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## 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*

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## Conflicts of Interest

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

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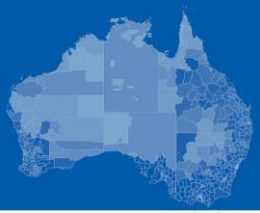
## Overview

- What we know already about Hepatitis B in the NT
- What the CHARM study has added so far
  - Characterising Hepatitis B in northern Australia through Molecular epidemiology
- Potential implications
- Future direction

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## Hepatitis B in the NT

- Prevalence estimates 1-15%<sup>1-7</sup>
- 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%



**HEPATITIS B MAPPING PROJECT**  
Estimates of chronic hepatitis B prevalence and cultural and linguistic diversity by Medicare Local Area

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

**ASHM** **VIDBL** **NATIONAL REPORT 2011**

AUSTRALIAN SOCIETY FOR HIV MEDICINE & PICTORIAN BY CECILIA OZGALES REYNOLDS, LANCASHIRE


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## 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


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## 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<sup>1</sup>
  - ❖ D not sub typed x 2<sup>2</sup>

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




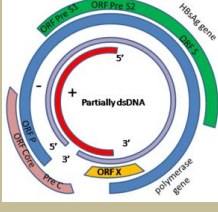


- ✓ Ethics approval obtained
- ✓ Patients diagnosed with hepatitis B
- ✓ Born and spent at least first 5 years of life in NT
- ✓ Over 18 years of age
- ✓ Likely acquisition of Hepatitis B in first 5 years of life
- ✓ Informed consent



Photography © Andrew Peter Parker

## CHARM NT

CHARM NT (Characterizing Hepatitis B in northern Territory Indigenous Communities) is a research project funded by the Northern Territory Government and the Victorian Infectious Diseases Reference Laboratory (VIDRL).

**Job Roles:** Research Officer, Research Assistant, Research Fellow, Research Nurse, Research Administrator, Research Support Officer, Research Coordinator, Research Manager, Research Director.

**Locations:** Darwin, Alice Springs, Tennant Creek, Katherine, Nhulunyu, Tennant Creek, Darwin, Alice Springs, Tennant Creek, Katherine, Nhulunyu.

**Research Objectives:** To determine the prevalence of HBV in the Northern Territory Indigenous population, to identify the genetic diversity of HBV in the Northern Territory Indigenous population, and to determine the impact of HBV on the health of the Northern Territory Indigenous population.



**Research Methods:** Serological, Molecular, and Clinical.

**Research Sites:** Darwin, Alice Springs, Tennant Creek, Katherine, Nhulunyu.

**Research Funding:** Northern Territory Government, Victorian Infectious Diseases Reference Laboratory (VIDRL).


**Research Contact:** Dr. David S. Bowen, Director, Northern Territory Indigenous Hepatitis B Research Program, Darwin, Northern Territory.

**Research Website:** [www.charm-nt.gov.au](http://www.charm-nt.gov.au)

- ❖ 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** Gastroenterology and Hepatology **ASHP**

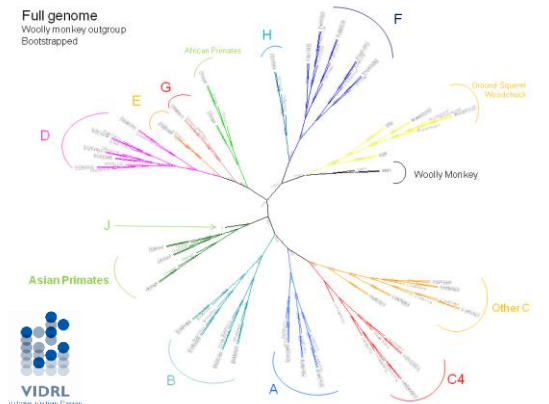
doi:10.1111/jgh.12172

**HEPATOLOGY**

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

Janis Davies,<sup>1,2</sup> Margaret Littlejohn,<sup>3</sup> Stephen A. Locarnini,<sup>1</sup> Sarah Whiting,<sup>4,5</sup> Krispin Hajkowitz,<sup>6,7</sup> Benjamin C. Cowie,<sup>8</sup> David S. Bowen,<sup>9</sup> Steven Y. C. Tong<sup>9</sup> and Joshua S. Davis<sup>9\*</sup>

<sup>1</sup>Menzies School of Health Research, and Charles Darwin University, <sup>2</sup>Department of Infectious Diseases, Royal Darwin Hospital, Darwin, Northern Territory, <sup>3</sup>Victorian Infectious Diseases Reference Laboratory, North Melbourne, and <sup>4</sup>Victorian Infectious Diseases Service, Royal Melbourne Hospital, Parkville, Victoria, Australia



**Full genome**  
Woolly monkey outgroup  
Bootstrapped

**African Primates**

**Asian Primates**

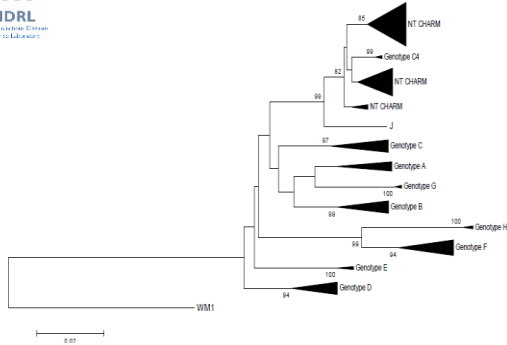
**Ground Squirrel Woodrat**

**Woolly Monkey**

**Other C**

**C4**

**VIDRL**  
Victorian Infectious Diseases Reference Laboratory



## Recombination analysis

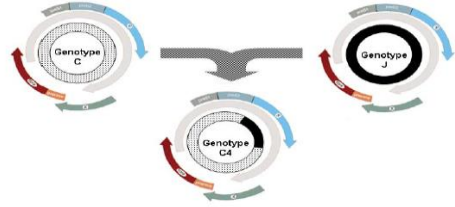


Figure 1: HBV genomes with genotype C (grey) and J (black). The recombinant genotype C4 has a 600bp genotype J like region encompassing HBsAg.

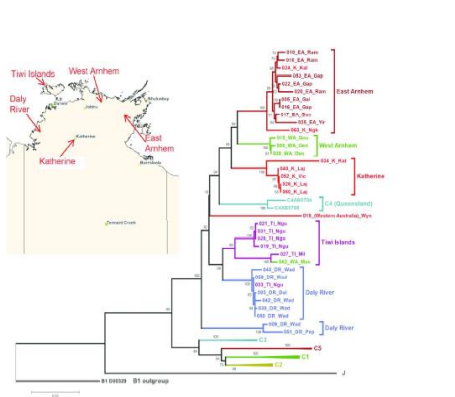
TABLE II. Presence of Viral Mutations and Substitutions Known to Have Public Health Significance or to Be Associated With Disease Progression Including HCC.

Sample	Basal core promoter (BCP)				Precore		PreS deletion	Core deletion	Vaccine escape (HBsAg)
	G161S	T175S	A176Z	G1764	C1766	G1896			
HBsAg negative									
011_EA_Rsm	G/A			A	T	A			
020_EA_Rsm				A	T	A			
025_EA_Yir				A	T	A			
040_DR_Wad			T	A	C/T	A		PreS2_20-21 (2aa)	
053_EA_Gsp				G/A	C/T	A			
055_WA_Oen			A/T	G/A	C/T	G/A			
062_WA_Man		A/T		A				G145R/S	
HBsAg positive				A/T	G/A				
003_DR_Dal				A/T	G/A				
005_EA_Gal				A/T	G/A				
009_DR_Wad	A			A/T	G/A	T	G/A	PreS1_1-7 (8aa)	
010_EA_Rsm				T	A				
015_WA_Goa				A/T	G/A	C/T			
016_EA_Gsp	G/T			A					
017_EA_Goa				G/A	C/T				
018_WestAusst_Wyn				A	T				
019_TI_Ngo									
021_TI_Ngo									
022_EA_Gsp				T	A			80-114 (34aa)	
024_EA_Kat									
026_KA_Lsj			T	A					
027_TI_MH			T	A		G/A		G145R/S	
028_TI_Ngo									
031_TI_Ngo									
033_TI_Ngo									
034_KA_Kat	G		A/T	G/A	A	T	A	PreS1_111 to PreS2_23 (31aa)	
038_DR_Wad									
039_WA_Oen									
040_KA_Lsj				A/T	G/A				
042_DR_Wad				A/T	G/A				
050_DR_Wad									
051_DR_Php	A	A							
052_KA_Vic				A	T				
059_DR_Wad									
060_KA_Lsj				T	A			81-119 (38aa)	
063_KA_Ngk									

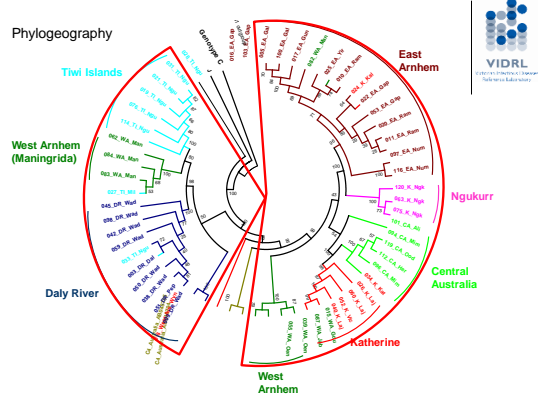
## Mutation Analysis (53 FG samples)




- ❖ 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.



## Phylogeography




## 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
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- ❖ Stephen Locarnini
- ❖ Tina Sozzi
- ❖ Kathy Jackson
- ❖ Ros Edwards

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- ❖ Laboratory staff at NT government pathology service & VIDRL






## Questions?



### Hep B Story

- ▶ English
- ▶ Yolŋu
- Select Chapter
- Women's Business





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