064

Original Contribution

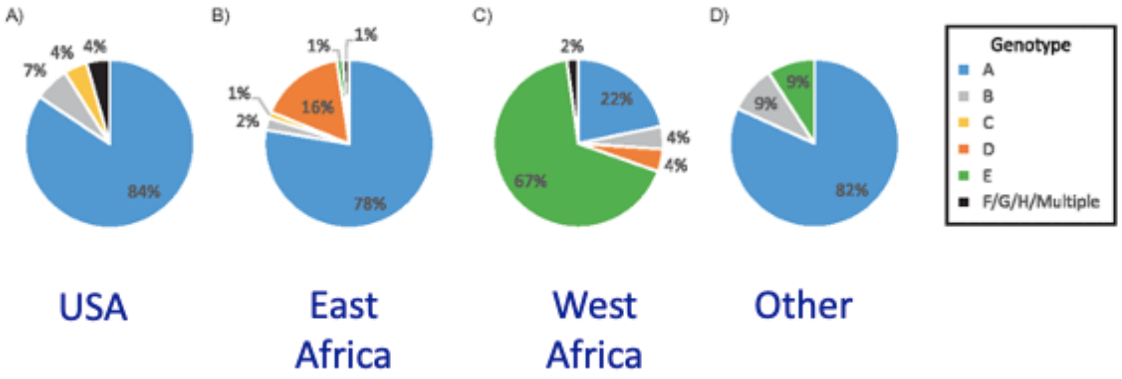
Characteristics of US-Born Versus Foreign-Born Americans of African Descent With Chronic Hepatitis B

Celia et al J Med Virol 2017' 89:639-646
Hassan et al Am J Epidemiol 2017; DOI:10.1093/aje/kwx064
Takano et al J Gastroenterol 2017; DOI:10.1007/s00535-017-1315-4

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

A Comparison of US Born *versus* Foreign Born Africans with CHB

	USAA	FBAA
Age*	47 years	40 years
Sexual transmission*	59%	3%
HBeAg-positivity*	19%	9%
Phase	CH	ASC
Genotype	A2	A1/E



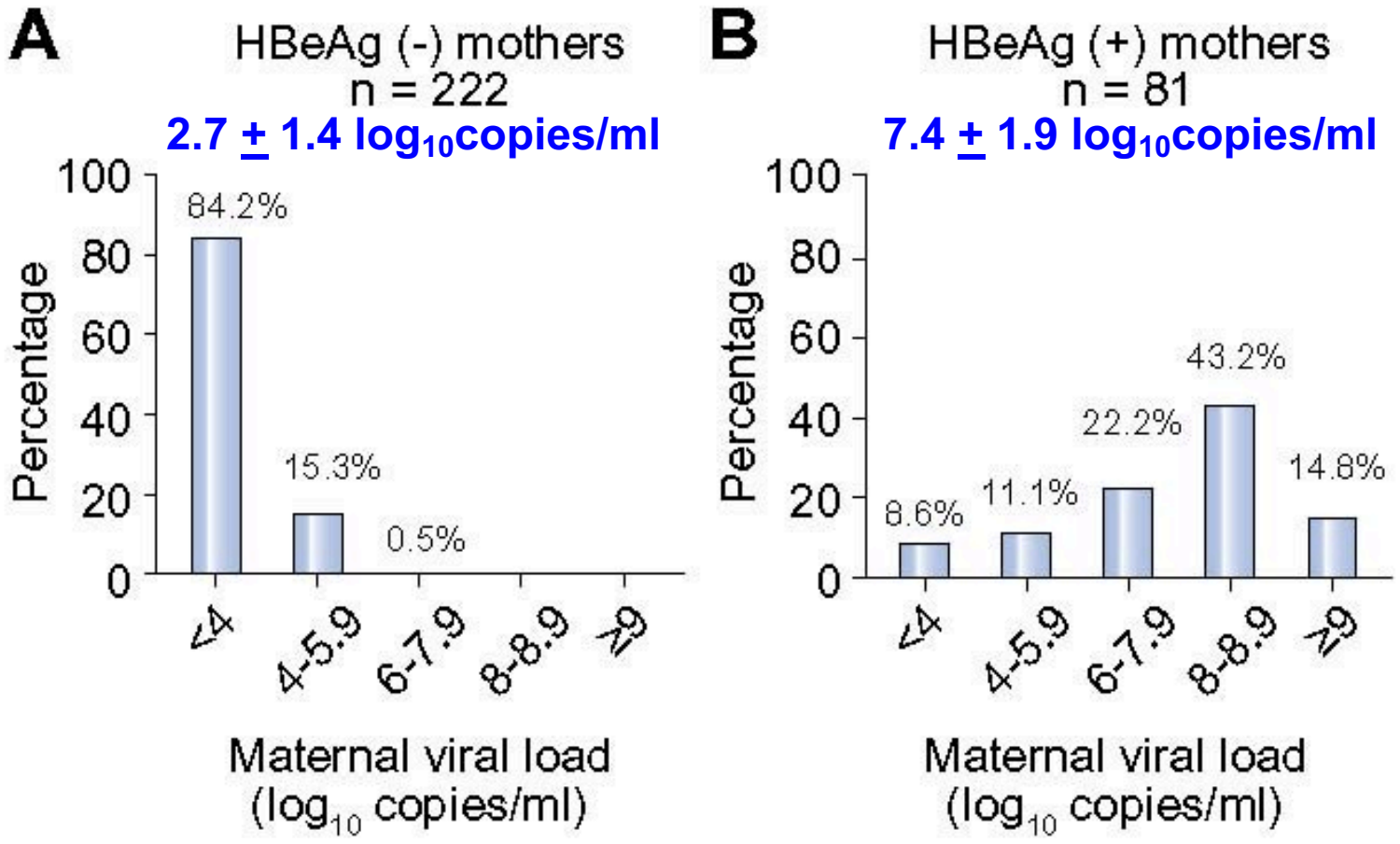
Hassan et al Am J Epidemiol 2017; DOI:10.1093/aje/kwx064

Genotype C versus Genotypes A/B in Japanese Children

Genotype	C	A or B
HBeAg-positivity at 15 years of age	67%	55%
Hepatitis <4 years	Lower	Higher
Transmission	PMCT	Horizontal
HCC at 30 years	6%	11%

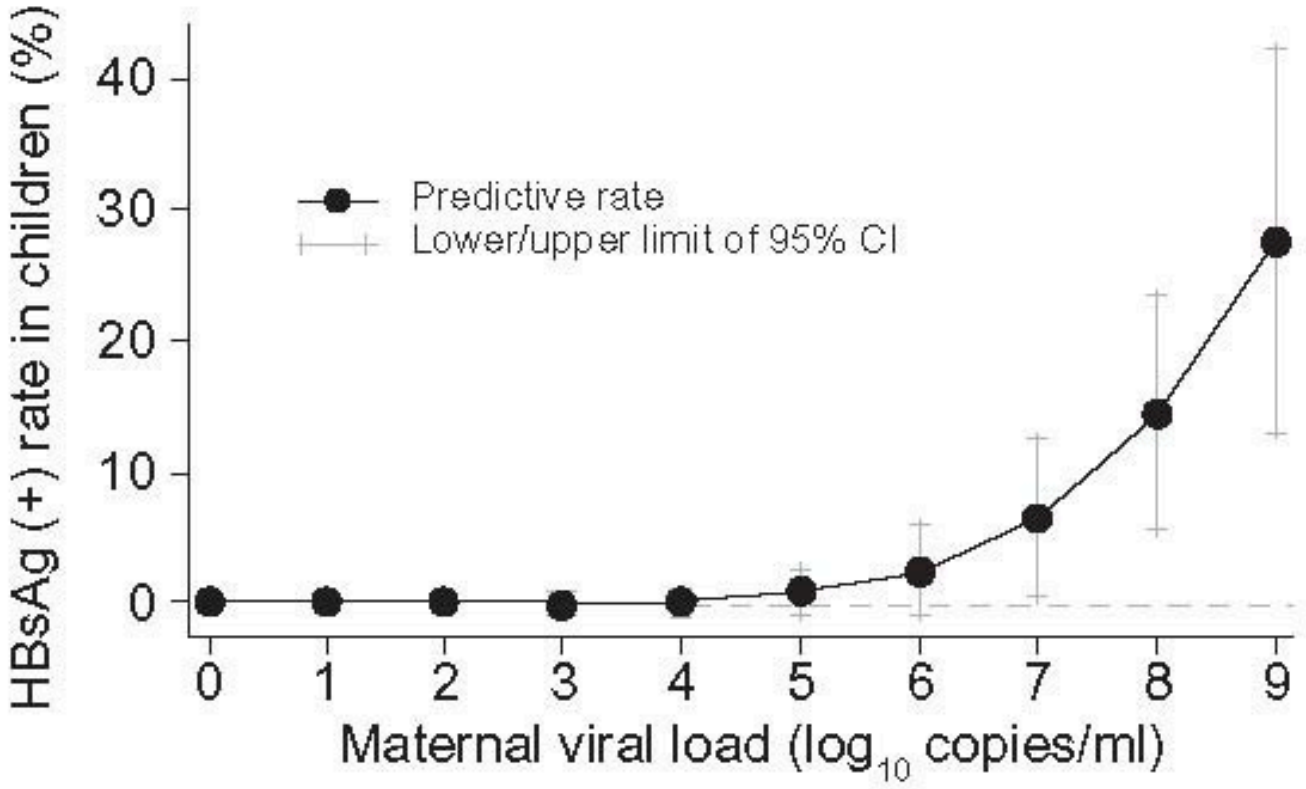
Takano et al Gastroenterol 2017; DOI:10.1007/s00535-017-1315-4

HBV Viral Load
HBeAg-ve versus HBeAg+ve



Wen et al, J Hepatol 2013; 59:24 -30

Predictive Rates of HBV Infection versus Maternal VL



Wen et al, J Hepatol 2013; 59:24 -30