Hepatitis B virus Genotype C4 in Australia’s Northern Territory

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Outline

• Background
• CHARM1 study
• Implications for vaccine efficacy
• Implications for virulence and cancer potential
• Using HBV/C4 for inferring human population movements
Background on HBV in the NT
The NT

- Population ~220,000
- Area ~1.1 million km$^2$
- 30% Indigenous Australian (cf. 3% Australia)
- HBV vaccine from birth introduced for all in NT in 1990, for all Indigenous people in NT in 1988.
- Major hospitals with specialist hepatitis services at Darwin and Alice Springs
HBV in the NT

• Liver clinic at Royal Darwin Hospital established 2006
• HBV research program at Menzies School of Health Research followed from 2009

Some early questions:
• What is the seroprevalence of HBV in the NT?
• What genotypes of HBV circulate in the NT?
• How can we communicate better about HBV with community members and health care workers?
HBV is endemic in Indigenous Territorians

- All HBV serology from across NT 2007-2011
- Data from 35,633 individuals
- HBsAg positive in 3.5% overall, **6.1% Indigenous**
- HBcAb positive in 38% Indigenous people

Davies et al. – unpublished - submitted 2017
CHARM

Characterising Hepatitis B in northern Australia through Molecular Epidemiology
Previous data on HBV genotypes in NT

• None
• Expected a range of (sub)genotypes, C and D
• Previously published HBV genotypes in Indigenous Australians (all from QLD):
  • D4 x 3, “novel variant C” x 2¹
  • D not sub typed x 2²

CHARM study

- People with HBV recruited with consent
- Over 200 participants enrolled thus far
- From 5 towns and 33 remote communities across NT
- Results from first 128
  - 100% genotype C4
  - No co-infection with HIV or HCV or HDV
• G1896A stop codon mutation in 30%
• G1764A/C1766T or A1762T/G1764A in 58%
• Increased risk of cirrhosis & HCC<sup>1,2</sup>
• G1053A in 74%
  • independent risk factor for HCC<sup>3</sup>
• 2 sG145R & 1 sP120T vaccine escape mutants detected
What does this mean for the vaccine program?
Implications of C4 for vaccine

- HBV/C4 is serotype ayw3
- The standard HBV vaccine used in Australia is based on genotype A and serotype adw
- *In-vitro* assays suggest Abs elicited by standard vaccine bind poorly to HBV/C4 sAg
- 5 small studies of fully vaccinated Indigenous people\(^2-6\)
  - HBcAb positive in 6-66% (~40%)
  - HBsAg positive in 0-29% (~10%)

The end of the Australia antigen? An ecological study of the impact of universal newborn hepatitis B vaccination two decades on

Bette Liu f,*, Steven Guthridge b, Shu Qin Li b, Peter Markey b, Vicki Krause b, Peter McIntyre c, e, Elizabeth Sullivan d, James Ward a, Nicholas Wood c, e, John M. Kaldor f

Vaccine 30 (2012) 7309–7314

Fig. 1. Chronic hepatitis B prevalence in Aboriginal birthing mothers according to birth cohort.

*Prevalence plotted against the mean year of birth in each birth cohort category
Vaccine – summary and future directions

• The current standard vaccine appears to work well to prevent chronic infection (HBsAg) but not infection *per se* (HBcAb)

• Gathering further data from
  • Galiwinku serosurvey
  • BAMBI study (HBV in Mothers and Babies)
  • Mouse model of HBV/C4 (Pellegrini, WEHI)
Is there an increased risk of cirrhosis and liver cancer with HBV/C4?
Liver cancer case numbers in NT

Parker et al. MJA 2014; 201: 470
Liver cancer incidence in NT

Rate per 100,000 population

HCC – poor survival

Survival curve comparing Indigenous to non-Indigenous Australians over the first year after diagnosis
Risk of cirrhosis with HBV/C4

• Currently unclear
• CHARM study converted to longitudinal cohort
• Data from ~4 years follow up, median age 40 years, 22% have cirrhosis
• See Jane Davies’s talk tomorrow for more details
The future of CHARM

Figure 3 – Current and proposed CHARM cohort recruitment sites
What else can we learn from HBV/C4?
An African origin for the intimate association between humans and *Helicobacter pylori*

Bodo Linz¹, François Balloux², Yoshan Moodley¹, Andrea Manica³, Hua Liu², Philippe Roumagnac¹, Daniel Falush⁴, Christiana Stamer¹, Franck Prugnolle⁵, Schalk W. van der Merwe⁶, Yoshio Yamaoka⁷, David Y. Graham⁷, Emilio Perez-Trallero⁸, Torkel Wadstrom⁹, Sebastian Suerbaum¹⁰, and Mark Achtman¹
HBV phylogeography study

- Locarnini, Yuen – VIDRL – see Locarnini talk tomorrow
- 59 full genome sequences of HBV/C4
- 216 published sequences of other HBV strains
- Compared with phylogenetic trees and Bayesian models used to estimate time of key evolutionary events
Recombination of HBV/J and HBV/C to form HBV/C4 71 kya

Introduction of HBV/C4 54 kya with first humans and subsequent spread in Australia.
Key outstanding HBV/C4 questions

• Should we be intervening with antiviral therapy earlier?  
  • i.e. in Immune Tolerant phase. CHARM cohort study

• Is HBV/C4 really more pathogenic than other genotypes?

• Does positive HBcAb (in absence of HBsAg) matter at all? (i.e. does the vaccine mismatch matter)
  • HINT data linkage study

• If yes, is there a more effective vaccine?
Thanks!

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