

Hepatitis B Virus Genotypes and Subgenotypes Circulating in sub-Saharan Africa and Clinical Implications

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Disclosure

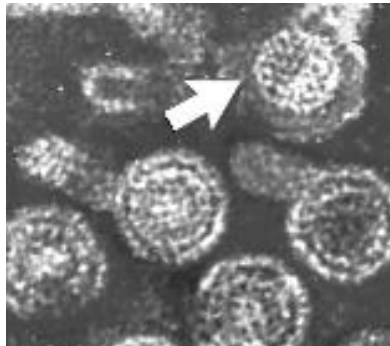
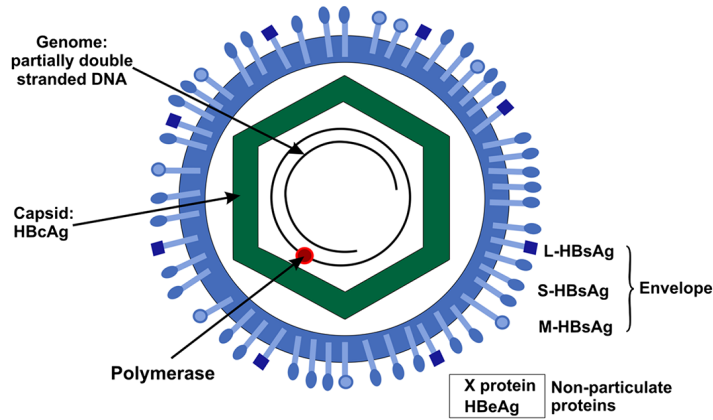
Relations that could be relevant for the meeting	Company names
Sponsorship or travel funds	<ul style="list-style-type: none">• Wits (non-profit)
Payment or other financial remuneration for consultancy (August 2022)	<ul style="list-style-type: none">• Roche
Shareholder rights	<ul style="list-style-type: none">• None
Other relations	<ul style="list-style-type: none">• None

Overview

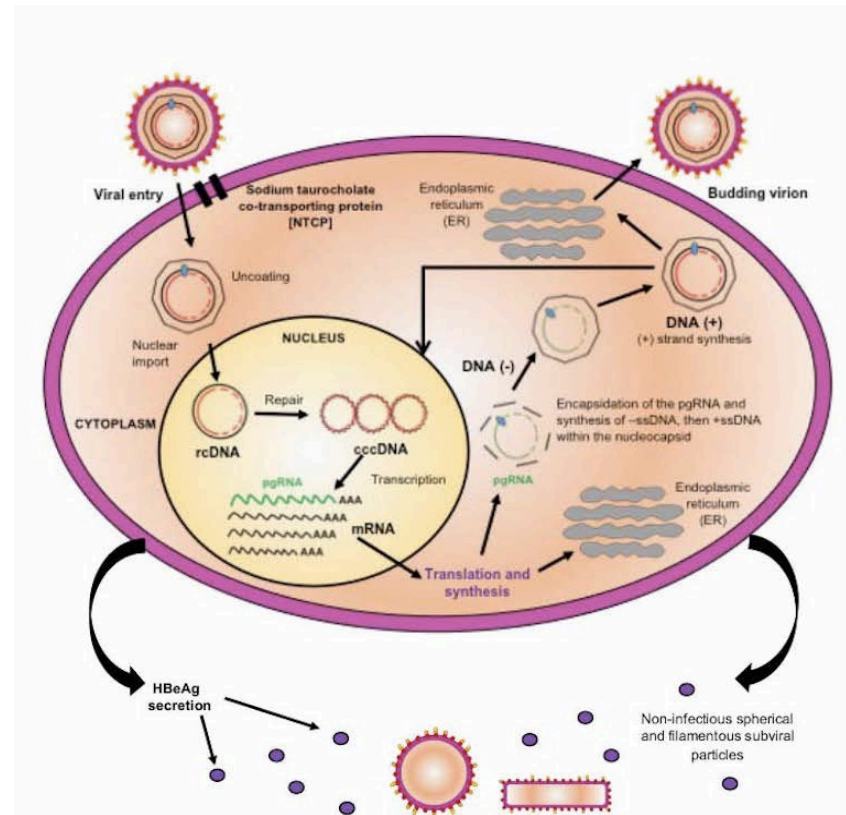


- Definitions: genotypes/subgenotypes
 - Geographical distribution
 - Genotype E and subgenotype A1 prevail in sSA
 - Effect of (sub)genotypes on:
 - Natural History
 - Transmission
 - Prevention
 - Diagnosis
 - Treatment
 - *In vitro* systems for studying (sub)genotypes
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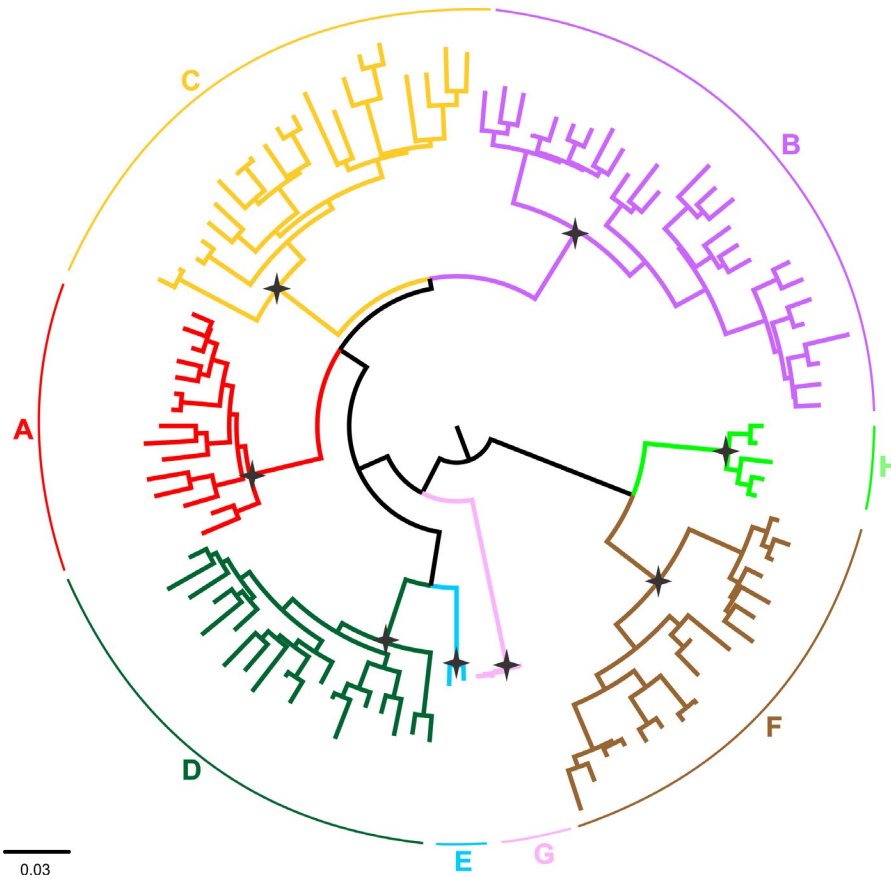
Molecular Biology of HBV



- **Family:** *Hepadnaviridae*
- **Genus:** *Orthohepadnavirus*



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



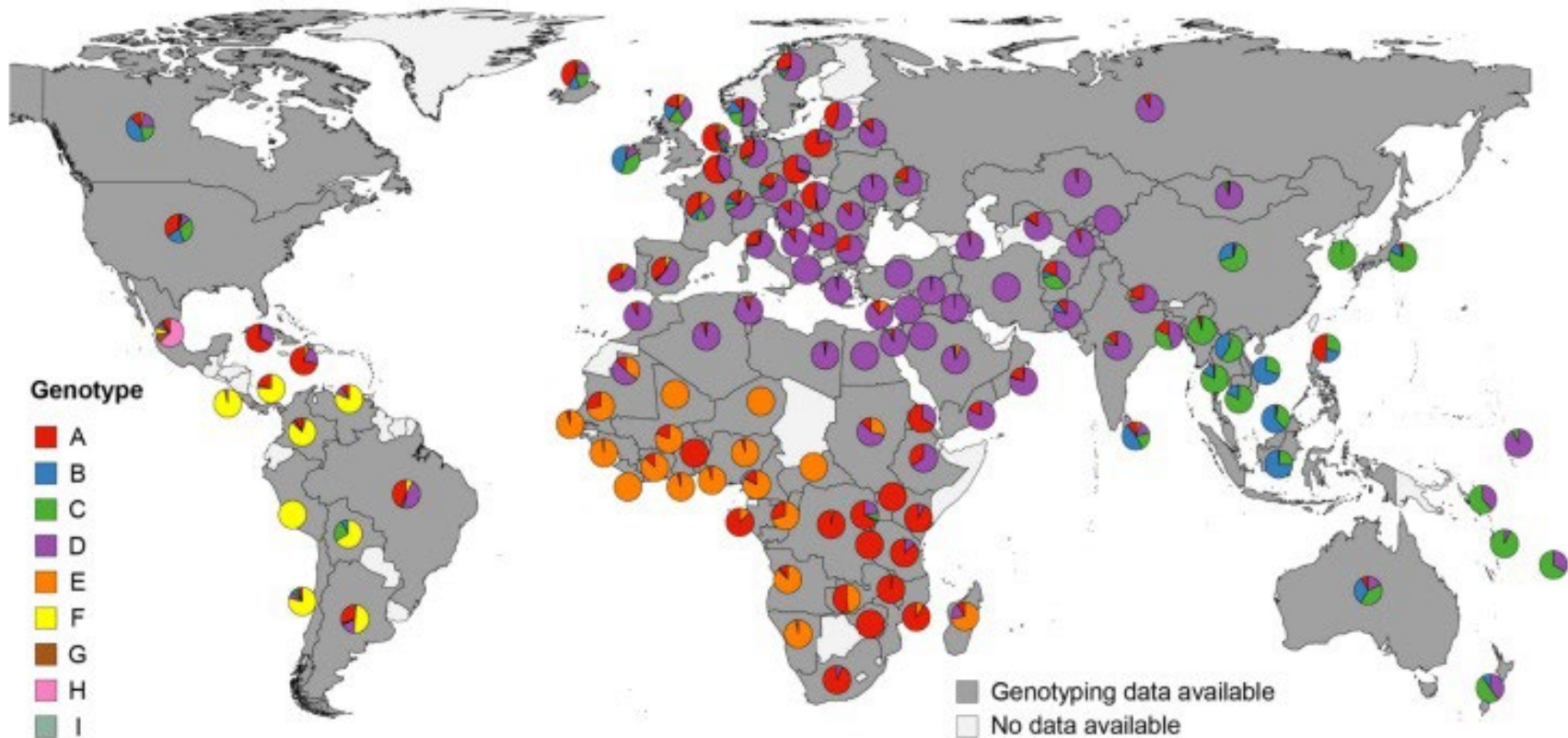
Kramvis Intervirology. 2014;57:141-50

Kramvis Rev Med Virol 2016;26:285-303

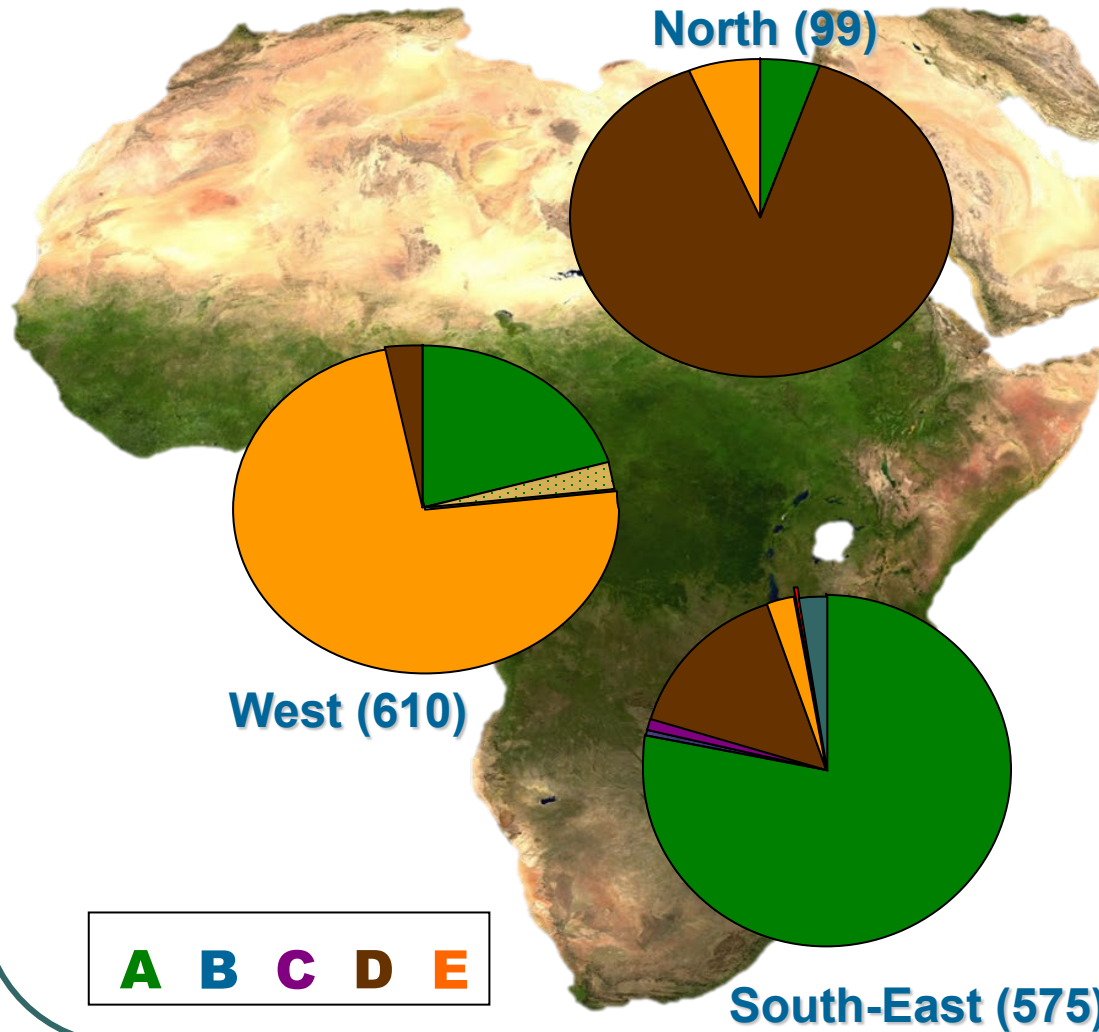
Kramvis Frontiers et al in Microbiology 2018; 9:2521

Velkov et al Genes 2018, 9, 495

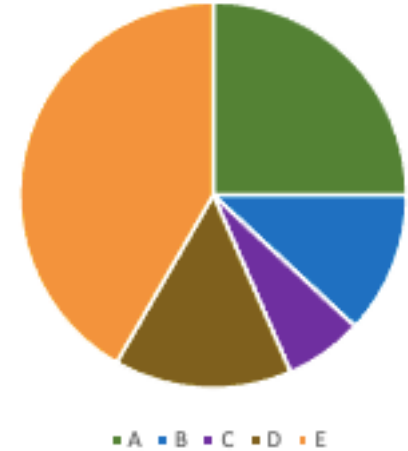
Geographical Distribution of Genotypes



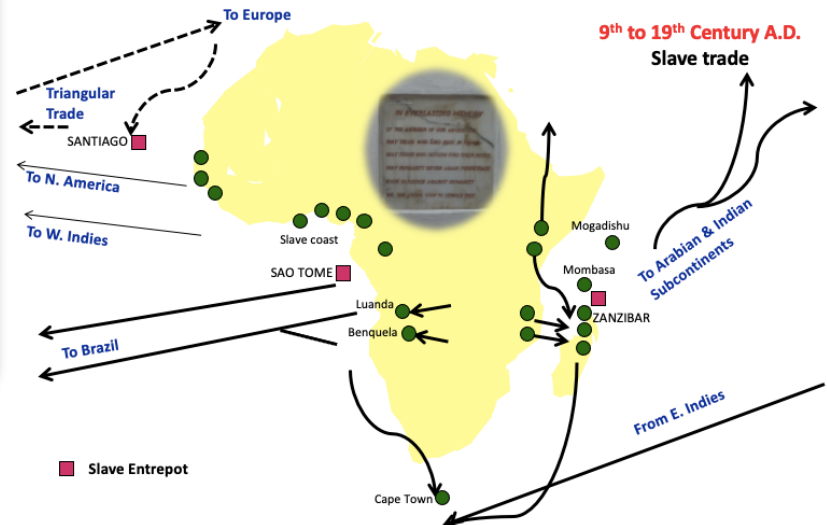
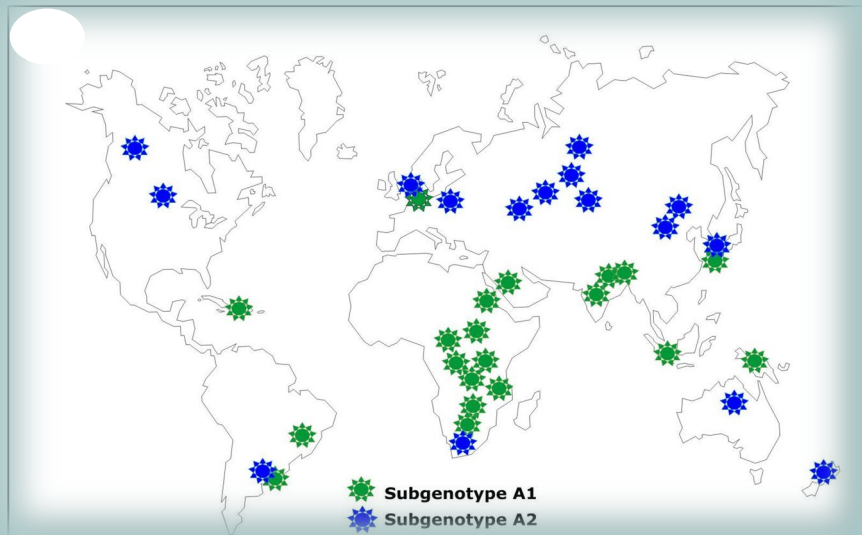
Genotype Distribution of HBV in Africa



Percentage of Genotypes in Africa



Phylogeography of the subgenotypes A1 and A2



Kramvis Antiviral Ther 2013; 18:513

Kostaki eLife 2018; 7: e36709

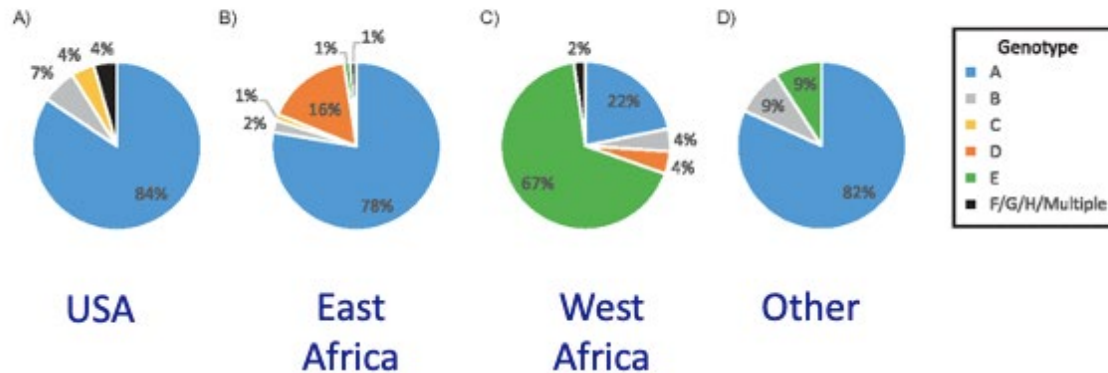
Bowyer et al J Gen Virol 1997; 78:1719-1729

Kimbi, Kramvis et al J Gen Virol 85:1211-1220



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



Relative clinical characteristics of subgenotype A1

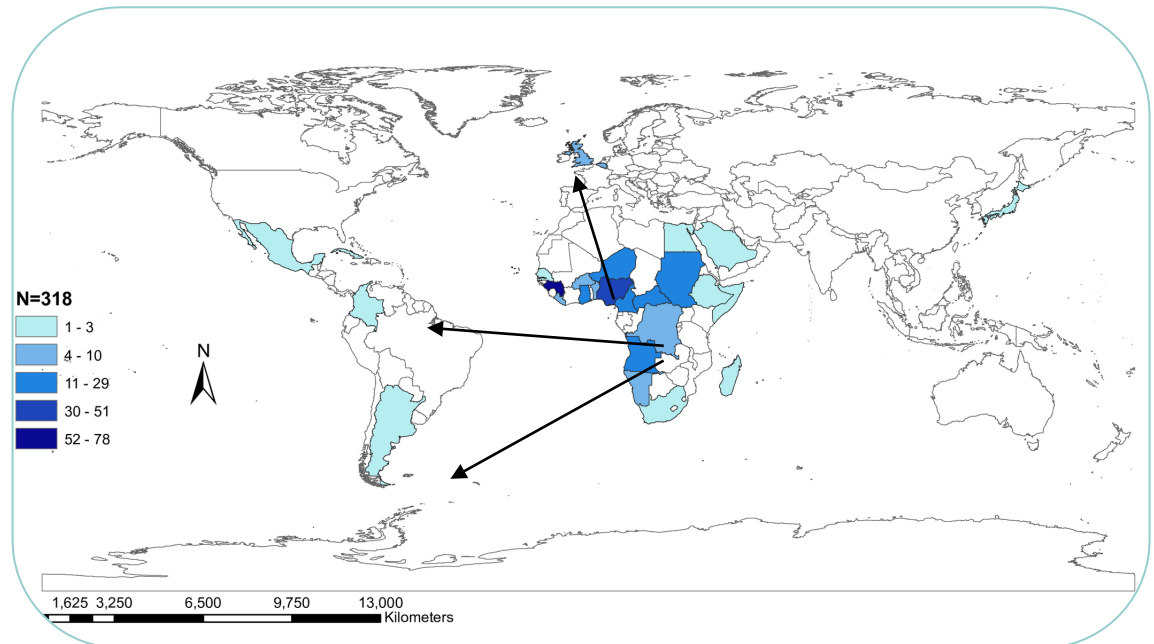
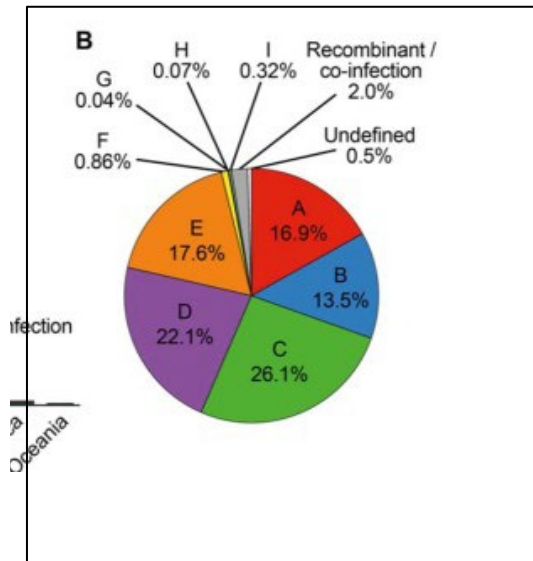
Subgenotype A1 has molecular characteristics that can account for the different clinical features

Compared to patients infected with subgenotype A2 or genotype D, patients infected with subgenotype A1 have:

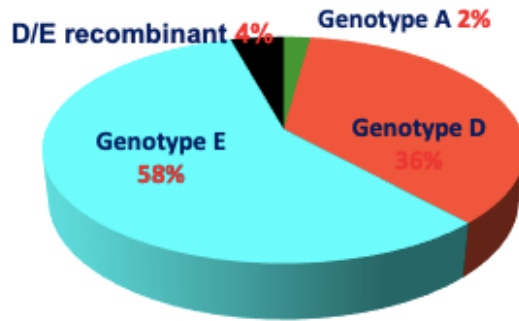
- Lower HBV DNA levels
- Lose HBeAg in the serum much sooner
- Higher levels of liver damage
- Higher and earlier risk of HCC development

Genotype E: The neglected genotype of hepatitis B virus

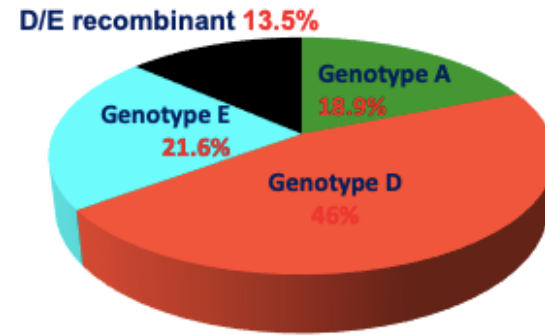
Luicer Anne Olubayo Ingasia, Constance Wose Kinge, Anna Kramvis



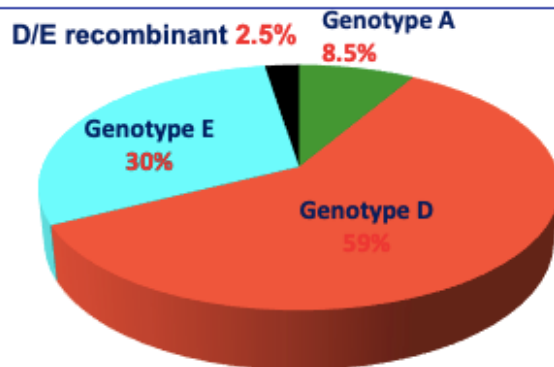
Molecular Characterization of HBV in Sudan



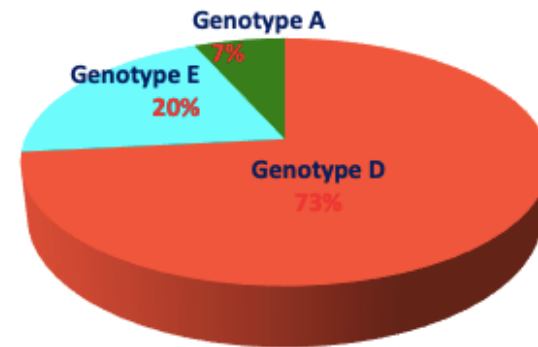
47 HBsAg+ve Blood Donors¹



37 HBV/HIV co-infected Patients³



81 HBsAg+ve Liver Disease Patients²



15 ESRD Patients on haemodialysis

¹Maghoub et al J Clin Microbiol 2011;49:298-306

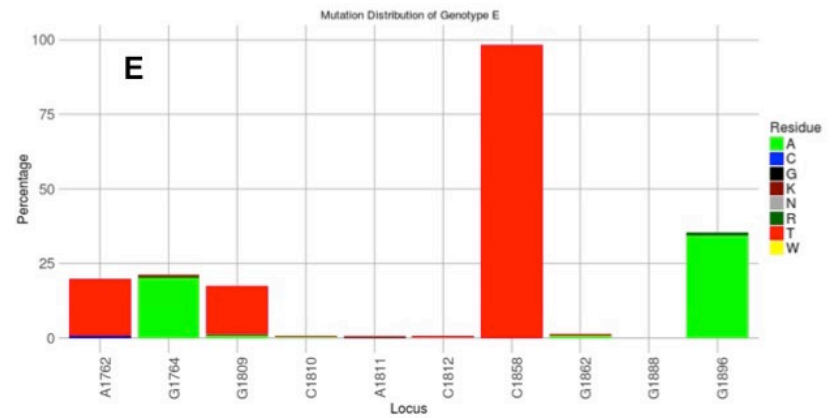
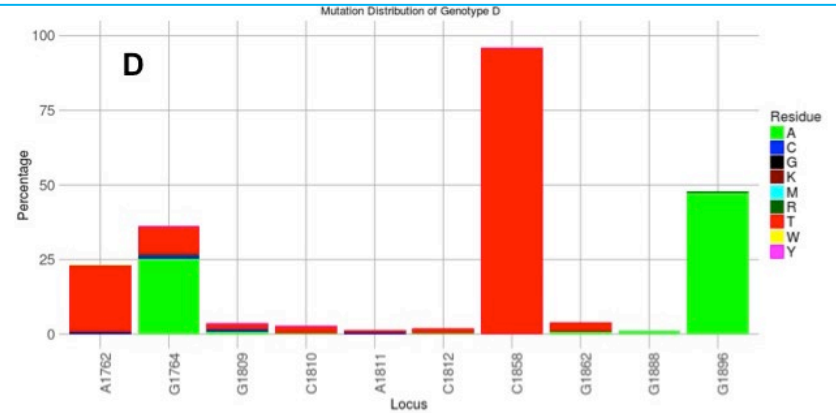
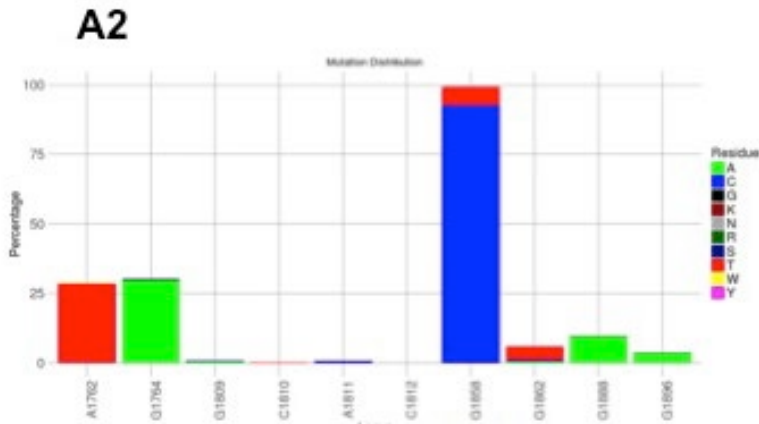
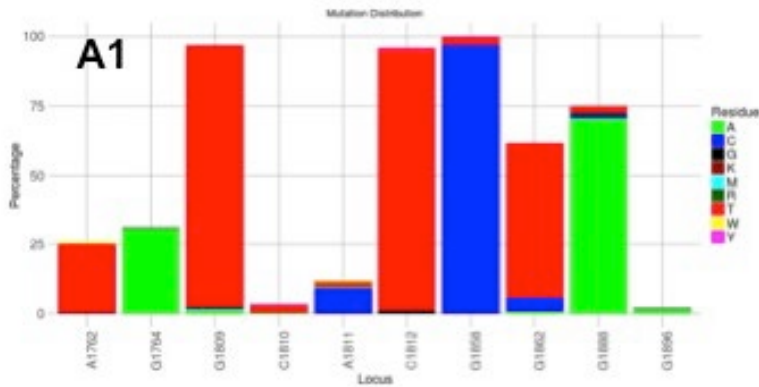
²Yousif et al. BMC Infectious Diseases 2013, 13:328

³Yousif....Kramvis Int J Infect Dis 29 (2014): 125-32

Subgenotype E *versus* D

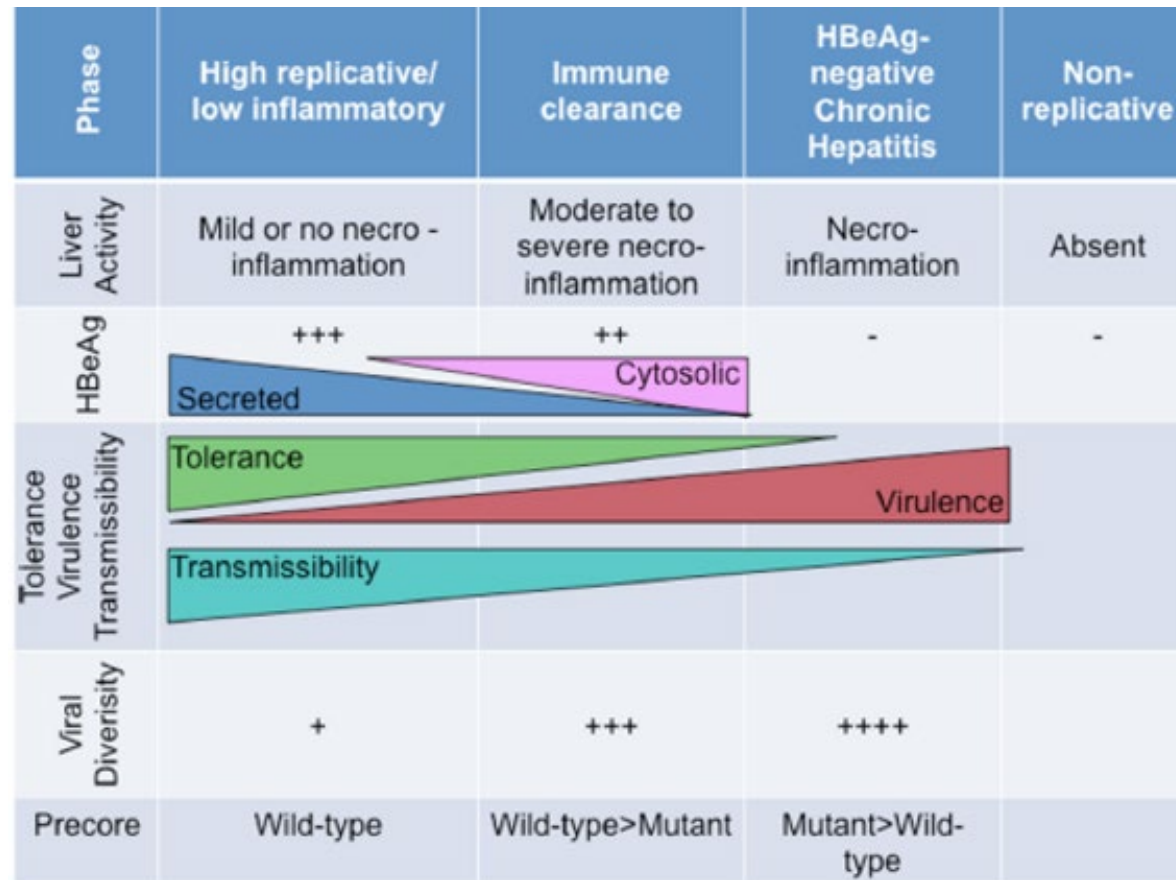
	Genotype E	Genotype D
Clinical group	Asymptomatic/ blood donors	Liver disease patients
Viral loads	↑	↓
<u>HBeAg-positivity</u>	↑	↓

Basic Core Promoter/Precore Mutants



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

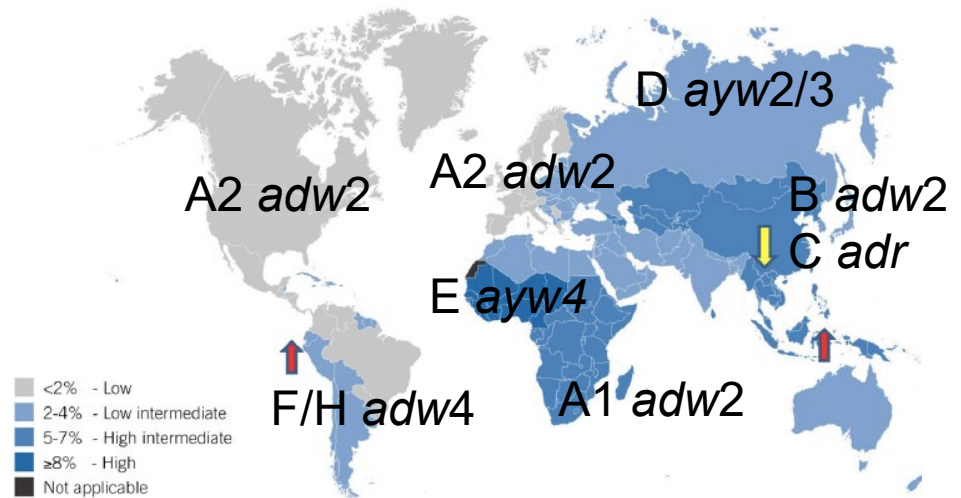
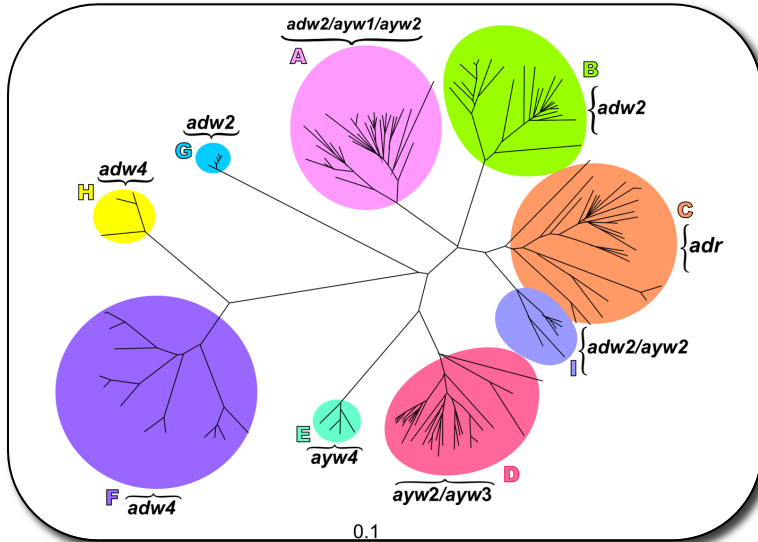
Relationship of HBeAg Expression on the Natural History of HBV Infection



Transmission of HBV



Vaccination



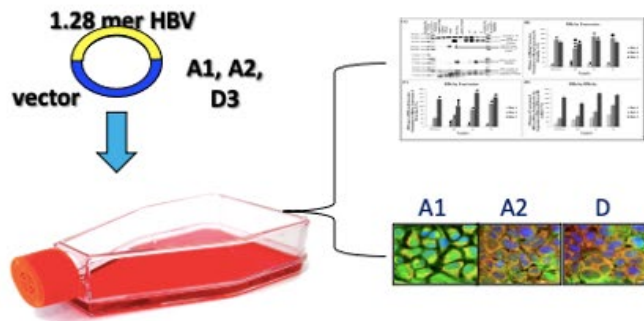
- Although the consensus is that there is a high-degree of vaccine cross-protection between HBsAg serological subtypes, there are studies, which have shown better protection against homologous HBV strains, compared to heterologous ones



Treatment

- Patients infected with genotype A respond better to interferon-based therapy compared to patients infected with genotype D
- Although overall no significant difference in response of the different genotypes/subgenotypes to nucleos(t)ide analogue therapy has been found, response to adefovir may be lower in patients infected with subgenotype A2 because of the presence of L217R polymorphism in the S region

In vitro systems for studying subgenotypes



	Genotype E	Subgenotype A1
Extracellular HBsAg	↑↑↑	↓
Intracellular HBeAg	↓	=
Extracellular HBeAg	↑↑	↑

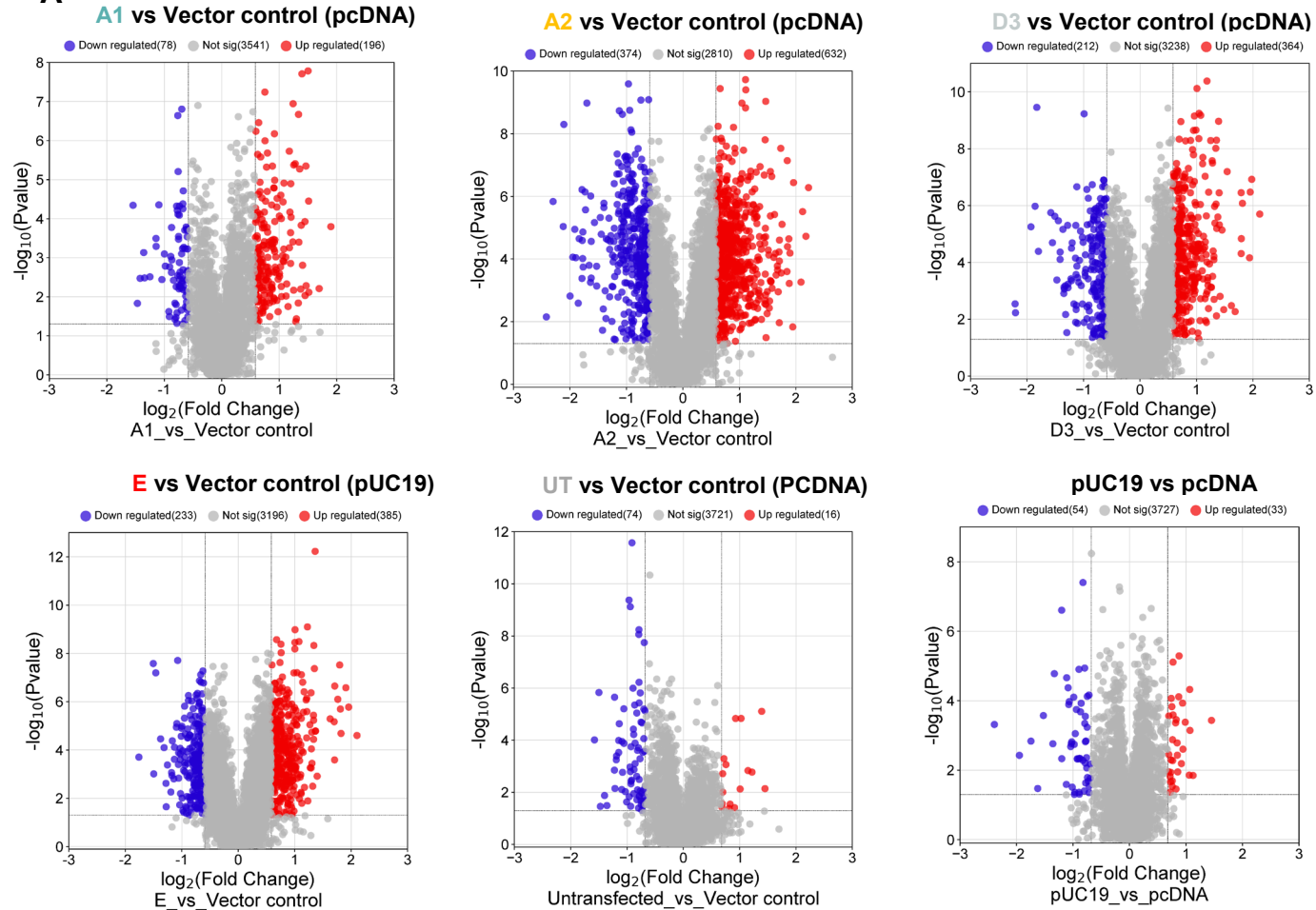
The arrows show either increase (↑) or decrease (↓) in the expression or similar (=) levels relative to A2

In Vitro Model Systems Based on:

- Hepatoma Cells (HepG2, Huh7, HepG2.2.15, and HepAD38)
- Primary Human Hepatocytes (PHH)
- Differentiated Hepatoma Cell Lines (HepaRG)
- NTCP Expressing Cell Lines
- Inducible Pluripotent Stem Cell (iPSCs)
- Micropatterned Co-Cultured Cells (MPPCs)
- Liver Organoids

Protein Expression of (Sub)genotypes *in vitro*

A



B

WHF ~Lisbon- 12 April 2024

Kiyasha Padarath PhD





Subgenotype A1 and genotype E circulating in Africa, differ molecularly and functionally from (sub)genotypes prevailing out of Africa and from each other!!!

Take Home Message



The natural history of HBV infection can be influenced by the genetic heterogeneity of the (sub)genotypes and therefore this should be taken into account when designing and testing various preventative, diagnostic and antiviral modalities.

There are more questions than answers

- Comparison of natural history of infection in individuals infected with genotype E and subgenotype A1
- Host factors that predispose individuals to infection with the different (sub)genotypes
- Hepatocarcinogenic potential of genotype E
- Does genotype E have different mechanisms of hepatocarcinogenesis to subgenotype A1?
- Why does genotype D develop the G1896A mutations at higher frequency than genotype E, even though the precore of the 2 genotypes is identical?
- Patterns of integration of the two African strains of HBV

~ A compassionate team, creating knowledge, developing capacity ~



Back row: Khudani Nhekwevha (MSc), Trodia Zitha (MSc), Luicer Olubayo (PhD), Mukhlid Yousif (former Post-doc), Daniel Mak PhD), Suzanne Wohuter (MSc-graduated), Daniel Simelane (MSc)

Front row: Micah Oyaro (Intern from Kenya), Chien Yu Chen (Researcher), Nimisha Bhoola (Post-doc), Anna Kramvis (Director), Constance Wose-Kinge (Post-doc), Aurelie Deroubaix (Research associate), Trevor Bell (Post-doc)

Absent: Boiphelo Kgosinkwe (Financial Officer), Hillary Vos (MSc), Thanusha Pillay (MSc), Lanish Singh (MSc)

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Miyakawa
Connolly
Dickens
Yousif
Mudawi
Bukofzer
Kew
Adhikari
Orito
Acharya
Chen
Mizokami
Bhimma
Bell
Kato
Koutsaftiki
Skelton
Paterson
Makondo
Kimbi
Kurbanov
Coovadia
Glebe
Nemeri
Kato
Greenough
Khan
Mammas
Sugauchi
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Gopalakrishnan

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