Are booster immunisations needed for lifelong hepatitis B immunity?

European Consensus Group on Hepatitis B immunity, following meeting in Florence in October 1998

"To date there are no data to support the need for booster doses of hepatitis B vaccine in immunocompetent individuals who have responded to a primary course"

Lancet 2000;355: 561-565

Groups traditionally considered for booster HB vaccination

- **Immunocompetent individuals**
  Adolescents (immunzed in infancy)
  Adults
- **Immunocompromised individuals**
  Haemodialysis
  Chronic renal failure/liver disease
- **High risk groups**
  Persons changing sexual partners frequently
  Intravenous drug users
  Haemophiliacs
  Mental institution residents
  Healthcare workers and others at occupational risk
  Travellers to endemic area

Groups considered for booster HB vaccination in new recommendation

- **Immunocompromised individuals**
  Haemodialysis
  Chronic renal failure/liver disease
  HIV positive

Lancet 2000:Vol.355: (561-565)

Four years after this recommendation, is there now further evidence to support or express caution over this viewpoint?

PROTECTION AGAINST HBV AMONG THOSE VACCINATED SUCCESSFULLY

Distinguish between protection against subclinical and breakthrough infection

- *Subclinical infection (benign)*

  Development of anti-HBc (antibodies to HB core antigen resulting from transient viraemia but without symptoms or disease)

- *Breakthrough infection*

  Development of HBsAg resulting in clincial disease

Do breakthrough infections among immunocompetent vaccinees occur among those who have responded satisfactory to a primary course?

DECLINE IN ANTI-HBs AMONG 79 MEDICAL STUDENTS GIVEN THREE DOSES OF ENGERIX B (0,1,6 month schedule)

Lineair regression analysis (plotting on a log scale) showed:

- Final titre at 5 years is proportional to the initial titre at 7 months
- By 5 years, the final titre is approximately about 5% of the initial one (e.g. If initial titre is 4,000 mIU/ml by 5 years, it has declined to 200 mIU/ml and by 10 years to ~ 10 mIU/ml)

Tilzey A.J. et al. Lancet 1994:1438-1439

IMMUNOLOGICAL MEMORY AND HEPATITIS B VIRUS

- During the primary response and following challenge by non-cytopathic viruses like hepatitis B, CTL responses are essential for their elimination

- CTL must re-circulate through peripheral organs

- Cytolytic effector functions are dependant upon, and driven by persisting antigen

Zinkernagel R. et al. Annul.Reg.Immunol. 1996;14:333-67

IMMUNE MEMORY

- Rapid (3-5 days) and effective anamnestic response despite low levels or loss of anti-HBs antibody via pool of memory B lymphocytes

- Strength is dependant on size of initial clonal burst following vaccination which is dependant on antigen content, including its strength and the presence of a highly repetitive structure

MECHANISTIC BASIS OF IMMUNE MEMORY

Complex interplay between:

- Memory B cells
- Memory T helper cells
- Memory CTL
- Ag/ab complex

EXPOSURE TO HEPATITIS B AMONG VACCINEES

If anti-HBs levels are low or undetectable, then

- Anamnestic anti-HBs response produced by specific memory B lymphocytes, will terminate viraemia which will be transient
- Anti HBc (core antibody) may develop and persist, but only occasionally
- Primed T-helper cell population will stimulate cytotoxic T cells from precursors and together with NK cells will recognise and eliminate HBV infected hepatocytes

DETECTION OF IMMUNE MEMORY: FOLLOW UP STUDIES AMONG HOSPITAL EMPLOYEES IN THE NETHERLANDS

No	Follow up	Anti-HBs < 10 mIU/ml	B cell memory by spot ELISA or anamnestic response after boosting
456	15 yrs	124 (30%)	124 (100%)

Boland G.J. Et al. Hepatology 1995; 22:325

T CELL LYMPHOCYTE PROLIFERATION TO RECOMBINANT HBsAg

Group	*n*	Anti-HBs Titer (IU/L)	Net Count (mean)	T cell proliferation positive	ConA stimulation (mean ± SD)	Tetanus+ diphtheria (mean±SD)
1	9	Unvaccinated	252	0/9 (0%)	6,100±29,058	19,075±13,688
2	12	≤ 10	2,810	7/12 (58%)	55,203±25,071	10,651±7,533
3	6	11-100	4,718	6/6 (100%)	35,273±33,140	19,448±16,171
4	13	>100	12,167	13/13 (100%)	40,668±20,695	21,266±17,025

Wang RX, Boland GJ, van Hattum J, de Gast GC, World J Gasteroenterol, 2004

CELL MEDIATED AND HUMORAL IMMUNE RESPONSES TO HB VACCINATION IN 118 INFANTS DELIVERED OF MOTHERS WITH HBeAg IN TAIWAN 10 YEARS POST-VACCINATION

Marker	Pre-booster	Post-booster (10 years)
HBsAg	0	-
Anti HBs < 10mIU/ml	39/118 (33%)	34/34 (100%)
T-cell LPR to HBsAg	30/64 (47%)	30/52 (58%)
IL-2 (T-cell stimulation by HBsAg)	48/59 (89%)	18/20 (90%)
IL-5 (T-cell stimulation by HBsAg)	47/47 (100%)	10/10 (100%)

Huang L-Min et al. Hepatology, 1999; 29: 954-959

FOLLOW UP STUDIES FOLLOWING HEPATITIS B VACCINATION IN NON-ENDEMIC COUNTRIES

Countries	No of subjects	Time since vaccination	≥ 10mIU/ml (%)	Anti-HBc	HBsAg	Clinical
USA (carrier mothers)	70	4-9	83	3	0	N/A
Belgian adults	40	8	93	0	0	0
NZ children	125	9	95	11	0	N/A
Italian infants	587	5	33-91	0-2	N/A	0
US HCW	985	6	85	N/A	N/A	N/A
Spanish children	462	6.5	85	9	0	0
TOTAL	2,269	4-9	33-95	24	0	0

Banatvala JE & Van Damme P, 2003

FOLLOW UP STUDIES FOLLOWING HEPATITIS B VACCINATION ENDEMIC COUNTRIES

Countries	No of Subjects	Time since vaccination	% ≥ 10mIU/ml	Anti HBc	HBsAg	Clinical	Comments
Alaska (adults and children)	1017-1497	7	74	8	0	0	3 of 8 initial response ≥ 10mIU/ml
Hong Kong (children)	63-101 63-101	5 5	87 84	0 0	0 0	0 0	
India (adults)	34	8-10	84	0	0	0	
Senegal (infants)	92	9-12	88	18	2	N/A	No difference in HBsAg between boosted & non-boosted. Increase antiHBc with time
Taiwan (neonates)	1357	7	77	25 (1.9%)	9 (0.6%)	N/A	
New Caledonia	527	10	84	49 (8.3%)	8 (1.3%)	N/A	
Gambia	~990	~ 14	63-100	25%	10	N/A	Different schedules include I/D, I/D+ IM & IM only 7 of 10 HBsAg positive were ≤ 10mIU/l post vaccination

Harpaz et al. 2001, Shih, Hsiang-Hung et al. 1999, Belioz-Arthaud et al. 2003, Whittle et al. 2002, Banatvala J & Van Damme P, 2003.

SIGNIFICANCE OF CORE ANTIBODIES TO HEPATITIS B (ANTI-HBc)

- In the absence of HBsAg, anti-HBc, is a marker of past infection often transient to HBV
- But could the apparently transient infection of hepatocytes result in long-term chronic liver disease?
- Could reactivation of HBV infection occur in immunocompromised patients (e.g. HIV)?

CAVEATS FOR INTERPRETING HEPATITIS B VACCINATION STUDIES FROM DEVELOPING COUNTRIES

- Maternal hepatitis B status for infant immunisation
- Dose and route of vaccination
- Immediate post-vaccination response usually not documented
- Other infections, particularly HIV
- Nutritional status

FURTHER STUDIES

- Long term follow-up studies to assess protection (including immunological memory) in adolescents and even later, following vaccination in infancy
- Above studies should include burden of disease from breakthrough infections
- Long term assessment, as above, for two-dose schedules (CDC recommends this for adolescents)
- DNA vaccines
- Role of escape mutants

TO BOOST OR NOT TO BOOST

Further studies in HBV endemic countries will determine whether susceptibility to persistant carriage of HBV increases with time

"In developing countries the benefit of a small increase in the long-term protection against viral replication must be compared with the cost and difficulties of a booster dose at school age"

Coursaget P, 1974

BOOSTER DOSES OF VACCINE

- Immunocompromised
- Vaccinees with $\leq$ 10mIU/ml after a full course of vaccination, measured 1-3 months post vaccination
- ? Vaccinees who were not tested post-vaccination for antiHBs, but at high risk of exposure
- Other categories?