Novel diagnostics in viral hepatitis : How can they address the liver cancer burden?

Scott Bowden
VIDRL, The Doherty Institute
Melbourne

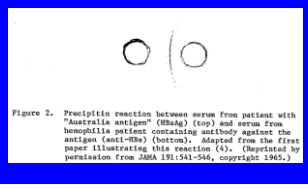


Figure 2. Precipitin reaction between serum from patient with "Australia antigen" (HBsAg) (top) and serum from hemophilia patient containing antibody against the antigen (anti-HBs) (bottom). Adapted from the first paper illustrating this reaction (4). (Reprinted by permission from JAMA 191:541-546, copyright 1965.)

Viral Hepatitis and HCC

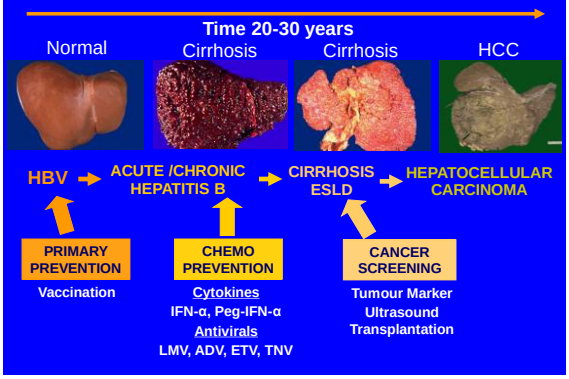
GBD Study 2010* - HBV-related mortality 800,000 pa
- HCV-related mortality 500,000 pa

Approx 25% of chronic viral hepatitis leads to HCC
- 5th most common cancer world-wide
- 3rd highest cause of cancer mortality
- HBV = 2nd most potent carcinogen after tobacco

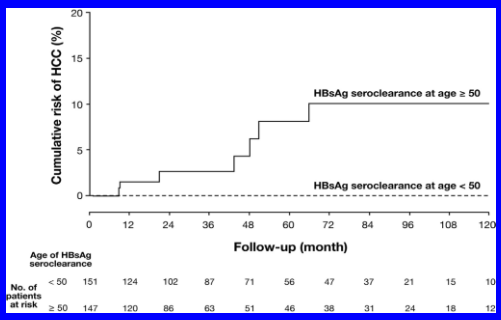
In Australia – liver cancer is the fastest increasing cause of cancer mortality (AIHW 2012) +

* *Lozano et al 2012 Lancet 380: 2095* + *Robotin MC et al. Med J Aust. 2008*

CHB - Liver Disease Progression

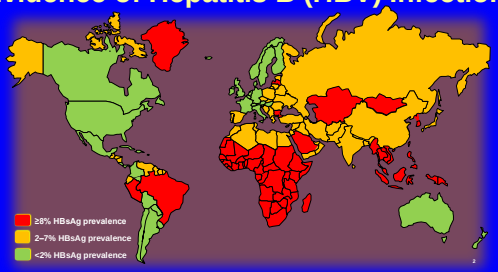


CHB - Cumulative Risk for HCC



Yuen M-F, et al. Gastroenterology 2008; 135:1192

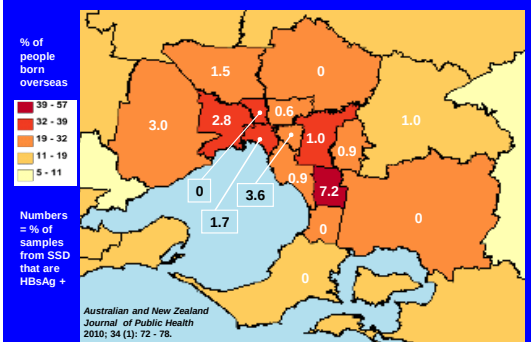
More Than 2 Billion People Show Evidence of Hepatitis B (HBV) Infection[1]



350–400 million people are chronically infected with HBV worldwide[1,3]

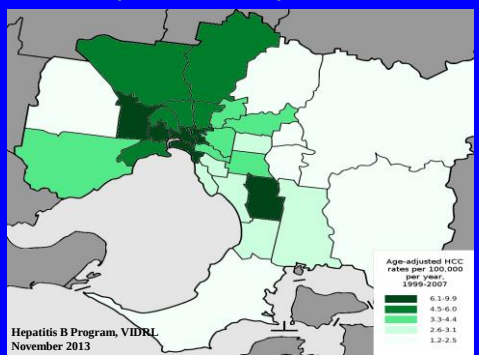
1. World Health Organization. Hepatitis B.
2. Map: Adapted from Liaw Y-F et al. Antiviral Therapy. 2010; 15 (suppl 3): 25–33.
3. Hepatitis B Foundation Statistics. Accessed on 4 March 2011. Available at

Victorian Hepatitis B Serosurvey 1995 - 2005 HBsAg seroprevalence by region, Melbourne



Australian and New Zealand Journal of Public Health 2010; 34 (1): 72 - 78.

Age-standardised HCC incidence by LGA, Melbourne, 1999-2007



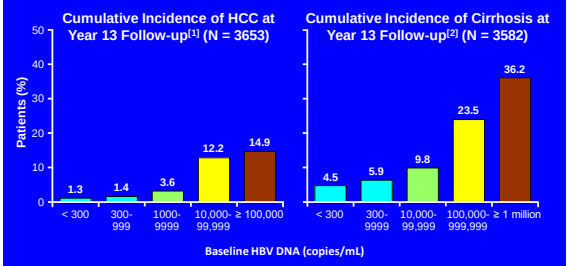
CHB - Risk Factors for HCC Development

Complex and multifactorial

- Older age
- Cirrhosis
- High HBV DNA load
- HBeAg positive
- Basal Core Promoter mutations
- Family history
- HBV genotype

High Baseline HBV DNA Associated With Increased Risk of HCC and Cirrhosis

REVEAL: Long-term follow-up of untreated HBsAg +ve individuals in Taiwan



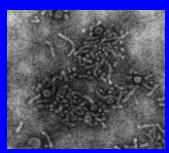
1. Chen CJ, et al. JAMA. 2006;295:65-73.
2. Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

CHB - Risk Factors for HCC Development

- HBsAg positivity

Hepatitis B Surface Antigen

HB virions & HBsAg



1. HBsAg - "Australia antigen" recognized (1965)
2. Provided first diagnostic marker of HBV infection (1972)
3. Provided an immunogen for a sub-unit vaccine (1982)
4. Presence > six months defines chronic infection

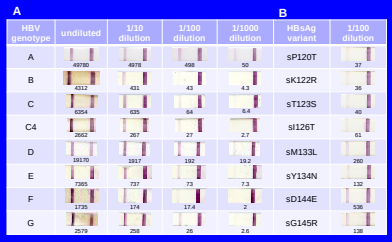
Point-of Care or Rapid Tests (HBV)

- Several available for HBsAg detection
- Alternative to EIAs in resource-limited settings
  - inexpensive, no sophisticated equipment, rapid turnaround so less call-back and fewer lost to follow-up
- May also be useful for marginalized high-risk populations in developed countries
- High specificity but lower sensitivity than EIAs

HBsAg PoC – Evaluation – Genotypes & Variants[1]

NanoSign HBsAg strip (Bioland, South Korea)

[1] *Gish et al 2014 J Viral Hep*



*Field testing showed only 74% sensitivity but 98% specificity

Comparison of Different Phases

	Immune Tolerant	Immune Reactive	Low Replicative	HBeAg Negative	ANOVA P Value
n	32	55	50	83	-
Age	30 (23, 33)	30 (24, 37)	36 (28, 45)	43 (35, 50)	<0.001
Sex M/F	9 / 23	17 / 38	18 / 32	48 / 35	NS
HBV DNA Log10 IU/mL	8.22 (7.96, 8.47)	8.02 (6.8, 8.9)	<2.55 (<2.55, 3.05)	4.95 (3.96, 5.83)	<0.001
ALT IU/mL	18 (16, 30)	101 (51, 163)	23 (15, 28)	50 (33, 88)	<0.001
Genotype B / C (%)	65/35	49/51	60/40	61/31	
HBsAg Log10 IU/mL	4.53	4.03	2.86	3.35	<0.001

* Results expressed in median, and 25th / 75th interquartile range

Nguyen, T. et al 2009. J.Hepatol;50(Suppl. No.1);S141. Abstract 370

Point-of Care or Rapid Tests (HCV)

- Several available for anti-HCV detection
  - fingerprick blood and saliva
- HCV core antigen assays available as an alternative to HCV RNA assays
  - Sensitivity equivalent to approx 1,000 IU/mL
  - Not suitable for monitoring antiviral therapy
- HCVcAg not available as PoC

Point-of-Care Testing - Issues

- Regulatory approval
- Specificity and sensitivity
- Quality control & Quality assurance
- Training
- Counselling & follow-up
- Traceability

National Pathology Accreditation Advisory Council Draft Guidelines for Point of Care Testing May 2014

Dried Blood Spot (DBS) Testing

- Several reports showing DBS are reliable for detection of anti-HCV and HCV RNA (qual)

Tuaillon et al 2010 Hepatol 51: 752; Bennett et al 2012 JCV 54: 106; Dokubo et al 2014 JCV 59: 223

- Also specific for HBV serological markers and HBV DNA *Mohamed et al 2013 PLoS 16: e61077; Ross et al 2013 Virol J 10: 72*
- DBS can be used for AFP detection

Mendy et al 2005 J Viral Hep 12: 642

Similar issues exist as for PoC testing

Reduce Liver Cancer Burden? WHO Global Hepatitis Programme

Four Axes for Global Action

1. Raise awareness & resources
2. Develop evidence for policy & action
3. Prevent transmission
4. Increase access to screening, care and treatment

Reduce Liver Cancer Burden?
WHO Global Hepatitis Programme
Four Axes for Global Action

1. Raise awareness & resources
2. Develop evidence for policy & action
3. Prevent transmission
4. Increase access to screening, care and treatment