Can the current Hepatitis B vaccine mark the end of the Australia antigen in the Northern Territory or is the Territory just different?

Davies J, Littlejohn M, Yuen L, Edwards R, Sozzi T, Jackson K, Cowie B, Locarnini S, Tong S, Davis J

discovery for a healthy tomorrow

Conflicts of Interest

- I have received an unrestricted educational grant from Gilead Sciences which funded a separate qualitative Hepatitis B project.

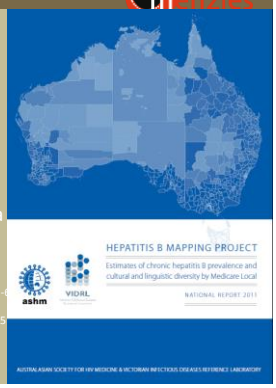
discovery for a healthy tomorrow

Overview

- What we know already about Hepatitis B in the NT
- What the CHARM study has added so far
  - **C**haracterising **H**epatitis B in northern **A**ustralia th**R**ough **M**olecular epidemiology
- Potential implications
- Future direction

Hepatitis B in the NT

- Prevalence estimates 1-15%[1-7]
- ASHM mapping study
  - NT Medicare local has highest Hepatitis B sero prevalence in Australia
- Liu et al
  - Antenatal women
  - Pre and post vaccination era
  - 3.5% versus 0.8%



1. Barrett. *Aust NZ J Public Health*. 1976; 6(2): 106-11
2. Schultz R et al. *Aust NZ J Public Health*. 2008; **32**(6): 575-
3. Gardner ID et al. *Med J Aust*. 1992; **156**(9): 638-41
4. Wood N et al. *Aust NZ J Public Health*. 2008; **32**(3): 272-5
5. Carroll et al. Internal medicine Journal. 2010; **40**:784-7
6. Aratchige PE et al. NT Dis Cont Bull. 2012; 19(2):1-12
7. Liu B et al Vaccine. 2012; 30(50):7309-14

Vaccine concerns

- Griffiths et al 2014 – Kimberley region
  - 17 cases, 10 chronic infection
- Hanna et al – north Queensland
  - 239 fully vaccinated 16% no immunity & 6% past infection
- Wood et al – Northern Territory
  - 437 children in ABC study anti core positivity rate of 21%
- Malcolm et al – north Queensland
  - 10 of 14 fully vaccinated had prior infection, 4 active
- Dent et al - Northern Territory
  - 37 fully vaccinated adolescents 4 active infection, 7 past

Molecular epidemiology

Adapted from Schaefer, S. *World J Gastroenterol 2007.*

Genotypes in the NT

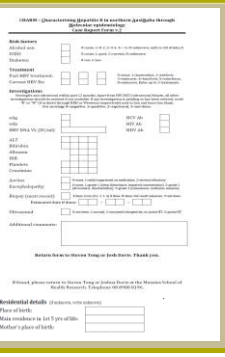
- Unknown in NT
- Expected to be a range of different genotypes
- Genotypes in Aboriginal and Torres Strait Islanders
  - D4 x 3, "novel variant C" x 2[1]
  - D not sub typed x 2[2]

1. Sugauchi F et al. *J Gen Virol* 2001; 82: 883-892.
2. McIntosh et al. J Med Virol 1998; 56: 10-17.

CHARM NT

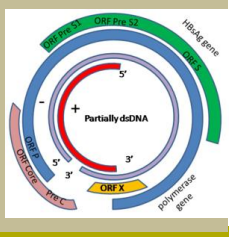
- ✓Ethics approval obtained
- ✓Patients diagnosed with hepatitis B
- ✓Born and spent at least first 5 years of life in NT
- ✓Over 18 years of age
- ✓Likely acquisition of Hepatitis B in first 5 years of life
- ✓Informed consent

CHARM NT



Northern Territory Government

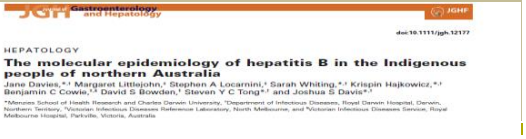
VIDRL



- ❖132 patients enrolled
- ❖All Aboriginal
- ❖Age range 21-81 years
- ❖38 communities
- ❖ 9 born after 1988, all vaccinated
- ❖90% born and raised in the same location as their mother

Results so far……

- **❖100% sub-genotype C4**
- **❖100% serotype *ayw3***
- **❖100% wild type polymerase**
- **❖100% mono infection**



JGH Journal of Gastroenterology and Hepatology

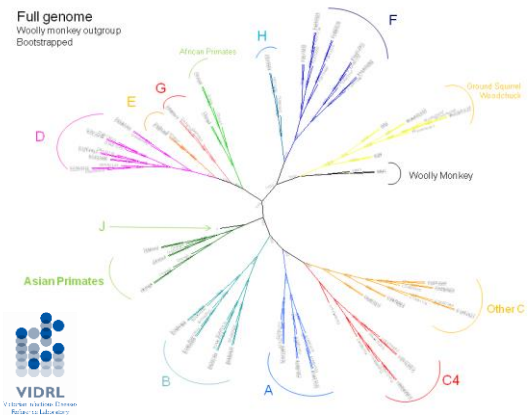
doi:10.1111/jgh.12177

HEPATOLOGY

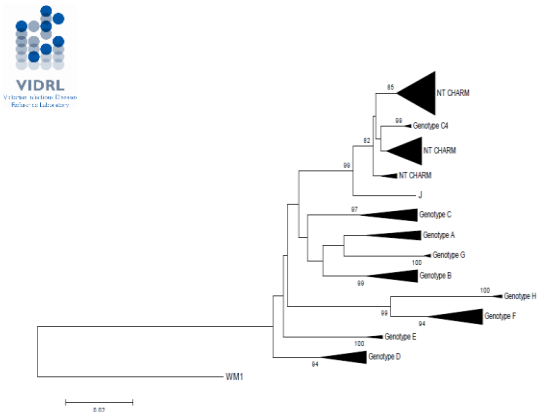
The molecular epidemiology of hepatitis B in the Indigenous people of northern Australia

Jane Davies,*,† Margaret Littlejohn,† Stephen A Locarnini,† Sarah Whiting,*,† Krispin Hajkowicz,*,† Benjamin C Cowie,*,‡ David S Bowden,† Steven Y C Tong*,† and Joshua S Davis*,†

*Menzies School of Health Research and Charles Darwin University, †Department of Infectious Diseases, Royal Darwin Hospital, Darwin, Northern Territory, ‡Victorian Infectious Diseases Reference Laboratory, North Melbourne, and §Victorian Infectious Diseases Service, Royal Melbourne Hospital, Parkville, Victoria, Australia



VIDRL



Recombination analysis

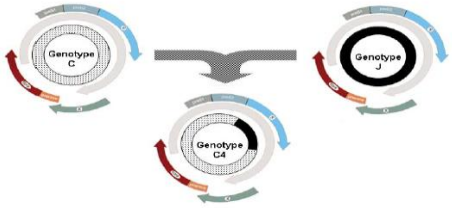


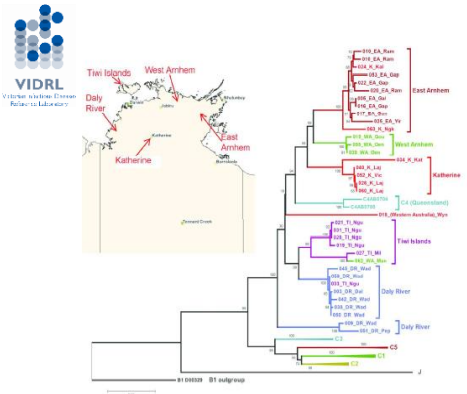
Figure 1: HBV genomes with genotype C (grey) and J (black). The recombinant genotype C4 has a 600bp genotype J like region encompassing HBsAg.

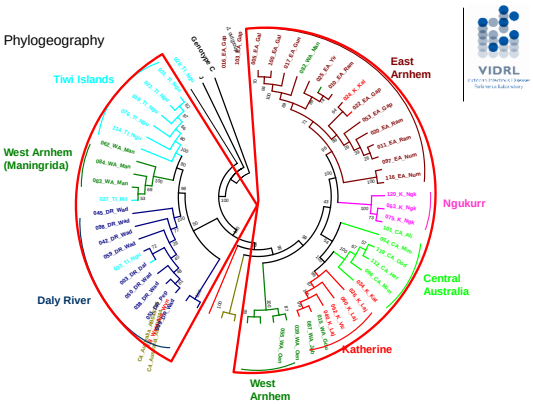
TABLE II. Presence of Viral Mutations and Substitutions Known to Have Public Health Significance or to Be Associated With Disease Progression Including HCC

Sample	Basal core promoter (BCP) G1613	T1753	A1762	G1764	C1766	Precore G1896	G1899	PreS deletion	Core deletion	Vaccine escape (HBsAg)
HBeAg negative										
011_EA_Ram	G/A			A	T	A	G/A			
020_EA_Ram				A	T	A		PreS2_20–21 (2aa)		
025_EA_Yir						A				
045_DR_Wad			T	A		A	A			
053_EA_Gap				G/A	C/T	A				
055_WA_Oen			A/T	G/A		G/A				
062_WA_Man		A/T	A/T	A	C/T					G145R/S
HBeAg positive										
003_DR_Dal			A/T	G/A						
005_EA_Gal										
009_DR_Wad	A		A/T	G/A	T		G/A	PreS1_1–7 (6aa)		P120P/T
010_EA_Ram										
015_WA_Gou			T	A		G/A				
016_EA_Gap		G/T	A/T	G/A	C/T					
017_EA_Gun				G/A	C/T					
018_WestAust_Wyn				A	T					
019_TI_Ngu										
021_TI_Ngu										
022_EA_Gap										
024_KA_Kal										
026_KA_Laj			T	A					80–114 (34aa)	
027_TI_Mil			T	A						G145R/S
028_TI_Ngu						G/A				
031_TI_Ngu										
033_TI_Ngu			A/T	G/A			A			
034_KA_Kat		G		A	T		G/A	PreS1_111 to PreS2_23 (31aa)		
038_DR_Wad										
039_WA_Oen										
040_KA_Laj			A/T	G/A						
042_DR_Wad			A/T	G/A						
050_DR_Wad										
051_DR_Pep	A	A		A	T					
052_KA_Vic										
059_DR_Wad							A			
060_KA_Laj			T	A					81–119 (38aa)	
063_KA_Ngk										

Mutation Analysis (53 FG samples)

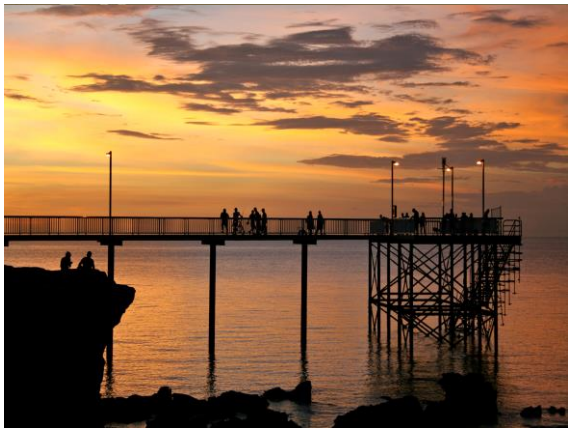
- ❖ BCP mutations 33/53 isolates (62%)
- ❖ Precore (G1896A) 14/53 isolates
- ❖ PreS deletion 4/53 isolates
- ❖ Variants associated with vaccine escape were detected as the predominant viral quasi-species in 4/53 samples.





Potential implications

- Unique Hep B sub-genotype – C4
- Mismatched serotype with vaccine
  - *ayw3* versus *adw2*
- Impaired vaccine effectiveness may be virological
- Taken to logical conclusion may need adapted vaccine



What else do we need to know?

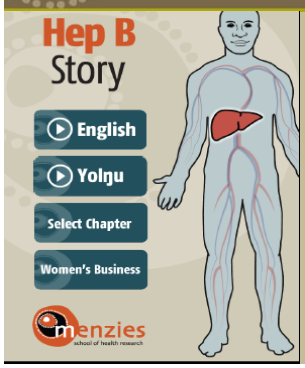
- Further investigation into the molecular virology of C4 with particular emphasis on the vaccine question
  - Epitope mapping
- Natural history of C4
  - Continued recruitment and clinical follow up
- Implications of;
  - exclusive sub genotype
  - molecular markers of aggressive phenotype

  for public health and individual management strategies

Acknowledgements

- Josh Davis
- Steven Tong
- Krispin Hajkowicz
- Sarah Whiting
- Ben Cowie
- Scott Bowden
- Margaret Littlejohn
- Stephen Locarnini
- Tina Sozzi
- Kathy Jackson
- Ros Edwards
- Outreach & infectious diseases specialists and registrars at Royal Darwin Hospital
- Laboratory staff at NT government pathology service & VIDRL

Questions?



- http://dmsdarwin.com/MenziesHepBStory/
- Free to download on the app store