Perinatal hepatitis B infection

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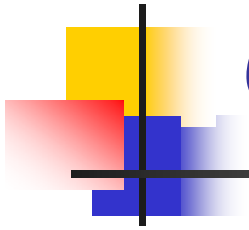
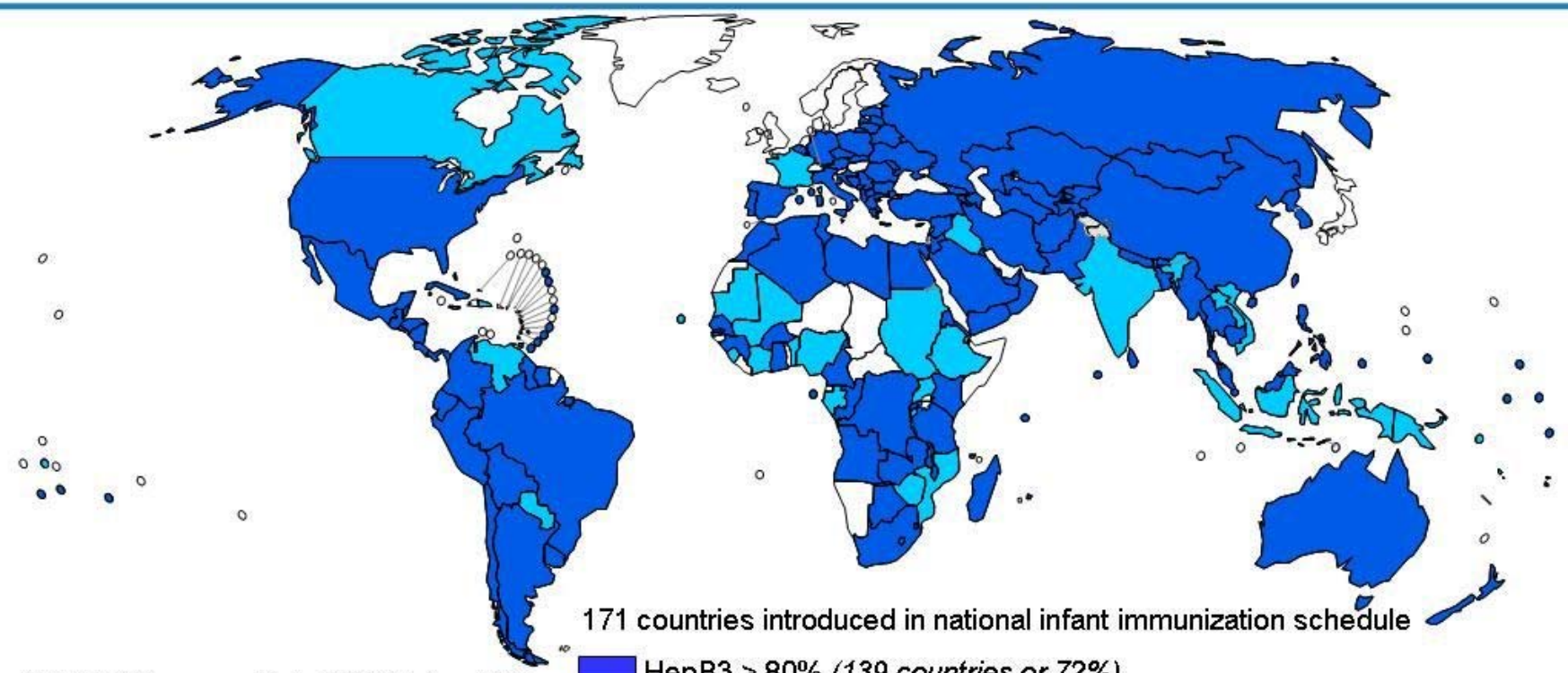


Outline

- Acute hepatitis B in pregnancy
- Mother to child transmission risk factors
- Transmission prevention strategies
  - Antenatal
  - Postnatal
- Natural history of perinatal hepatitis B infection
- Longevity of immunity

	Perinatal	Childhood	Adolescent/Adult
Acute symptoms	Rare	Uncommon	Common (30%–50%)
Chronic infection	80%-90%	30%	<5%
Immune tolerant phase	Prolonged	Variable	Short
Risk of advanced liver disease (% of exposed)	20%–30%	5%–10%	1%–2%
Risk of advanced liver disease (% of chronic)	20%–30%	20%–30%	20%–30%
Australian population groups	Asian born	Pacific Island born; Mediterranean, Middle East, and African born; Indigenous	Injecting drug users; homosexual men

Countries having introduced HepB vaccine and infant HepB3 coverage, 2007



171 countries introduced in national infant immunization schedule

- HepB3 ≥ 80% *(139 countries or 72%)*
- HepB3 < 80% *(31 countries or 16%)*
- HepB vaccine introduced but no coverage data reported *(1 countries or 0.5%)*
- HepB* vaccine not introduced *(22 countries or 11.5%)*

* 3 countries introduced HepB in adolescent immunization schedule

Source: WHO/UNICEF coverage estimates 1980-2007, August 2008

Date of slide: 4 September 2008

Acute HBV infection during pregnancy - outcomes

- 1st and 2nd trimester infection- no increased risk of congenital abnormality or spontaneous abortion
- 3rd trimester
  - Increased risk of premature labour
  - Increase risk of Mother to child transmission
- HBV DNA load can ↑ or ↓ under hormone influence

Hepatitis B exposure during pregnancy

- Check serology urgently
- Non immune (antiHBs <10 mIU/ml)
  - Maternal HBIG within 72 hours
  - Maternal HBV 3 doses (0, 1-2, 6 mo)
  - Vaccinate infant
- Immune
  - HBsAg neg = vaccinate infant
  - HBsAg pos = HBIG and vaccine to infant at birth

Mother to child transmission

- Antepartum or Intrauterine
  - Placental infection, leakage
- Intrapartum
  - Assumed to be most common >85% cases
  - Materno-fetal transfusion during labour
    - Repetitive uterine contractions
  - Contamination of mucous membranes or abraded skin
  - Ingestion of infected amniotic fluid or blood
    - HBsAg found in amniotic fluid and gastric contents of infants
- Post partum- horizontal

Risk factors for mother to child transmission

- Maternal factors
  - Acute HBV infection during 3rd trimester
  - e Ag positive status
  - High HBV DNA level (>10^8 genome equiv/ml)
  - Antepartum haemorrhage

- Vaccination failure
  - Failure to deliver HBIG and/or HB vax
  - prematurity

Timing of infection

Intrauterine

Acute HBV <10%

1st trimester	2nd trimester	3rd trimester
		50-70%

Intrapartum

delivery

- sAg/ eAg pos — 70-90%
- sAg pos only — 5-20%

Maternal HBV carriers

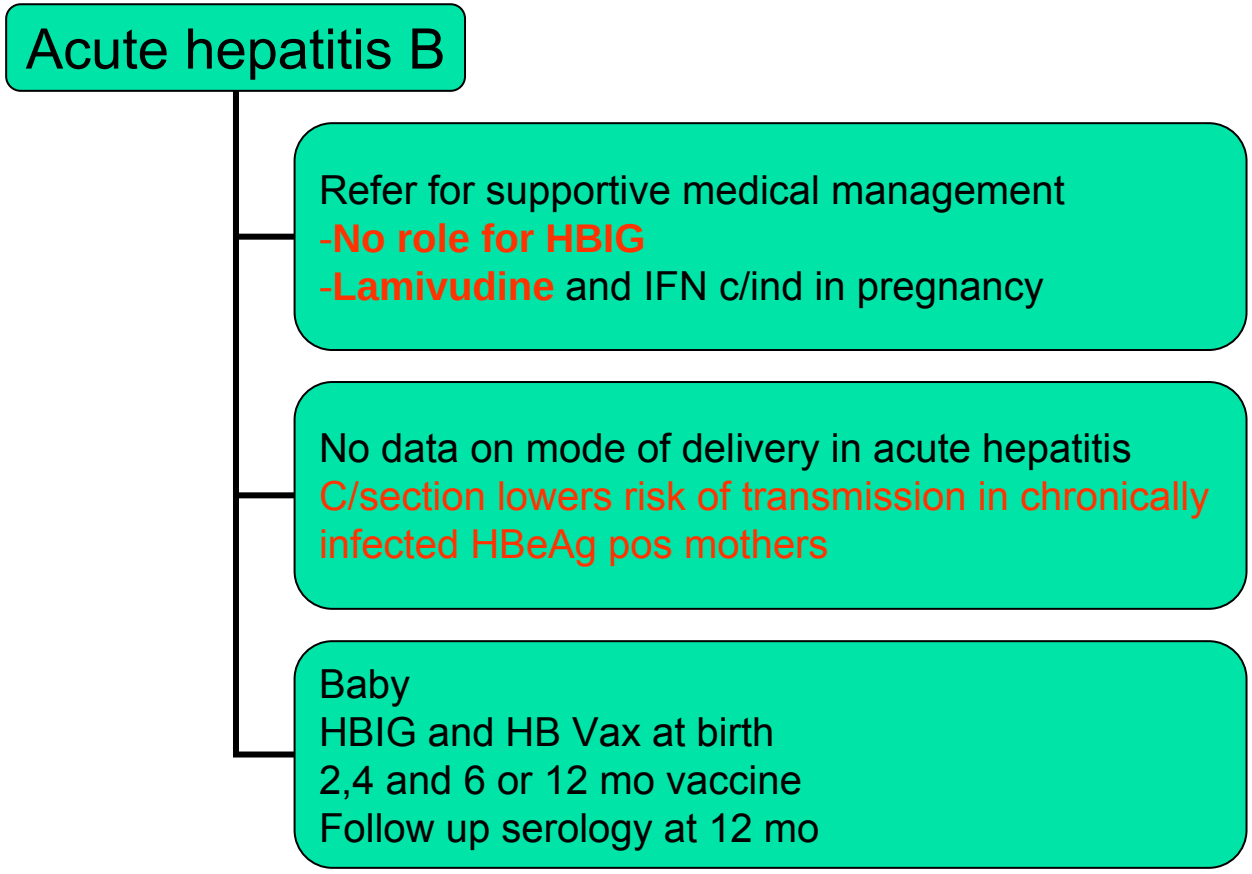
Site	HBsAg	HBV DNA	HBeAg
Amniotic fluid	26-32%	0-48%	
Cord Blood	20-50%	10-20% Lower in c/section	54-88%
Infant at birth prior to HBIG	9-22%	11%	6-70%

Wang J Med Virol 2003, Wang World J Gastro 2005, Yuan et al J Med Virol 2006, Ranger-Rogez ExpRevAntiInfectTherapy 2004
Towers et al. AmJ Obstet Gynae 2002

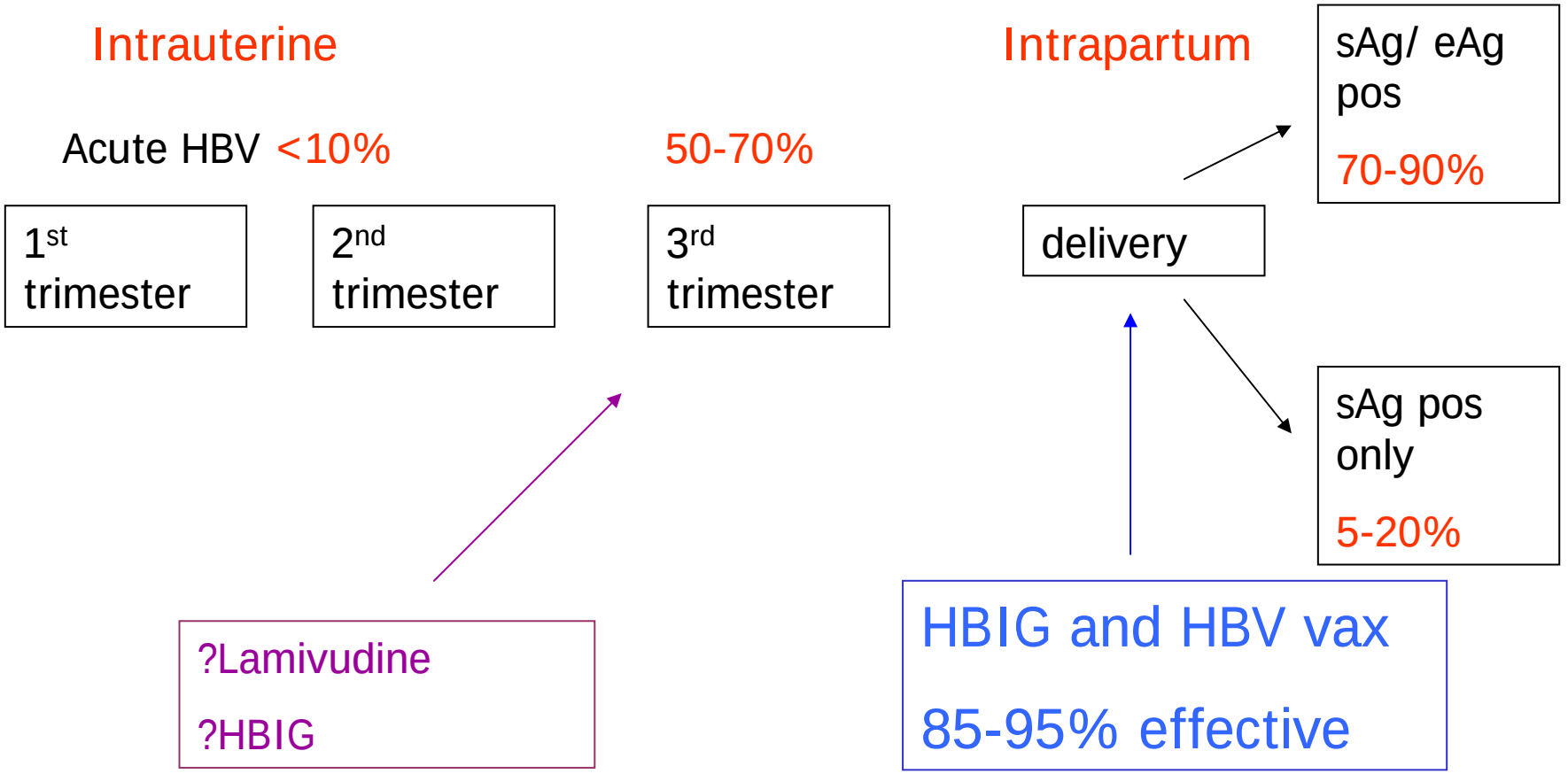
HBV markers at birth

Marker	Transplacental	Interpretation
antiHBe	Yes	Wanes by 1 yr
antiHBc -IgG IgM	Yes No	Wanes by 2 yr
HBsAg	Yes	Wane Pos >6mo = carrier
HBeAg	Yes	Wane Persists = carrier

Management of hepatitis B in pregnancy – ASID 2002



Timing of infection = timing of prevention



Perinatal HBV transmission in Sydney

- HBV DNA positive women (n=138)
- HBIG and HBV vax to infant
- At 9 months old
  - 4 infants HBsAg positive (3%)
  - All Maternal HBV DNA > 10^8 copies/ml

Wiseman et al MJA May 2009; 190: 489-491

Antenatal prevention - HBIG

- HBIG binds HBsAg ⟶ reduce infectivity
- High maternal load = high transmission risk
- HBIG crosses the placenta??
- 5 studies in China HBIG (n=1034) vs control
  - HBIG 200-400 IU at 28, 32, 36 weeks gestation
  - Reduction in maternal viral load during pregnancy
  - 4 studies = effective
    - reduced HbsAg positivity in infants born to carrier mothers at 6-12 mo follow up (n=4 studies)
  - One study showed **NO** effect at birth or 6 mo.
  - HBeAg positive mothers =more effective
- Nil studies outside of China

Antenatal prevention -Lamivudine

- HBV DNA load = higher risk of transmission
  - Lamivudine to reduce viral load
- 4 studies – Netherlands (n=2) and China (n=2) = 92 patients
- Lamivudine 100-150mg daily from week 28-36 gestation
- All maternal viral load decreased during pregnancy
- Reduced HBsAg and/or HBV DNA rates in infant
- Nil maternal or neonatal adverse effect
  - Lancet 1999 – nucleoside analogs and mitochondrial dysfunction
- More studies needed

1. Van Nunen et al J Hepat 2000.
2. Van Zonneveld J Viral Hepatitis 2003
3. Su et al World J Gastro 2004
4. Li et al World J Gastro 2003

Antenatal prevention -Lamivudine

- Single RCT in China (N=150)
- HbsAg positive and HBV DNA ~10^5 copies/ml
- 2 treatment arms
  - Lamivudine 100mg daily + Infants given HBIG + HBV vaccine
  - Placebo and Infant given HBIG and HBV vaccine
- Follow up
  - Infant weeks 0, 12, 28, 36, 52
  - Mother weeks pre delivery and 4,6,12 weeks post delivery
  - HBV serology and HBV DNA measured

1. Xu et al J Viral Hepatitis May 2009; 16: 94-103

Lamivudine efficacy - mother

	Lamivudine n=89 HBV DNA (MEq/ml)	Placebo n=61 HBV DNA (MEq/ml)
Baseline	2220	2692
Week 8	28.5	1955
During delivery	51.4	2168
Post partum		
Week 12	3035	2638

Lamivudine efficacy - infant

	Lamivudine + HBIG + HBV vax n=56	Placebo + HBIG + HBV vax n=59
HBsAg detectable		
Birth	30%	24%
Week 52	6%	12% (p=0.368)
Week 52 *ITT**	18%	39% (p=0.014)
HBV DNA detectable		
Birth	13%	41% (p=0.001)
Week 52	7%	15%

Lamivudine - summary

- Several studies – promising results in highly viraemic mothers
- Questions
  - ?? Critical HBV DNA level
  - ?? Safety
    - Antiretrovirals in HIV (PMTCT)
  - ?? When to commence
  - ?? When to cease
    - Hepatitis flares

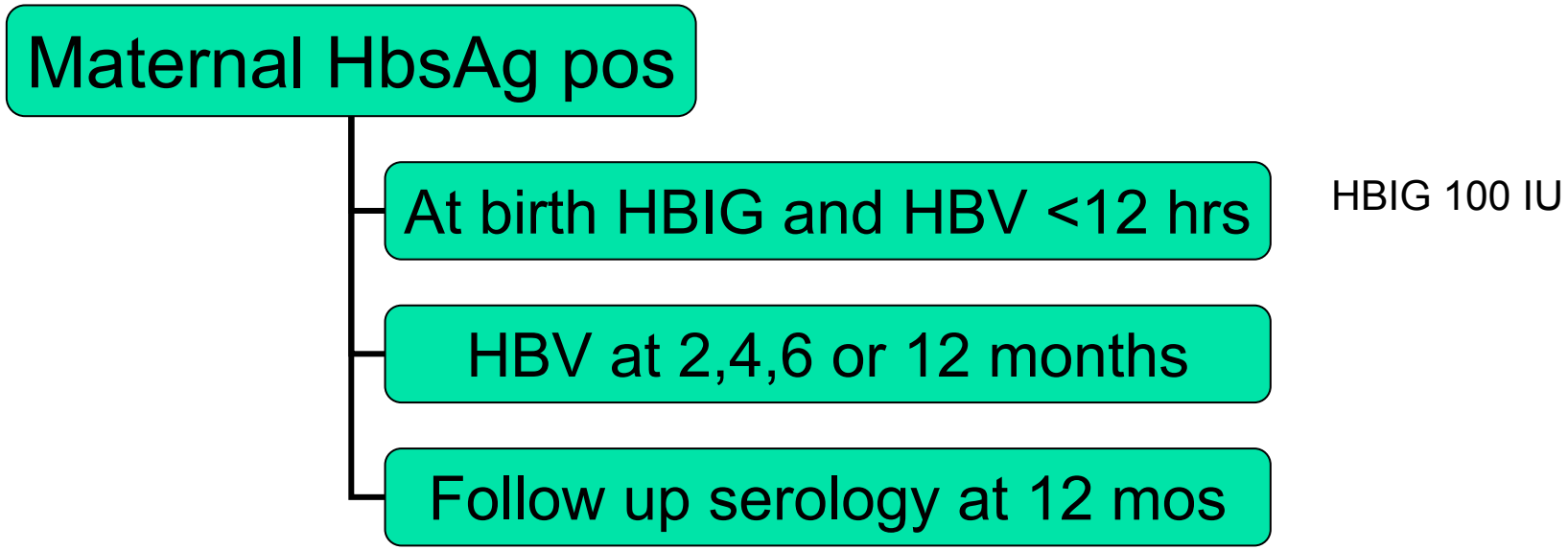
Management of HBV carrier women during pregnancy and labour

- Amniocentesis[1]
  - Theoretical inoculation of maternal blood into amniotic cavity
  - No increased risk of in utero infection with amnio – limited studies
- Fetal scalp electrodes
  - ? increase risk of infant exposure
  - Avoid if possible
- C/section – not routinely indicated

1. Towers et al. The presence of hepatitis B surface antigen and DNA in amniotic fluid and cord blood. Am J Obstet Gynecol 2002; 184: 1514-20

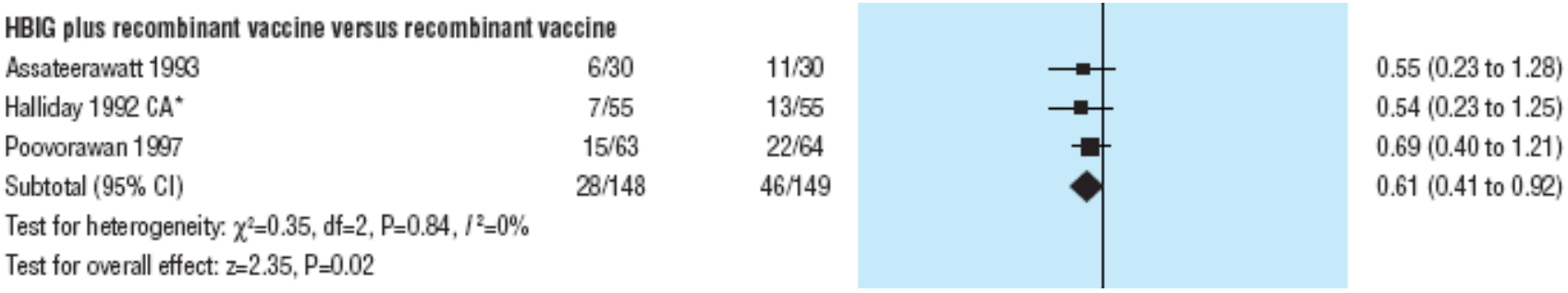
Management of infants of mothers with hepatitis B

- ASID 2002



Effectiveness of postnatal prophylaxis

- HBIG and HBV vax
  - 85-95% effective in preventing transmission from e Ag and s Ag positive mothers
- Vax alone
  - 70-95% effective
  - Possible that addition of HBIG may not be necessary in infants born to HBeAg negative mothers
- HBIG and HBV vs recombinant vaccine



Lee et al BMJ 2006 332; 328-336

Follow up of infants born to carrier mothers

- ACIP guidelines in US
  - HBsAg serology 3-12 months after completing the primary course.
    - > 9 mo. old as anti-HBs from HBIG may persist
    - Passive maternal HBcAb may persist until 24 mo old
  - If anti-HBs levels are adequate and HBsAg negative then children are considered to be protected
- UK guidelines “Green Book”
  - HBsAg at 1 yr old
- Aust immunisation Handbook
  - serology at 9-12 months in 9th edition?

Natural history of perinatal infection

- Immune tolerance
  - HbeAg pos, HBV DNA pos and normal ALT
  - Maternal HbeAg acts as a “tolerogen”
    - Unlike adult infection
  - Last 15-35 yrs – risk of transmission
- Immune clearance
  - ALT↑ “flares”, HBV DNA ↓
  - ? What causes transition
- Inactive carrier state → resolution

HbeAg clearance

- HBsAg clearance = 0.6% per year (cf adults 1.8%)
- HBeAg clearance
  - <2% per yr in under 3 yr olds
  - Increased clearance
    - with increasing age of acquisition
    - with horizontal infection
  - Decreased in Asia vs Mediterranean
  - Most cleared by 40 yrs old
  - Decreased with genotype C

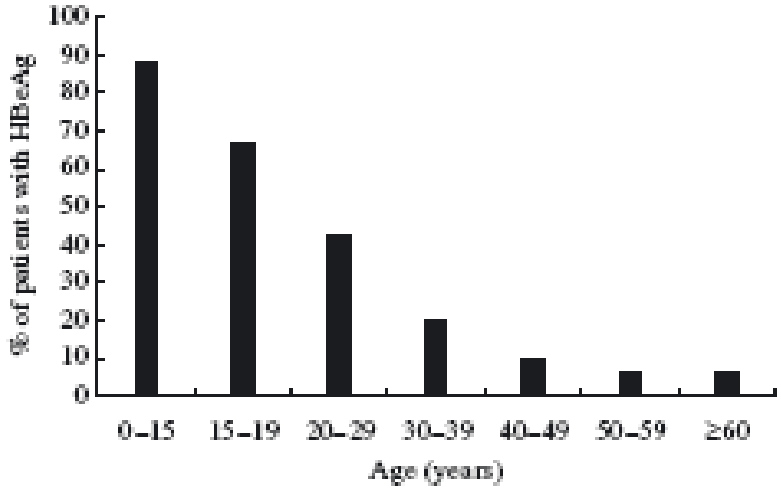


Fig. 1 Prevalence rate of serum HBeAg in asymptomatic HBsAg carriers in Taiwan. Data summarized from 415 children [19] and 10 431 adults [20].

Boxall et al. Arch Dis Child Fetal neonatal 2004; 89: 456-460

Bortolotti et al. Gastroneterology 1990; 99: 805-10 Chu et al. J Viral hepatitis 2007; 14: 147-52

Summary

- 5-10% HBsAg carriage
  - eAg positive or high HBV viral load mother
  - despite HBIG and HBV at birth
- Possibility of HBIG and Lamivudine during pregnancy
  - Limited studies
- Confirm seroconversion in children born to carrier mothers

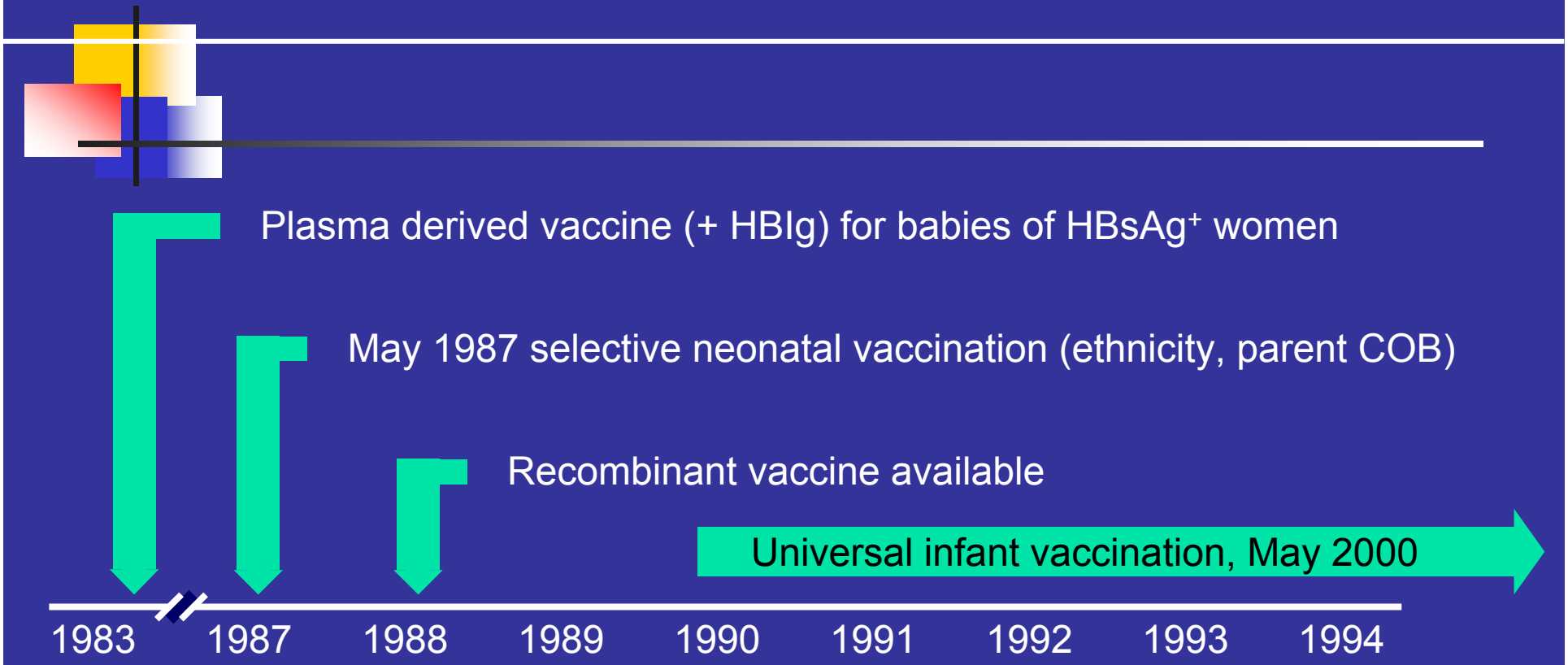
Longevity of immunity

- Immunity lasts until 2nd risk exposure period – adolescence

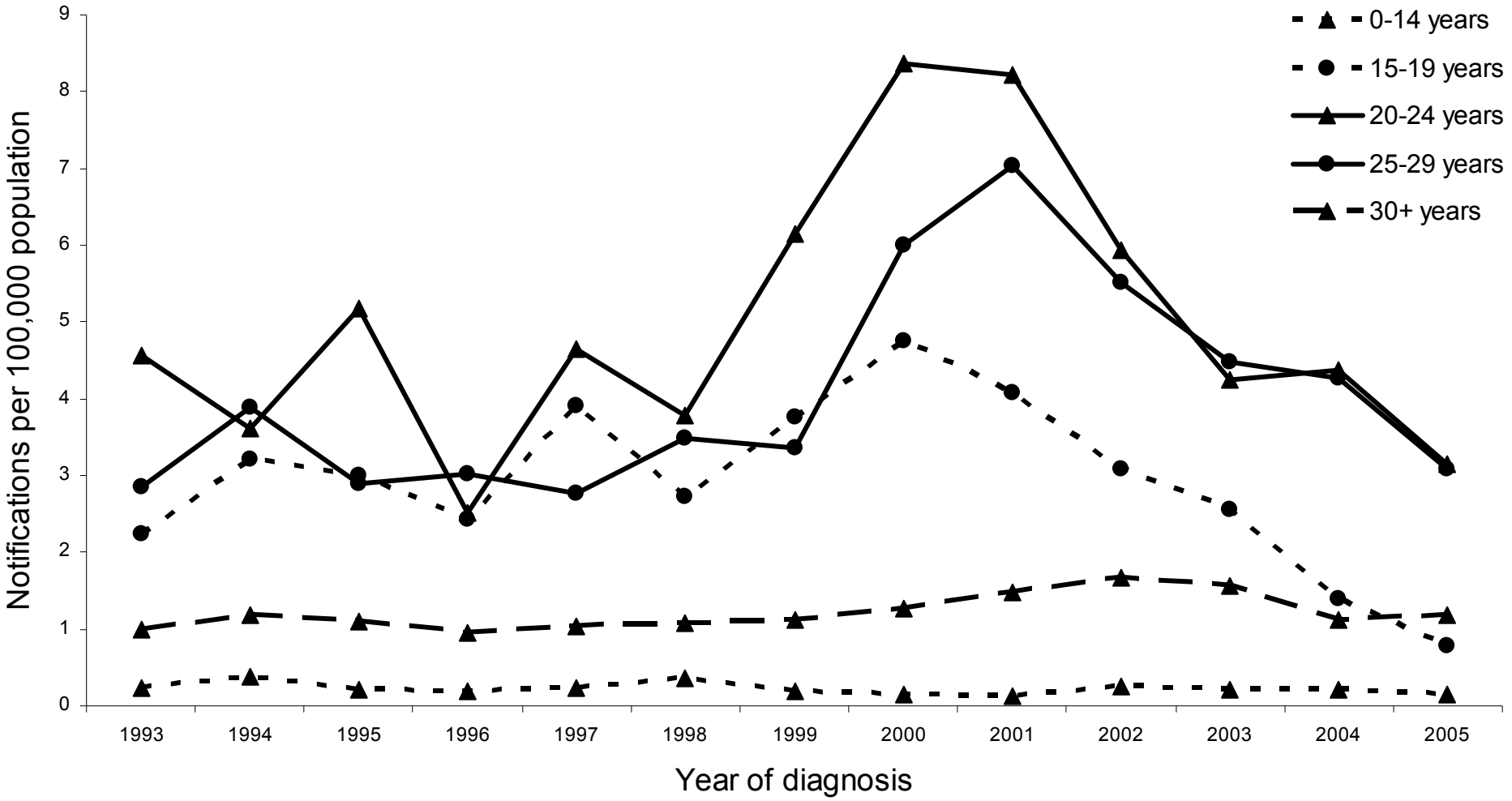
- European Consensus group
  - Hepatitis B booster doses NOT needed
  - Demonstration of immune memory – anamnestic responses
    - Many studies in high endemic countries

European consensus group on hepatitis B immunity. Lancet 2000

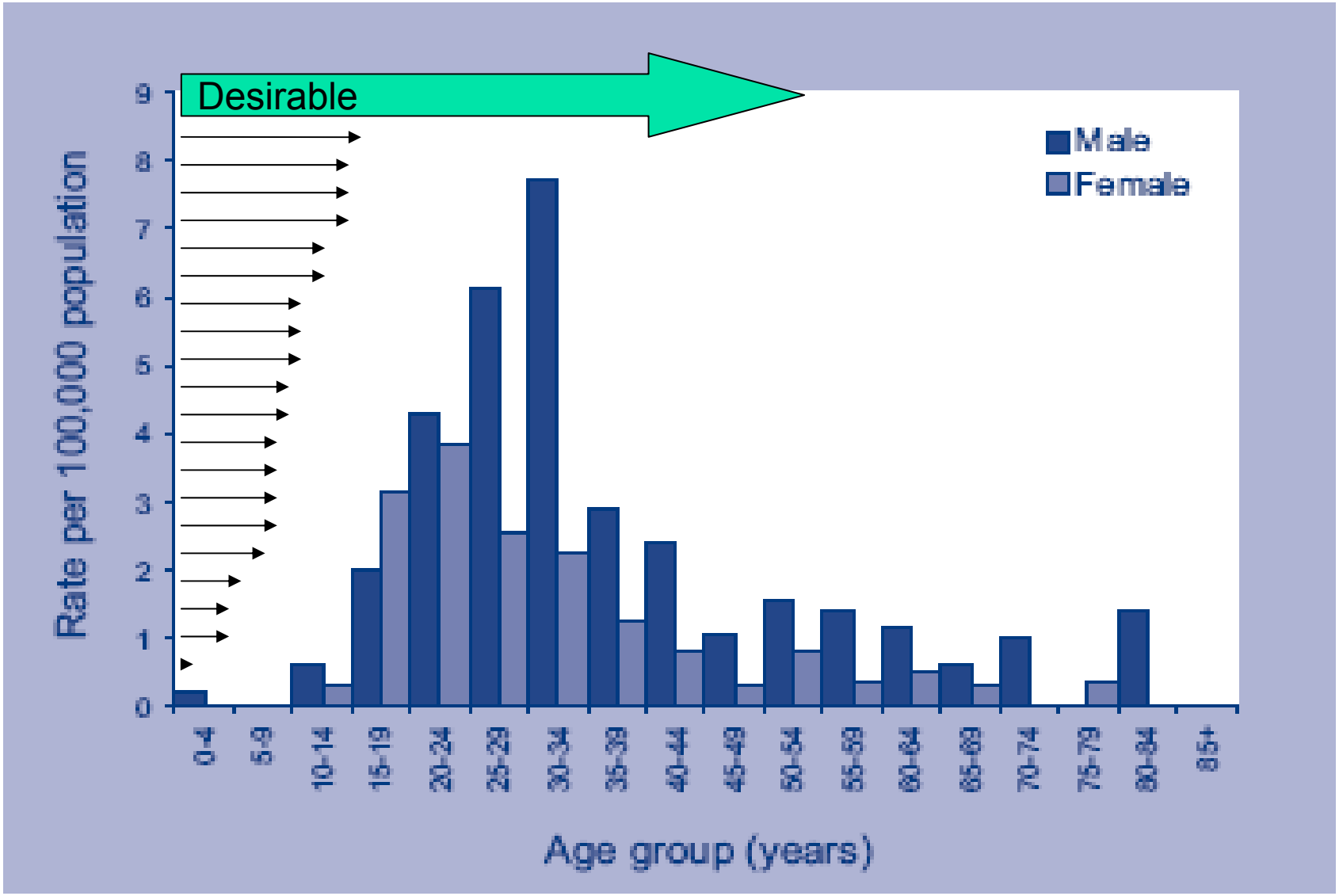
Hepatitis B vaccination of infants in Australia



Acute hepatitis B notification rates, Australia, 1993 to 2005 by age group



Notification rate for incident hepatitis B infections, Australia, 2005, by age group and sex

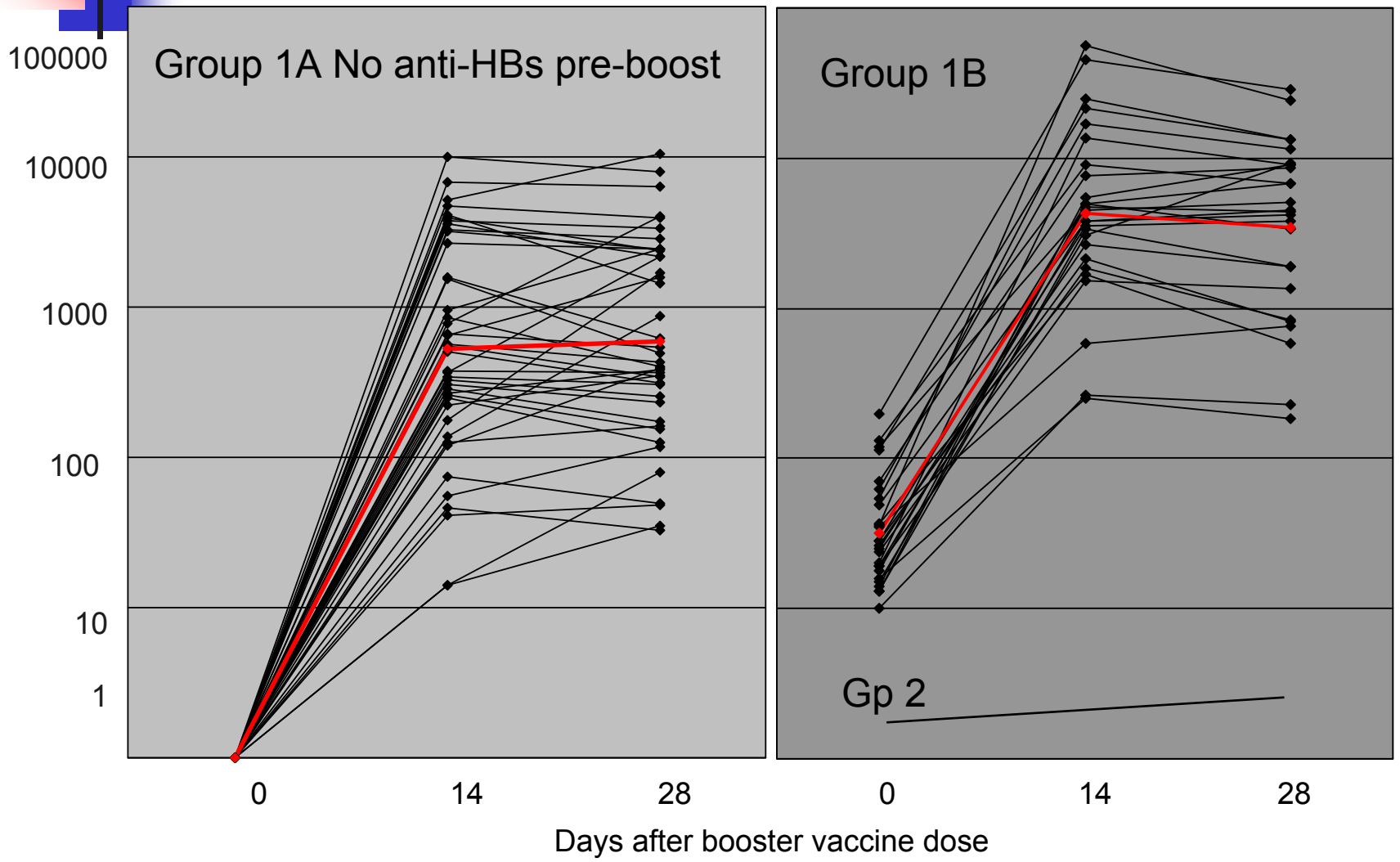


Miller M et al. Commun Dis Intell 2005;29:1

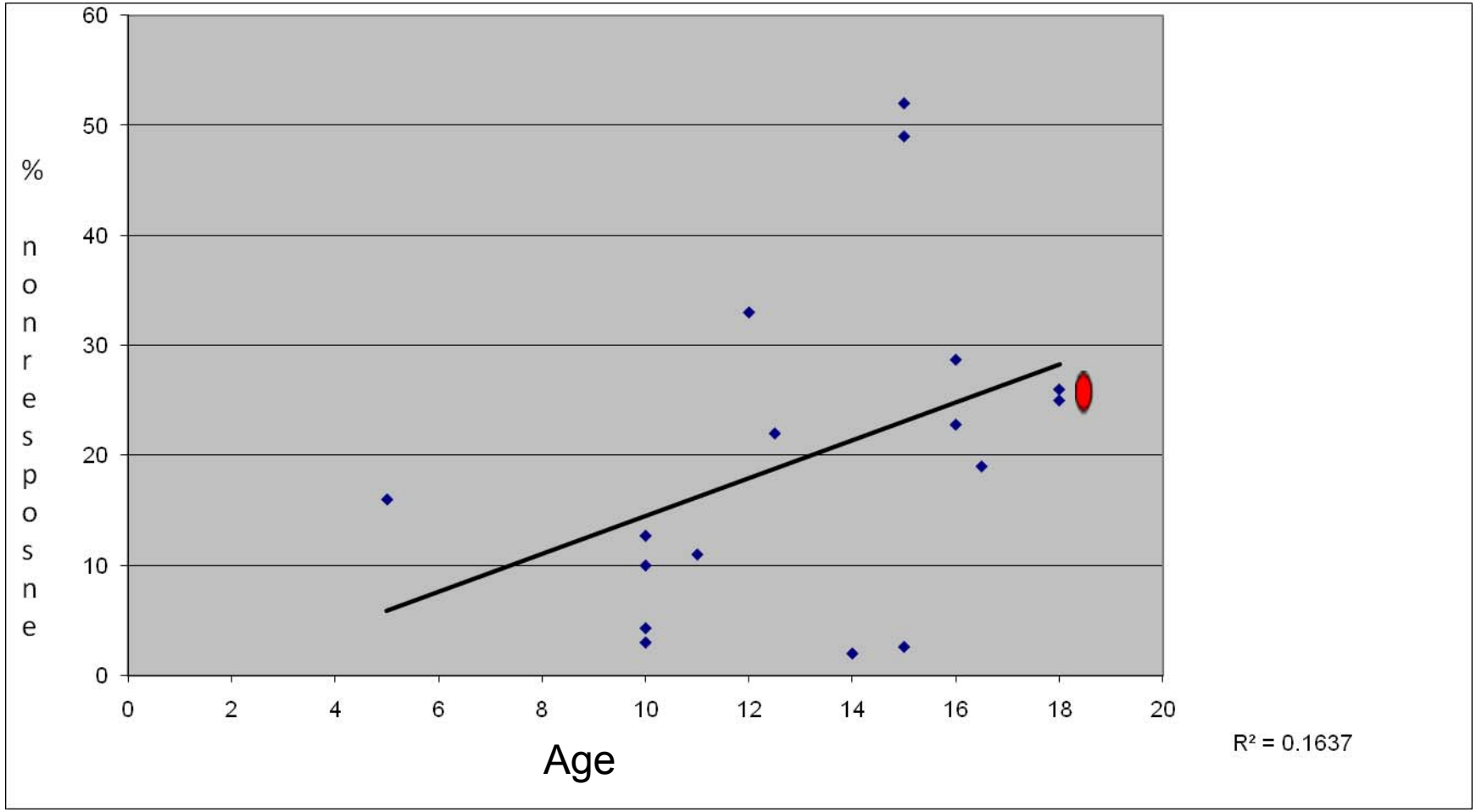
Long term persistence studies in Australia - >10 years

- South Western Sydney
  - Mean age 14.4 years
  - Born to “at risk” mothers
  - Anti-HBs
    - Baseline
    - 2 weeks
    - 4 weeks post booster

Anti-HBs (mIU/mL) following 10mcg H-B-Vax II™ booster

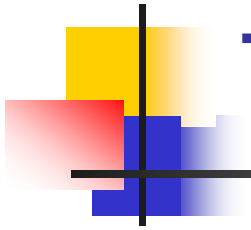


Non response to booster HBV vaccine according to time since infant vaccination in studies performed since 2002



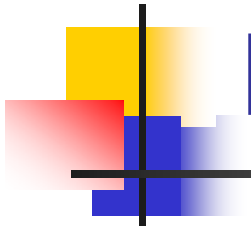
Summary

- Anti-HBs memory responses demonstrated
- Low rates of HBsAg detected in vaccinated cohorts
- Ongoing study



Thanks

- Professor Peter McIntyre
- Dr Leon Heron
- NCIRS staff



Back up

Summary

	Wood et al	Zanetti et al
Population	Australian (multi-ethnic)	Italian
Mother HBsAg	Negative	Negative
HB vaccine type	Undetermined	Engerix*
1^0 response	Undocumented	Undocumented
Subjects (n)	70	1212
Mean age (years)	14.4±1.08	10.9±0.30
Anti-HBs <10mIU/mL	42 (60%)	433 (36%)
Boosted	42‡	342§
Anamnestic response	41 (98%)	332 (97%)
GMT (95% CI) mIU/mL	524 (309-891)	886 (699-1122)

* Engerix (GSK) 10 mcg doses: 3, 5 & 11 months.
‡ H-B-Vax II (MSD) 10 mcg. Post boost blood sample at 14 days.
§ Engerix (GSK) 10 mcg. Post boost blood sample at 2 weeks.

Zanetti et al Lancet 2005;366:1379.

Longevity

- Booster response = anamnestic response
- Similar to other international studies

Does infant vaccination interfere with HBV clearance?

- Natural rate of HBeAg clearance
  - Hard to investigate as vax indicated for all
- Interest in using HB vax as therapy for chronic infection
- Rationale
  - T cell hypo-reactive in CHB and Th1↓ vs Th2
  - HB vax shown to reduce HBV DNA levels (Couillin et al
  - Can HB vax restore T cell reactivity?
    - Antigen presenting dendritic cell and HBsAg specific CD4 cell
  - Possibly in combination with IFN or Lamivudine
- No clear recommendation

Discussion

Vaccinated as infants

Boxall et al, England

Mother HBsAg	Positive		
HB vaccine type	Plasma derived*		
1^0 response	Documented (age >9m)		
Follow-up age (years)	14.5		
	HBIg† given	No HBIg	
Subjects‡ (n)	29	35	
Non-anamnestic response	8 (27%)	2 (6%)	p = 0.034

† 200 IU HBIg within 48 hours of birth.

* Manufacturer not reported 10 mcg doses: 0, 1, 2 & 6 months.

‡ Given booster of H-B-Vax II (Aventis Pasteur) 5 mcg. Post boost blood sample at 4 weeks.

Boxall et al J Infect Dis 2004;190:1264.

Risk of vertical transmission

- Acute hepatitis B
  - 1st or 2nd trimester – very low (<10%)
  - 3rd trimester or up to 2 months post partum = 50-70%

- HBsAg carrier
  - Mother s Ag and e Ag +ve = 70-90%
  - Mother s Ag + ve only = 5-20%

Timing of infection

- Timing of infection = Timing of preventive treatment
  - Intrapartum = HBIG and HBV vax at birth
    - Known to be effective (85-95%)
    - ??Breakthrough infections due to intrauterine infection
  - Intrauterine = Birth vaccination won't work
    - Other options including HBIG and Lamivudine during pregnancy
  - Postpartum = persistence of immunity becomes important

Intrauterine transmission

- Amniotic fluid – detection of HBsAg or HBV DNA
- Cord blood
  - Possible contamination with maternal blood
  - antiHBc crosses into infant – persists for up to 2 years
- Infant blood at birth
  - HBV marker detection at birth – does it indicate intrauterine infection?

Maternal HBV carriers

Site	HBsAg	HBV DNA	HBeAg
Amniotic fluid	26-32%	0-48%%	
Cord Blood	20-30%	10-20% Lower in c/section	54-88%

1. Towers et al. The presence of hepatitis B surface antigen and DNA in amniotic fluid and cord blood. Am J Obstet Gynecol 2002; 184: 1514-20
2. Milich et al. Is a function of the secreted HBeAg to induce immunologic tolerance in utero? Proc nat Acad Sciences 1990; 87: 6599-6603
3. Zhang et al. Mechanism of intrauterine infection of HBV. World J Gastro 2004; 10: 437-8

HBV markers at birth in infants born to carrier mothers

Study	HBsAg	HBV DNA	HBeAg
Wang et al (n=33 e Ag pos) 2003	9%	11% Pos. at 12 mo	70% Most neg. by 6 mo old
Yuan et al (n=251) 2006	20-22% Halved by 12 mo old		6-7%
Wang et al 2000 and 2005			50% - all neg. by 4 mo old
Xiao et al (n=152) 2007	14% Halved by 6 mo		

Definition of a carrier

- HBsAg positive for more than 6 months
- HBsAg positive at 9-12 post HBIG and HBV at birth
- Possible to clear HBeAg, HbsAg if detected at birth
- HBV DNA detected
- If measure HBV markers at birth
  - HBV DNA detected at birth = intrauterine infection
  - HOW TO INTERPRET?

Anti-HBs (mIU/mL) following 10mcg H-B-Vax II™* booster

Group 1A

Pre-booster

Subjects (n)	42
GMT (mIU/mL) (95% CI)	NA
Vaccine responders (n)	41

Day 14

GMT (mIU/mL)	524.0

Day 28

GMT (mIU/mL)	597.5

* Merck Sharp & Dohme; Preservative free formulation

Anti-HBs (mIU/mL) following 10mcg H-B-Vax II™* booster

	Group 1A	Group 1B
Pre-booster		
Subjects (n)	42	26
GMT (mIU/mL)	NA	32.3
Vaccine responders (n)	41	26
Day 14		
GMT (mIU/mL)	524.0	4313.0
Day 28		
GMT (mIU/mL)	597.5	3498.4

* Merck Sharp & Dohme; Preservative free formulation

Anti-HBs (mIU/mL) following 10mcg H-B-Vax II™* booster

	Group 1A	Group 1B	Unvaccinated Group 2
Pre-booster			
Subjects (n)	42	26	49
GMT (mIU/mL)	NA	32.3	NA
Vaccine responders (n)	41	26	2
Day 14			
GMT (mIU/mL)	524.0	4313.0	(11, 31)
Day 28			
GMT (mIU/mL)	597.5	3498.4	(17, <10)

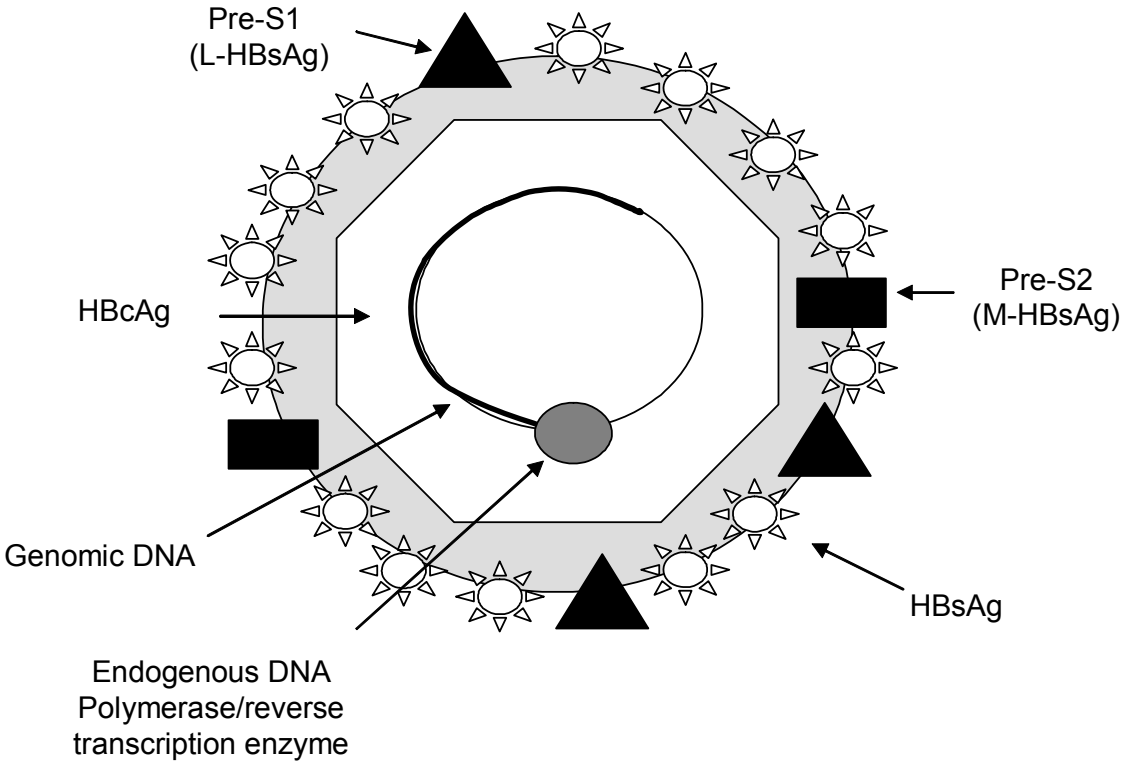
* Merck Sharp & Dohme; Preservative free formulation

HBeAg

HBsAg

HBV DNA

HBV Virion



ACUTE INFECTION

CHRONIC INFECTION

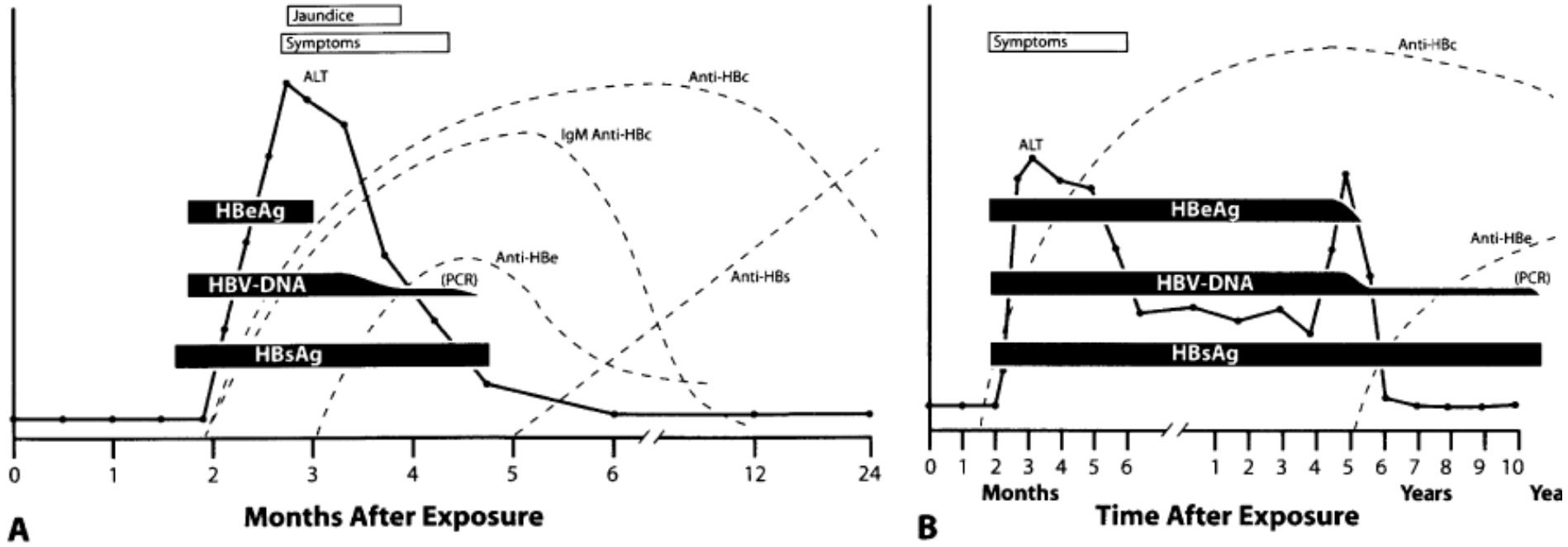


Fig. 2. Sequence of events after HBV infection. (*A*) Acute HBV infection with resolution. (*B*) Acute HBV infection progressing to chronic HBV infection. (*Fro*
Hoofnagle JH, DiBisceglie AM. Serologic diagnosis of acute and chronic viral hepatitis. Semin Liver Dis 1991;11:73–83; with permission.)