Emerging infectious threats in Indigenous populations

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discovery for a healthy tomorrow

- Facts & figures
- Why so disproportionate?
- Knowledge gaps
- Solutions

Influenza

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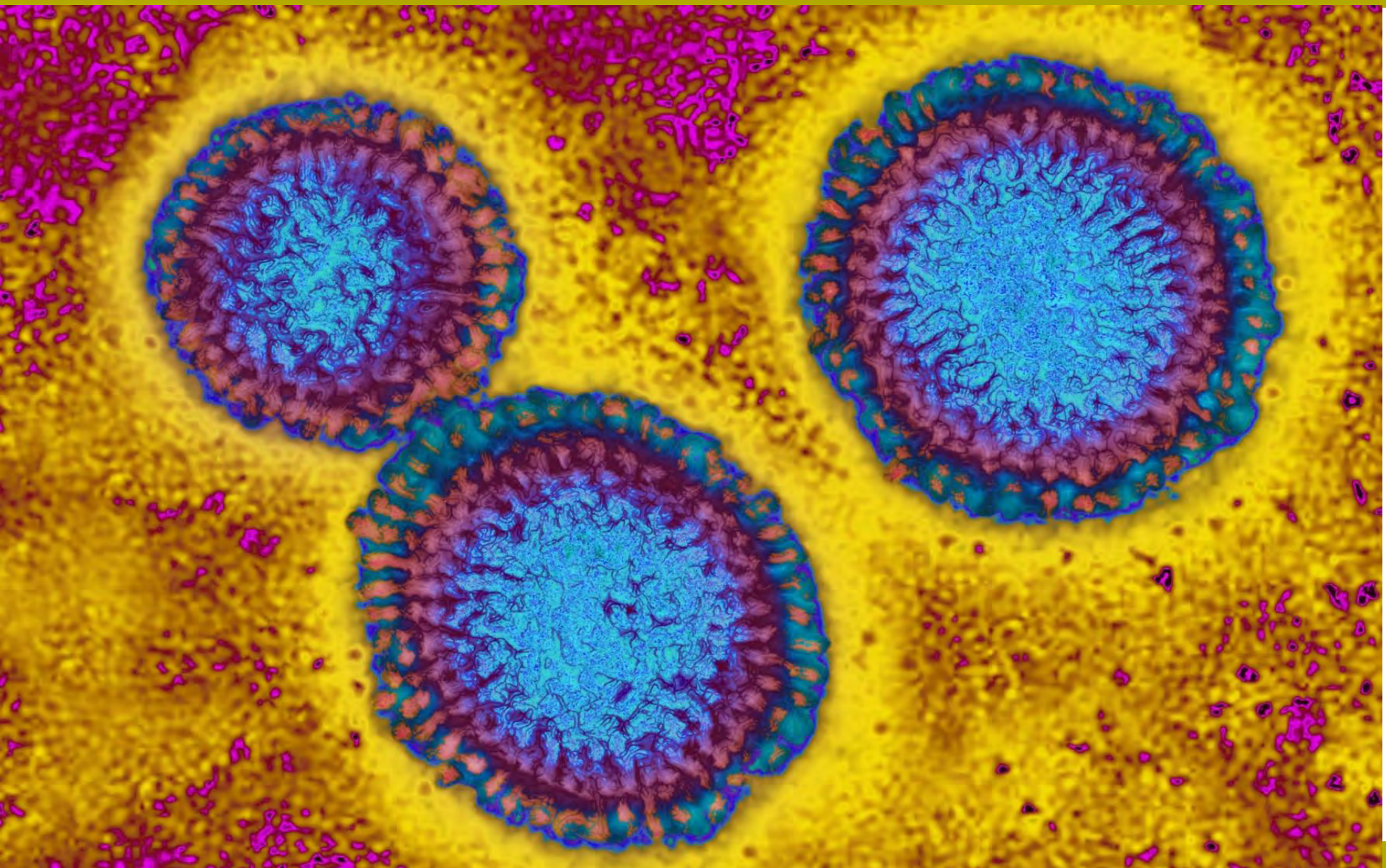


Influenza

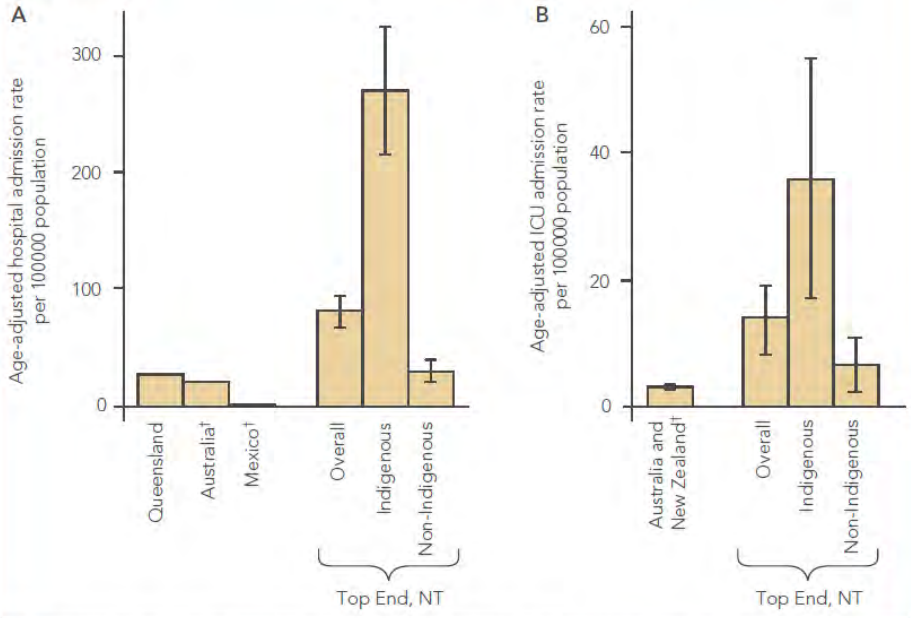
- 1919 – 20% of Indigenous Australians died from pandemic influenza (<1% of non-Indigenous Australians)
- 2009 H1N1 disproportionately affected 16% of hospitalised patients (2.5% of population), 9.7% of ICU admissions
- In NT 12 times more likely to be hospitalised in 2009 than non-Indigenous people

Disproportionate impact of pandemic (H1N1) 2009 influenza on Indigenous people in the Top End of Australia's Northern Territory

Shaun M Flint, Joshua S Davis, Jiunn-Yih Su, Erin P Oliver-Landry, Benjamin A Rogers, Aaron Goldstein, Jane H Thomas, Uma Parameswaran, Colin Bigham, Kevin Freeman, Paul Goldrick and Steven Y C Tong

918 notifications
1/6/09-31/08/09
Hospitalisation rate:
Indigenous
269/100,000
Non-Indigenous
29/100,000

4 Rates of admission to hospital (A) and ICU (B) with pandemic (H1N1) 2009 influenza in previous studies[2,13,14] and this study (Top End, Northern Territory)*



ICU = intensive care unit. * Rates are non-annualised, age-standardised unless otherwise indicated; 95% confidence intervals are shown where available; and rates for this study represent data for the three Top End hospitals for the period 1 June to 31 August 2009 based on estimated resident population. † Not age-standardised. ◆

Viral hepatitis

Hepatitis C

- Hepatitis C rates among Aboriginal and Torres Straight Islanders are 3 times higher
- In Canada, the Inuit and Métis First Nations Canadians also have rates 3 times higher
- In New Zealand, the data were insufficient to produce reliable estimates
- In the continental USA, American Indian tribal citizens overall had rates 2.5 times higher
- In Alaska, there was no statistically significant difference in the rate of hepatitis C in Alaskan natives.

Hepatitis B

- Aboriginal and Torres Straight Islanders in Australia were 4 times more likely to have hepatitis B infection
- Maori and Pacific Islander populations in New Zealand had double the rates of hepatitis B
- Canadian First Nations Inuit and Metis peoples had an even higher disparity, with hepatitis B rates five times higher

Table 5.1 Summary of demographics and HBsAg, anti-HBs and anti-HBc positive results broken down by Indigenous status and sex.

2007-2011 inclusive	Overall N=35,633	Indigenous n=14,025 (39%)	Non-Indigenous n=21,608 (61%)
Median age in years at sample date (IQR)	32.4 (24.5-43.7)	30.8 (21.5-43.3)	33.2 (26.3-44.0)
Sex	57.8	53.7	60.5
HBsAg positive % (95% CI)	3.40 (3.19-3.61)	6.08 (5.65-6.53)	1.56 (1.38-1.76)
[illegible] (95% CI)	[illegible] (4.59-5.40)	[illegible] (7.53-9.05)	[illegible] (1.86-2.62)
HBsAg positive women % (95% CI)	2.35 (2.13-2.59)	4.31 (3.83-4.84)	1.18 (0.99-1.40)
Anti-HBs >10IU/ml % (95% CI)	58.0 (57.3-58.7)	60.7 (59.7-61.6)	55.4 (54.4-56.3)
Anti-HBc positive % (95% CI)	25.2 (24.7-25.8)	38.3 (37.4-39.1)	11.7 (11.1-12.3)

Why?

- Remoteness logistics
- Low vaccination rates
- Cultural practices
- Incarceration rates
- IV drug use
- Lower socio-economic status
- Health literacy
- World view
- Health beliefs
- Over crowding
- Co-morbidities
- Health beliefs

- Historically isolated, lack of exposure prior to European invasion
- Lack of health hardware (taps, hot water, toilets, drains)

Funded and implemented

- anyone aged 65 years or older, regardless of medical conditions
- **Aboriginal children and adults:**
  - **all children aged six months to five years**
  - **all people 15 years and older**
- anyone aged six months and over with a medical condition that may increase their risk of severe influenza infection
- pregnant women at any stage of pregnancy - the vaccine protects the baby in the first six months of life.

Implemented

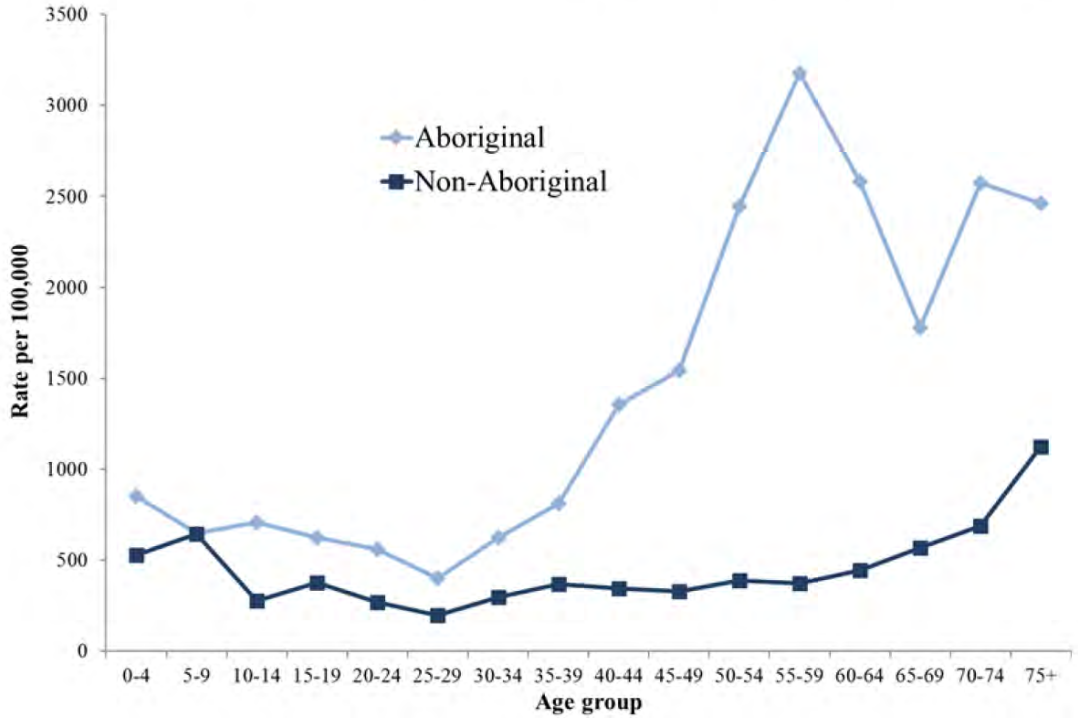
Differential Effects of Pandemic (H1N1) 2009 on Remote and Indigenous Groups, Northern Territory, Australia, 2009

James McCracken Trauer, Karen Louise Laurie, Joseph McDonnell, Anne Kelso, and Peter Gregory Markey

- Coverage 41% 2009 versus 24%, 52% 2017
- Attack rate of 22.9% versus 12.4% - 2009

2017 H3N2

Figure 3. Age-specific rates of laboratory-confirmed influenza by Indigenous status; 2017



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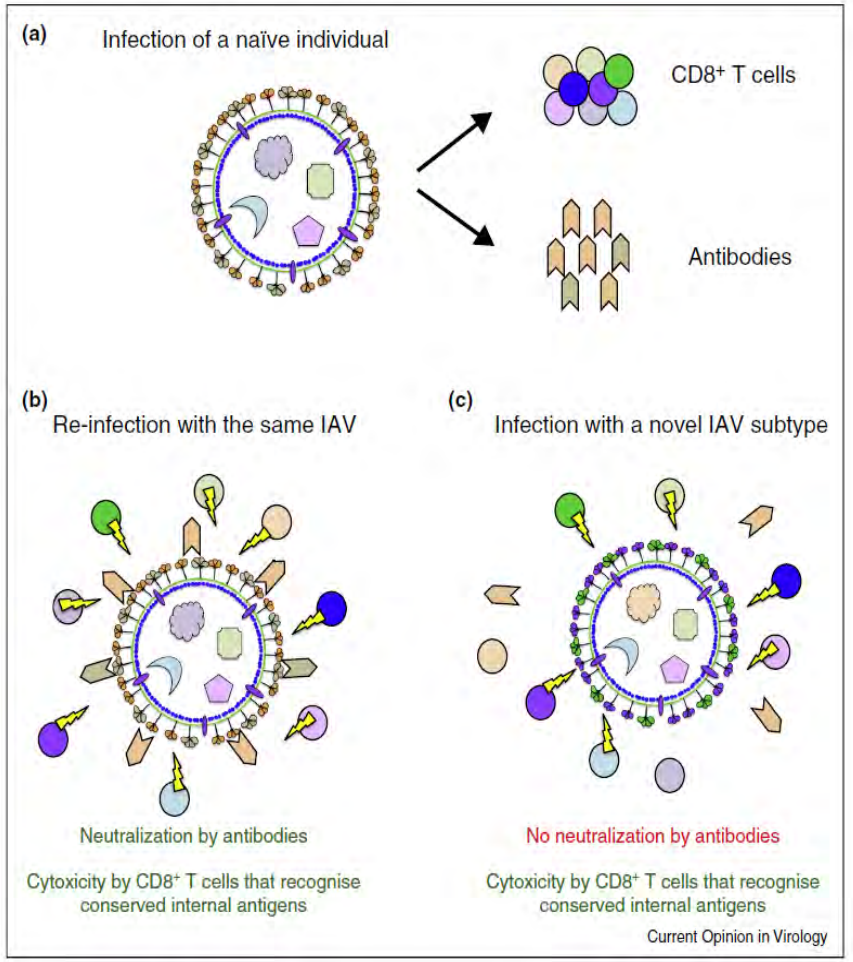
Doherty Institute
A joint venture between the University of Melbourne and Melbourne Health

- CD8 T cells directed at more conserved parts of influenza virus (internal peptides M NP PA)
- Potentially can confer protection to wide range of existing and novel influenza viruses
- HLA of individual important (genetically determined ethnically specific)
- Some evidence that severe disease may be related to certain HLA types i.e. lack of T cell immunity



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A joint venture between the University of Melbourne and Melbourne Health

- Lots of interest in T cell vaccines
- SEEK UK based Company trialled one
- Components would only cover ~50%
- Very little to cover to Indigenous population
- H7N9 work – Alaskan and Indigenous Australians may be particularly susceptible

Preexisting CD8$^+$ T-cell immunity to the H7N9 influenza A virus varies across ethnicities

Sergio Quiñones-Parra[a], Emma Grant[a], Liyen Loh[a], Thi H. O. Nguyen[a,b], Kristy-Anne Campbell[c], Steven Y. C. Tong[d], Adrian Miller[e], Peter C. Doherty[a,f,1], Dhanasekaran Vijaykrishna[g], Jamie Rossjohn[c,h], Stephanie Gras[c], and Katherine Kedzierska[a,1]

82 Indigenous Australians from Darwin without current influenza

Blood collected and PBMCs extracted

Influenza specific CD8 T cells studied

HLA restricted and different to non-Indigenous Australians

HLA-A*24:02, A*34:01,B*15:21, B*13:01, A*11:01 and 2 new allelles; HLA-A*02new, B*56new

HLA matters

- HLA A02 only present in 15% of Indigenous Australians in the NT
- HLA-A24 previously linked with severe disease
- Present in ~ 30 % NT and 70% Alaskans
- PB1 elicited robust response – not included in planned vaccines

T cell vaccine

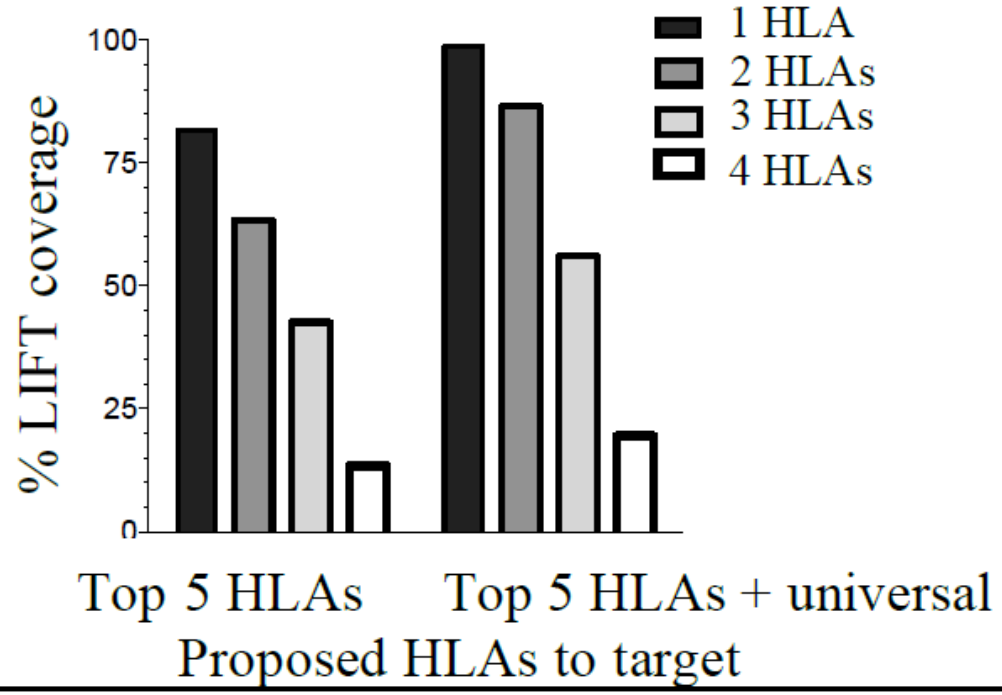

Fig 3. Proportion coverage of the LIFT cohort by the top 5 HLAs in Indigenous Australians with or without 5 universal influenza HLAs identified previously by CIA. Frequency coverage for 1, 2, 3 or 4 HLAs is shown.

LIFT V

- Currently recruiting Aboriginal Australians in the top end
- Pre vaccine bloods then vaccinate
- Post vaccine bloods day 7 and 28
- Looking for:

- **Aim 1:** To identify novel influenza-specific cytotoxic CD8+ T cell (CTL) targets for the HLA types dominant in Indigenous Australians.
- **Aim 2:** To define the magnitude, hierarchy and protective efficacy of the CD8+ T cells directed against novel influenza targets across specific HLAs.
- **Aim 3:** To understand the population coverage by our proposed mosaic CTL peptide pool.
- **Aim 4:** To understand immunogenicity of the current antibody-mediated seasonal influenza vaccine in Indigenous Australians, in the presence and absence of our proposed mosaic pool of CTL targets.

Hepatitis B

- 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.*

CHARM

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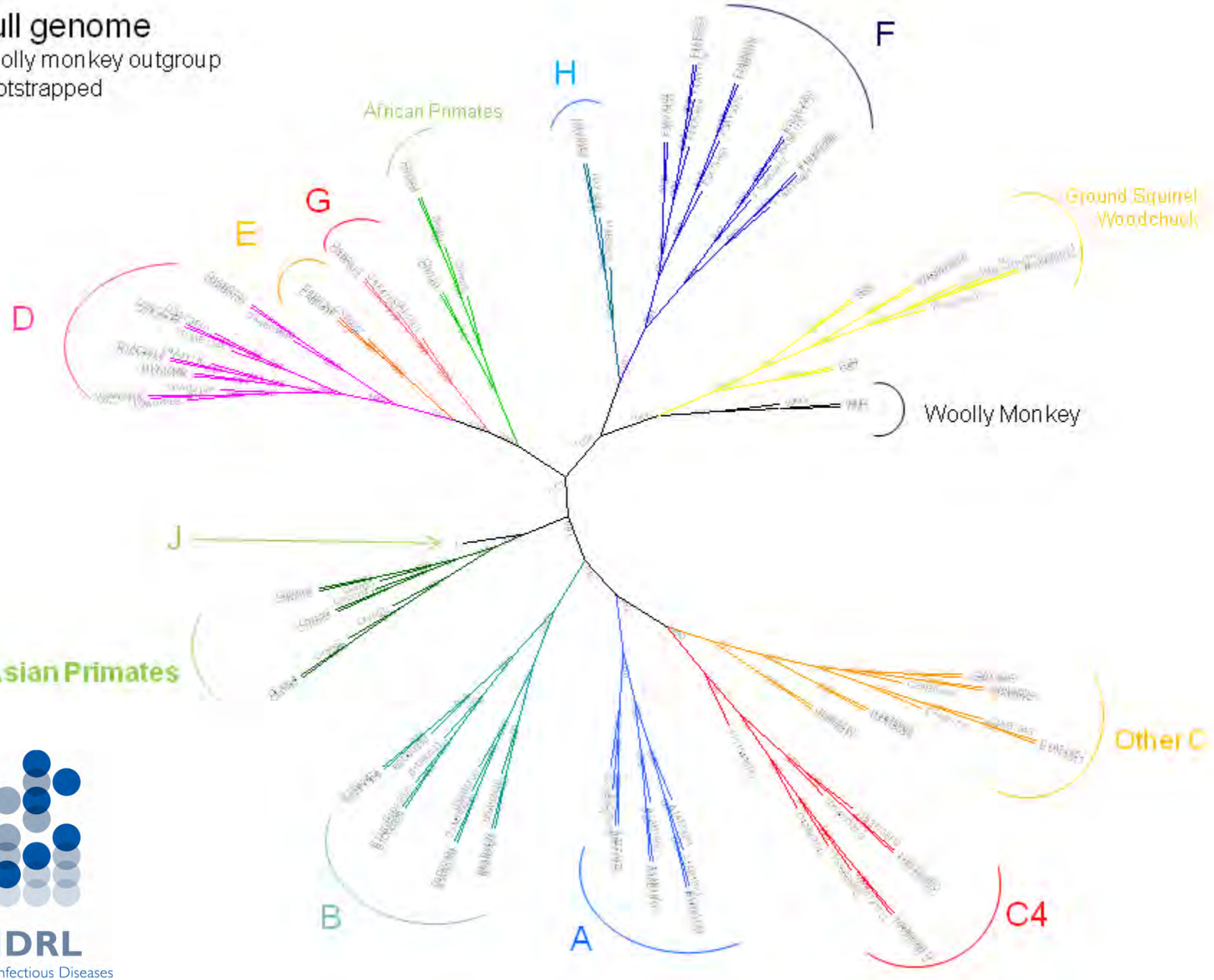
- 204 patients enrolled
- All Aboriginal
- 42 communities
- Single genotype identified **C4**
- 90% born and raised in the same location as their mother

Full genome

Woolly monkey outgroup

Bootstrapped



VIDRL

Victorian Infectious Diseases Reference Laboratory

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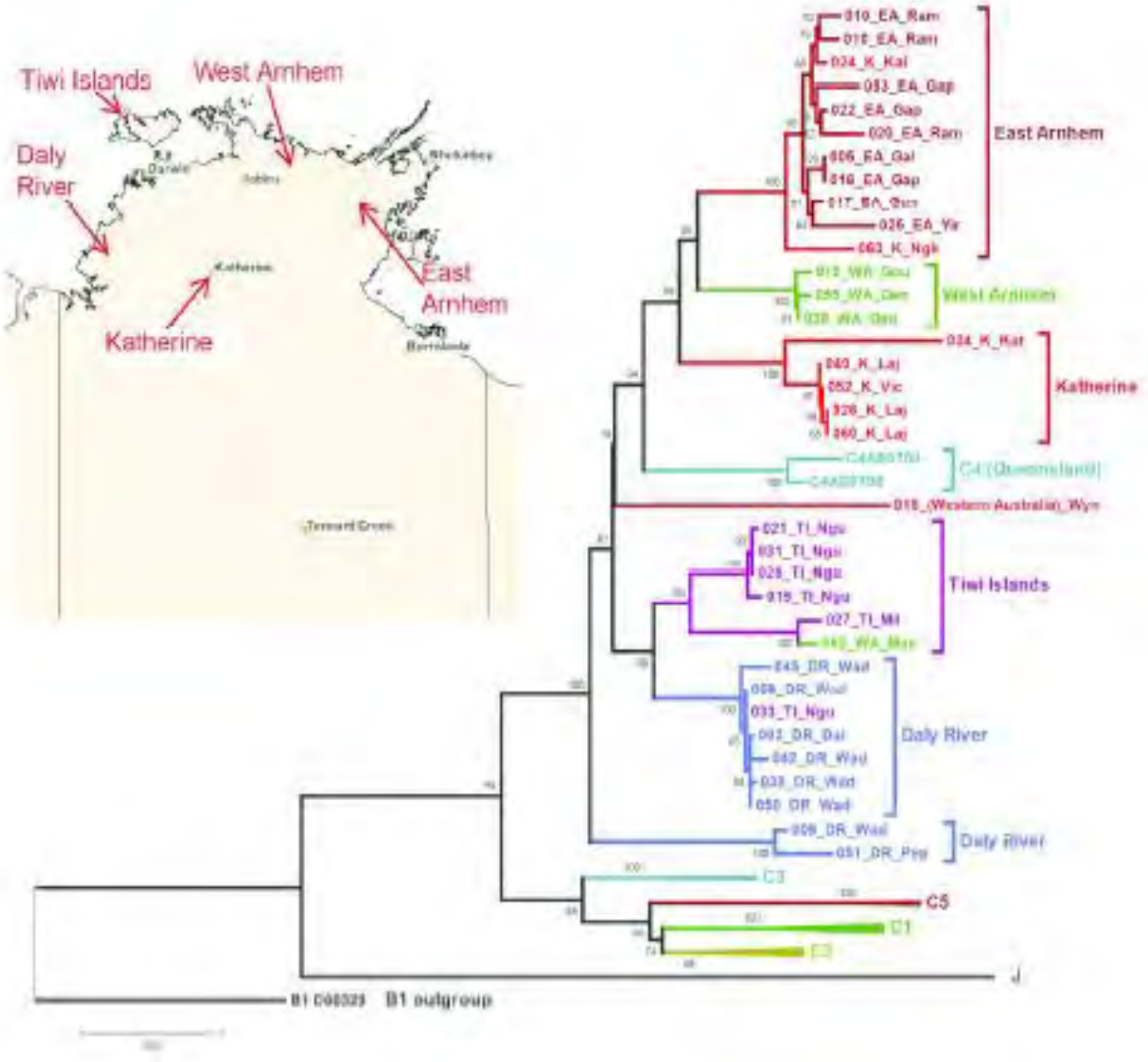

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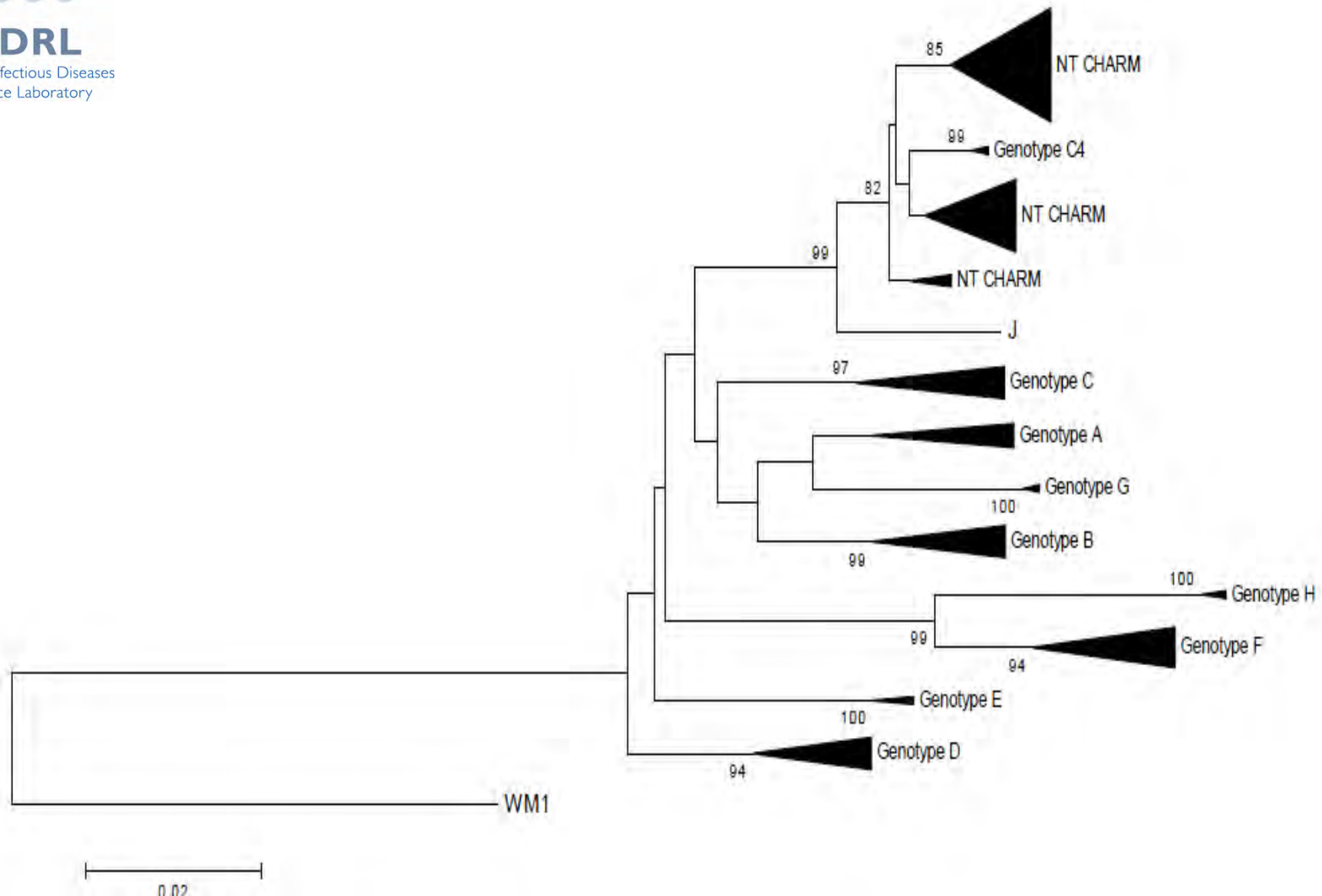

Recombination analysis

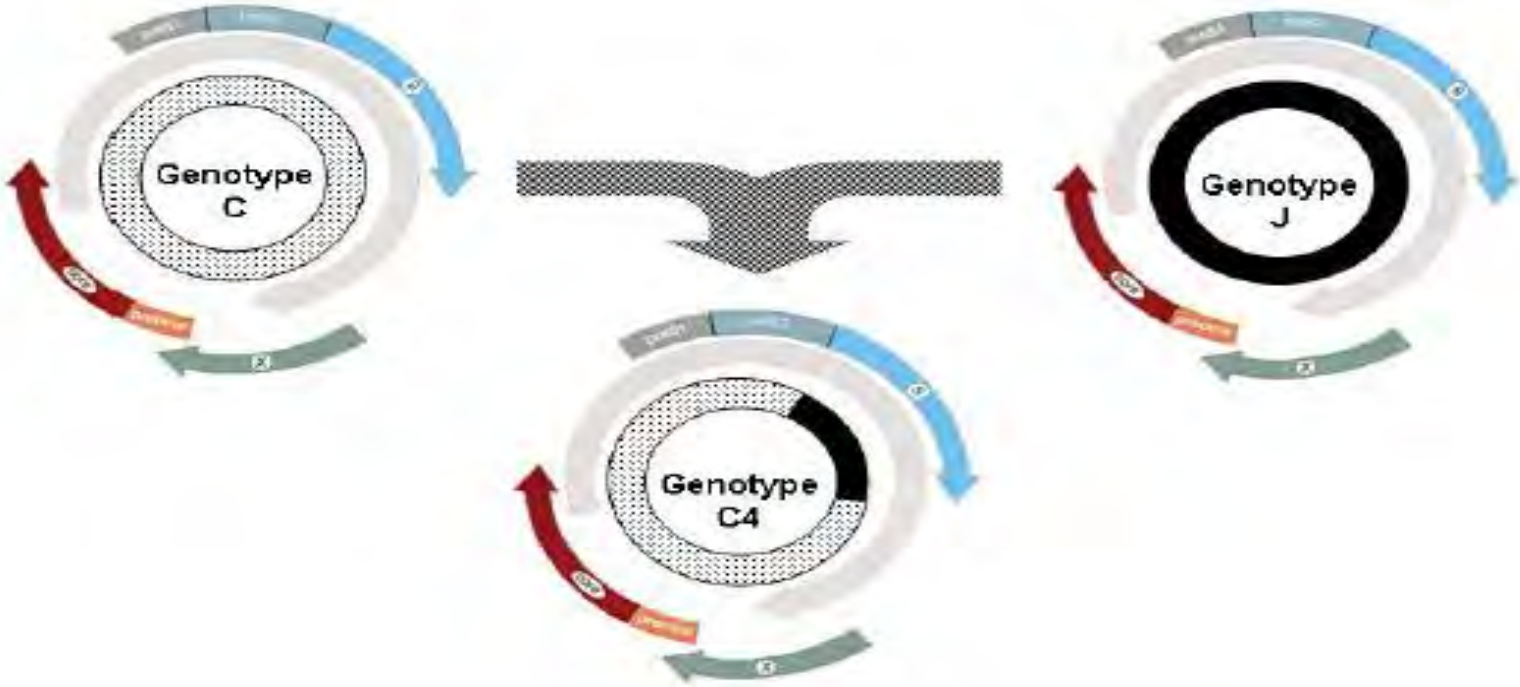

Figure 1: HBV genomes with genotype C (grey) and J (black). The recombinant genotype C4 has a 600bp genotype J like region encompassing HBsAg.

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

ABC study results

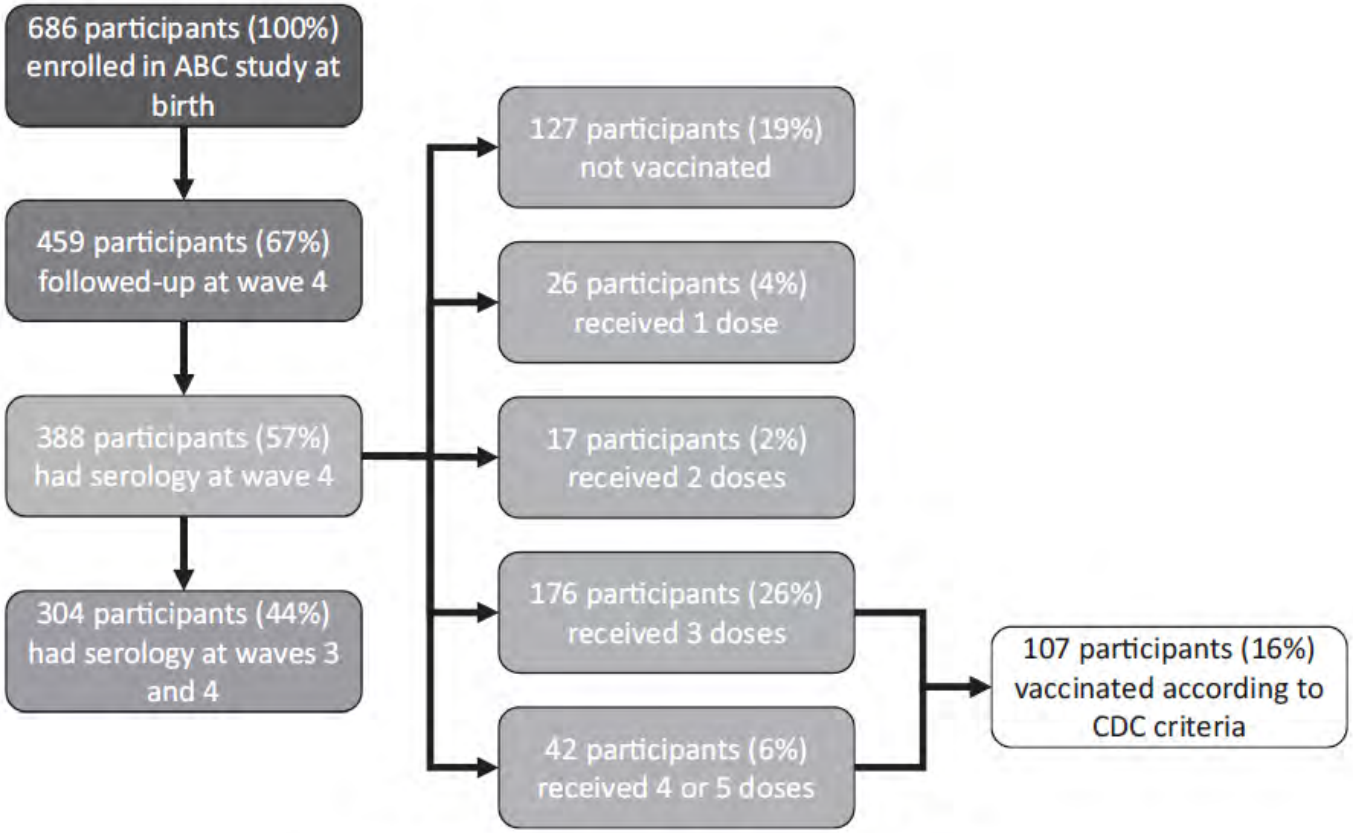

Fig. 1. Outline of participant flow through the ABC study.

Table 1
Characteristics of the seven participants with detectable HBsAg or HBV DNA at wave 4. Participant #1 was $HBsAg^+$, $anti\text{-}HBc^+$ and had undetectable anti-HBs nearly 1.5 years before wave 4. Participant #2 was $anti\text{-}HBc^+$ five months before wave 4. Participant #3 had insufficient sample to confirm HBsAg status at wave 4. Participant #6 was $HBsAg^+$ 2 years before wave 4 and had an HBV DNA viral load of 140 IU/L 9 months before wave 4. Participant #7 was $HBsAg^+$ and had an HBV DNA viral load of 33 IU/mL 1.5 years before wave 4. Abbreviations: =, equivocal; y, years; m, months; and d, days.

Participant	#1	#2	#3	#4	#5	#6	#7
Sex	Female	Male	Female	Male	Male	Male	Male
Family community location	Remote	Remote	Remote	Remote	Remote	Remote	Remote
Vaccine 1 age	5.2 y	10.1 y	6 d	11.3 y	–	–	5 d
Vaccine 2 age	5.3 y	10.3 y	43 d	11.5 y	–	–	1 m
Vaccine 3 age	5.7 y	10.7 y	9 m	19.1 y	–	–	11.6 y
Vaccine 4 age	–	–	5.3 y	–	–	–	–
CDC criteria	No	No	Yes	No	No	No	No
Location	Remote	Remote	Remote	Remote	Remote	Remote	Remote
Anti-HBs (IU/L)	<3.5	<3.5	<3.5	<3.5	<3.5	<3.5	<3.5
Anti-HBc	+ve	−ve	+ve	+ve	+ve	+ve	+ve
HBsAg	+ve	+ve	=	+ve	+ve	+ve	+ve
HBV DNA (IU/mL)	102×10^6	2265	125	910	<20	<20	84
HBeAg	+ve	−ve	−ve	+ve	−ve	+ve	+ve
Location	Urban	Remote	Remote	Remote	Remote	Remote	Remote
Anti-HBs (IU/L)	<3.5	<3.5	<3.5	Missing	<3.5	<3.5	7.7
Anti-HBc	+ve	+ve	−ve	+ve	+ve	+ve	−ve
HBsAg	Missing	+ve	−ve	+ve	+ve	Missing	−ve

VE any infection 67% (43-104%) HBsAg positive disease very small numbers

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

	Basal core promoter (BCP)					Precore				
Sample	G1613	T1753	A1762	G1764	C1766	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										

Sustainable, holistic care

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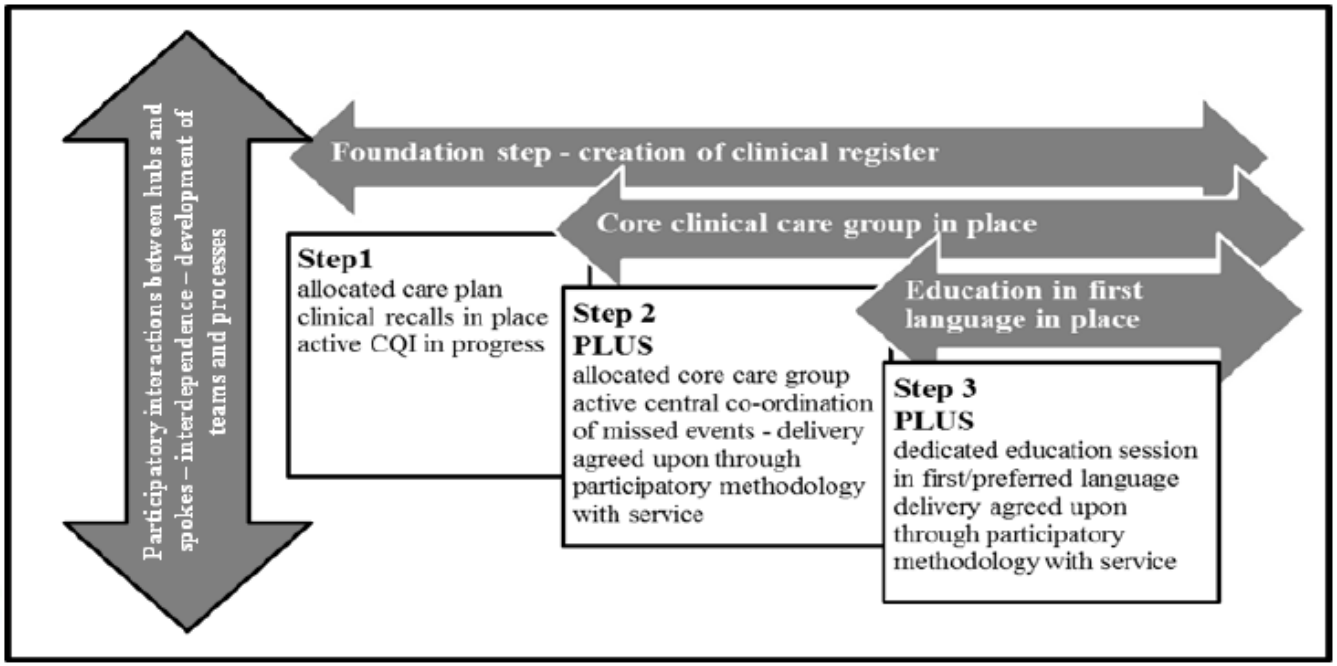
NORTHERN TERRITORY GOVERNMENT

DEPARTMENT OF HEALTH

ntahc northern territory aids & hepatitis council



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Hepatitis C

- Assumptions
- High prevalence in all Indigenous communities
- CHARM study no hepatitis C infected people
- Prison data from the NT - >80% Indigenous people < 5% Hepatitis C prevalence (personal communication, unpublished data)

Summary

- Indigenous populations across the world and in Australia disproportionately affected by many infections
- Important we continue to question our assumptions both about the viruses and the host responses
- So much more still to learn…….

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