Journal of Viral Hepatitis, 1997, 4, 221–230

Functional implications of hepatitis B surface antigen (HBsAg) in the T cells of chronic HBV carriers

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Received 29 August 1995; revised version accepted for publication 13 March 1997

SUMMARY. This study was undertaken to investigate the role of T-lymphocyte-derived soluble factors in the maintenance of the hepatitis B virus (HBV) chronic carrier state. Cell-free supernatants from the peripheral blood T lymphocytes of chronic HBV carriers were produced by incubating them for 48 h in tissue culture medium. These supernatants were added to *in vitro* hepatitis B s antibody (HBsAb)-producing cultures of peripheral blood mononuclear cells from hepatitis B surface antigen (HBsAg) vaccinees stimulated with HBsAg or pokeweed mitogen. T-cell supernatants from chronic carriers suppressed *in vitro* HBsAb antibody synthesis, whereas those from control subjects did not. This suppression was antigen specific as the supernatants did not suppress synthesis of total IgG or IgM. HBV viral sequences were demonstrable, by Southern and dot-blot hybridization, in the T cells secreting this factor. We also demonstrated the presence of HBsAg in T-cell supernatants derived from these cells. These results show that HBsAg of T-cell origin may have a role in suppressing HBsAb production. Our observations point to the role of HBsAg-specific cellular and humoral responses in favouring persistence of the chronic HBV carrier state.

Keywords: HBV DNA, hepatitis B surface antigen, *in vitro* HBsAb suppression, soluble suppressor factor, T-lymphocyte infection.

INTRODUCTION

Several host immune defects are known to contribute to the development and persistence of the chronic hepatitis B surface antigen (HBsAg) carrier state in hepatitis B virus (HBV) infection. Of these, the host's inability to mount a readily detectable hepatitis B 's' antibody (HBsAb) response is an important and consistent finding [1]. Several workers have shown that antibody production is suppressed by an antigen-specific suppressor factor [2–5]. In many viral infections, viral proteins may directly modulate cellular immunoregulatory functions; products of several viruses have been shown to inhibit the proliferative capacity of normal lymphocytes [6], as well as cytokine functions, by mimicking the structure of cytokine receptors. Examples of such phenomena include poxvirus-encoded tumor necrosis factor receptors [7] and interferon-γ receptors [8]. Herpes simplex virus-encoded proteins have also been shown to inhibit antigen presentation to CD8+ T cells [9].

In chronic HBV infection, the virus persists in an integrated state within the host for long periods. The presence of the virus has been shown in several types of cells that are involved in the host immune response [10–13]. We postulated that HBsAg produced from these cells into the local microenvironment might alter and influence host immune functions such as synthesis of HBsAb. As this possibility has not been previously investigated in HBV infection, we studied the effect of T-cell supernatants (TCS), from chronic HBV carriers, on *in vitro* HBsAb synthesis and its correlation with the presence of HBV DNA in T cells.

Abbreviations: HBsAb, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PBMC, peripheral blood mononuclear cells; PWM, pokeweed mitogen; TCS, T-cell supernatants.

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METHODS

Subjects

Twenty chronic HBV carriers were selected (18 men, two women; mean age ± SD = 37.5 ± 11.4 years) who were positive for HBsAg for more than one year from the time of initial testing. Of these carriers, 13 had chronic liver disease, fulfilling all diagnostic criteria, and the remaining seven were asymptomatic. For the purpose of this study, both groups were taken together as chronic HBV carriers. Cell-free supernatants were produced from the peripheral blood mononuclear cells (PBMC) of these carriers to test for suppressor activity. Twenty-nine healthy hospital staff (16 women, 13 men; mean age ± SD = 29 ± 6 years) who had recently completed their hepatitis B vaccination schedule were screened for HBsAb. They were seronegative for HBsAg by ELISA (Enzygnost-HBsAg micro-Hoechst, Behring, Germany), prior to vaccination, and had received three intramuscular 1 ml (20 µg) doses of hepatitis B vaccine (Hepavax-B, Korean Green Cross Corp., Seoul, Korea) at 0, 1 and 6 months. All the vaccinees had high titres of HBsAb (geometric mean titre 3397 IU l^{-1}) at 3–4 weeks following the third dose, as tested by a quantitative ELISA (Enzygnost anti-HBs, Combipack, Behring). Peripheral blood mononuclear cells from 11 of these vaccinees were used for *in vitro* HBsAb synthesis. Four healthy individuals, seronegative for HBV markers, were selected as unvaccinated controls.

Preparation of T-cell supernatants

Peripheral blood mononuclear cells from 20 carriers and four unvaccinated control subjects were separated from venous blood by density gradient sedimentation using Ficoll-Hypaque [14]. The final suspension was made in RPMI 1640 containing 10% fetal calf serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 25 mM hepes and antibiotics (100 U ml^{-1} penicillin, 100 µg ml^{-1} streptomycin) and was adjusted to a concentration of $10–15 \times 10^6$ cells ml^{-1}. The PBMCs were loaded on to a nylon wool column (Fenwal Laboratories, New Jersey, USA) packed in a plastic syringe and incubated for 1 h at 37°C. The column was then extensively washed to elute T cells, which were washed, counted and resuspended at a concentration of 5×10^6 cells ml^{-1} in RPMI. Cultures (1 ml) were incubated for 48 h, without any stimulant, in a flat-bottom 35 mm tissue culture dish. The supernatant was then harvested by centrifugation at 480 *g* for 10 min, filtered through 0.22 µm membranes and stored at –80°C.

Measurement of HBsAb in T-cell supernatants

We developed a solid-phase avidin-biotin ELISA for measuring HBsAb in TCS. In brief, flat-bottom 96-well microtitre plates (Nunc, Roskilde, Denmark) were coated with 100 µl of 0.5 µg ml^{-1} HBsAg (Pasteur Merieux, Cedex, France) in carbonate-bicarbonate buffer (pH 9.6). Plates were incubated and blocked with phosphate-buffered saline (PBS) containing 0.05% Tween 20 (PBS-T) and 2.5% bovine serum albumin (BSA). Neat and 1:2 diluted samples (100 µl) were added in duplicate wells. Following overnight incubation at 4°C, plates were washed and 100 µl of 1:15 000 biotinylated anti-human IgG (Sigma Chemical Co., St Louis, MO) antibody was added and incubated for 1.5 h. Plates were washed and 100 µl of 1:1000 diluted avidin peroxidase (Sigma) was added. Following a further incubation for 1 h at 37°C, the plates were washed and developed by adding 100 µl of freshly prepared substrate solution (10 mg orthophenylene diamine dihydrochloride, in phosphate-citrate buffer (pH 5.0) and 40 µl of 30% H_2O_2) and incubated at room temperature for 30 min in the dark. The reaction was stopped by adding sulphuric acid and absorbance was measured at 492 nm. A standard curve was produced by the inclusion, in the assay, of standard serum, containing known concentrations of HBsAb antibody (WHO first reference preparation, 1977). The antibody levels were expressed as mIU ml^{-1} of culture supernatants.

Measurement of total immunoglobulins (IgG and IgM) in T-cell supernatants

A solid-phase sandwich ELISA was standardized as described by Lane *et al.* [15] with minor modifications. Flat-bottom microtitre plates were coated with 100 µl of rabbit anti-human IgG or IgM (10 µg ml^{-1}) diluted in carbonate-bicarbonate buffer (pH 9.6) and were incubated overnight at 4°C. Plates were blocked with 2.5% BSA and 100 µl of the sample was added in duplicate to the wells. The plates were incubated at 4°C overnight and 100 µl of a 1:1000 dilution of heavy-chain specific rabbit anti-human IgG or IgM

conjugated to horse-radish peroxidase was added. After incubation for 1.5 h, plates were washed and colour was developed as described above for the HBsAb ELISA. Culture supernatants were tested at 1:10, 1:100 and 1:1000 dilutions and the concentrations of IgG and IgM in test samples were determined from the standard curve, which was plotted using known standard IgG and IgM concentrations (1000 ng ml^{-1} to 0.1 ng ml^{-1}); results were expressed as ng ml^{-1}.

Standardization of in vitro *antibody production*

To determine the optimum conditions for maximal *in vitro* antibody production, pilot experiments were performed to standardize the optimum time of bleeding after the last dose of the vaccination schedule and the optimal dose and conditions of the stimulatory agents. Normal healthy vaccinees were bled 2, 3 and 4 weeks after the third dose of vaccination. Their PBMC were cultured in parallel for 12 days either without stimulant or with the following stimulants: pokeweed mitogen (PWM), HBsAg or PWM + HBsAg. The supernatants were assayed for their HBsAb, total IgG and total IgM titres. Spontaneous HBsAb synthesis was evident in the week 2 samples and became undetectable in the week 3 and week 4 samples. The mitogen-induced HBsAb response was maximal at week 2, whereas the antigen-induced responses (HBsAg alone and mitogen + HBsAg) were maximal at week 3. HBsAb production declined by week 4, irrespective of the stimulant; therefore, the third week following vaccination was selected as the optimal time for collecting PBMC from vaccinees for *in vitro* HBsAb production.

Assays were set up at a concentration of 2.5×10^6 cells ml^{-1}, with or without stimulating agents. After incubation for 3 days at 37°C in 5% CO_2 and 95% air, under humidified atmosphere, cells were washed three times with RPMI to remove stimulants and resuspended in RPMI, without any stimulant, for another 9 days. The culture supernatants were harvested, passed through a 0.22 μm filter and stored at –40°C.

HBsAb was not detectable in the supernatants of stimulated cultures collected 1 day after stimulant removal, i.e. day 4 of the 12-day culture. This suggested that the HBsAb detected in the day 12 supernatant was caused by *de novo* antibody production rather than a carryover of serum cytophilic HBsAb. The stimulated cultures had a significantly higher level of HBsAb synthesis than the medium controls (Table 1). The antibody levels in cultures with each of the three stimulants were comparable. Therefore, suppression experiments were carried out using all three stimulants. Varying doses of HBsAg (100–1 ng l^{-1}) were tested and maximal HBsAb synthesis was seen with 10 ng ml^{-1} antigen, which was taken as the optimal dose for further experiments. Stimulation with varying doses of PWM (2000–250 ng ml^{-1}) showed that the HBsAb response was maximal at a dose of 2000 ng ml^{-1} and no HBsAb was detected at 250 ng ml^{-1}. For stimulation with PWM + HBsAg, various combinations of submitogenic doses of PWM (250–10 ng ml^{-1}) and stimulatory doses of HBsAg (2000–10 ng ml^{-1}) were tested and the maximal HBsAb response was found at a combination of 50 ng ml^{-1} PWM + 10 ng ml^{-1} HBsAg.

Table 1 *In vitro* HBsAb synthesis on stimulation with PWM, HBsAg and HBsAg + PWM as estimated by biotin-avidin ELISA

Stimulant	Dose (ng ml^{-1})	*n*	HBsAb* (mIU ml^{-1})	*P*†
Medium	–	10	293 ± 143	
PWM	2000	10	1130 ± 224	<0.005
Medium	–	7	257 ± 166	
HBsAg	10	7	1307 ± 324	<0.01
Medium	–	12	541 ± 143	
PWM + HBsAg	50 + 10	12	1351 ± 204	<0.005

* Values are expressed as mean + SEM.
† Wilcoxon's rank sum test.
HBsAb, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; PWM, pokeweed mitogen.

In vitro *HBsAb suppression experiments*

Parallel HBsAb suppression assays were set up by adding 100 μl of each T-cell supernatant (1:10 dilution) to *in vitro* antibody-producing cultures stimulated with HBsAg alone, PWM alone or HBsAg + PWM. Control cultures were set up simultaneously without addition of T-cell supernatants (TCS) but with medium alone or with stimulant alone. Specific HBsAb and total IgG and IgM were estimated in the culture supernatants.

Detection of HBV DNA by Southern and dot-blot hybridization

Genomic DNA from each sample was prepared from 5×10^6 T cells by the standard phenol:chloroform extraction procedure [16]. A 20 µg sample of the DNA was digested with *Eco*RI (New England Biolabs, Beverly, USA) and electrophoresed (0.7% agarose gel) at 0.75 V cm^{-1} for 16 h. The DNA was transferred to nitrocellulose membrane and the membrane was baked in a vacuum oven at 80°C for 2 h. Linearized HBV genome (HBV:adw: ATCC No: 45028) was labelled with [α-^{32}P]dCTP using a nick-translation kit (5×10^8 Ci $mmol^{-1}$) (Boehringer Mannheim, Mannheim, Germany). The membranes were prehybridized (6×SSC, 5× Denhardt's, 0.5% SDS and 100 µg ml^{-1} denatured salmon-sperm DNA) for 6 h at 68°C and hybridized with fresh buffer containing radiolabelled probe for another 48 h at 68°C. The membranes were washed in approximately 400 ml of 2×SSC and 0.5% SDS for 5 min at room temperature followed by 2×SSC and 0.1% SDS for 20 min and finally with 0.1×SSC and 0.5% SDS at 68°C for 10 min, briefly washed with 0.1% SSC and exposed for 48 h at –80°C using Kodak XAR-2 film.

A 10 µg sample of DNA, extracted from some T cells, was also blotted onto membranes (Schleicher & Schuell, Germany) using a microfiltration unit (Biorad, CA, USA). The membranes were baked for 2 h at 80°C in a vacuum oven. The membranes were then prehybridized for 1 h and hybridized with a linearized HBV probe, labelled using the DIG-DNA labelling kit (Boehringer Mannheim), for 16 h at 68°C in a water bath and washed twice for 5 min in large volume of 2×SSC, 0.1% SSC at room temperature. This was followed by two washes of 15 min in 0.1×SSC, 0.1% SDS at 68°C with constant agitation. The blots were developed using the DIG-DNA detection kit (Boehringer Mannheim).

Electrophoresis and Western blotting of TCS

T-cell supernatants were resuspended in 4× sample loading buffer and boiled for 1 min. The suspension was electrophoresed by SDS–PAGE (12.5%) at 30 mA and electrophoretically transferred to polyvinylidene difluoride (PVDF) membranes. The molecular weights were marked using a lead pencil after staining with Ponceau-S. The blots were blocked with 2.5% BSA followed by incubation with HBsAb. The membranes were developed with a streptavidin-biotin system using DAB (diaminobenzidine) as substrate.

RESULTS

Effect of TCS on in vitro *HBsAg production*

We studied the effect of TCS from 20 carriers and four unvaccinated control subjects on PWM and antigen-stimulated HBsAb production (Table 2). HBsAb synthesis was suppressed only by the TCS of chronic HBV carriers. Suppression was observed in cultures stimulated with PWM alone, with HBsAg alone or with a combination of HBsAg + PWM. Of the eight TCS added to PWM-stimulated cultures, all suppressed HBsAb synthesis and the suppression ranged from 25–100% (median 79%). Of the five TCS tested on HBsAg-stimulated cultures, four showed suppression ranging from 94–100% (median 100%), while one (C15) failed to show suppression. Of the 17 TCS tested on PWM + HBsAg-stimulated cultures, 15 showed suppression, ranging from 22–100% (median 94%), while TCS from two carriers, C15 and C20, did not suppress HBsAb synthesis. The TCS from carriers C4, C5, C6, C7, C12 and C16 also caused the suppression of HBsAb synthesis, by PBMC, of two different vaccinees (Table 2). A TCS, which did not suppress the PWM + HBsAg-stimulated synthesis (C15) was unable to suppress, even in cultures stimulated with HBsAg alone. Thus, 90% (18/20) of TCS from chronic HBV carriers showed suppression of HBsAb production.

When PBMC were incubated with TCS alone for 8 h, the subsequent addition of stimulants could not reverse the suppression; suppression seen with three TCS tested was 27%, 40% and 88%. However, when cells were activated with stimulants, the subsequent addition of TCS did not suppress HBsAb synthesis (Fig. 1).

The per cent viability of lymphocytes in cultures at the end of the 12-day period was as follows (carrier no., viability on addition of TCS, suppression): C1, 48%, 99%; C3, 60%, 75%; C6, 57%, 25%. Addition of TCS from an unvaccinated control subject (N1) led to 49% lymphocyte viability with no HBsAb suppression.

Effect of TCS on in vitro *immunoglobulin synthesis*

Total immunoglobulin synthesis (IgG and IgM) was significantly increased on stimulation with PWM + HBsAg, PWM and HBsAg. Total IgG synthesis was greater than total IgM synthesis in cultures stimu-

Table 2 Effect of T-cell supernatants (TCS) on suppression of *in vitro* production of antibody to hepatitis B surface antigen (HBsAb) and correlation with the presence of HBV DNA in T cells and hepatitis B surface antigen (HBsAg) in the TCS

	Suppression (%)					
			PWM + HBsAg			
TCS	PWM	HBsAg	(Experiment 1)	(Experiment 2)	HBV DNA in T cells	HBsAg in TCS
C1	84	ND	90	ND	Positive	Positive
C2	96	ND	96	ND	Positive	Positive
C3	40	ND	94	ND	Positive	Positive
C4	100	ND	90	100	Positive	Positive
C5	ND	ND	96	100	Positive	Positive
C6	ND	ND	94	40	Positive	Positive
C7	ND	ND	100	31	Positive	Positive
C8	ND	ND	22	ND	Positive	Positive
C9	ND	100	100	ND	Positive	Positive
C10	ND	ND	100	ND	Positive	Positive
C11	ND	ND	100	ND	Positive	Positive
C12	ND	100	50	81	ND	Positive
C13	ND	ND	66	ND	ND	Positive
C14	25	ND	22	ND	ND	Positive
C15	ND	NS	NS	ND	Negative	ND
C16	75	ND	40	89	ND	Positive
C17	75	94	ND	ND	ND	Positive
C18	ND	100	ND	ND	ND	Positive
C19	100	ND	ND	ND	Positive	Positive
C20	ND	ND	NS	ND	Negative	ND
N1	NS	ND	NS	ND	Negative	Negative
N2	NS	ND	NS	ND	Negative	Negative
N3	ND	NS	ND	ND	Negative	Negative
N4	ND	NS	ND	ND	Negative	Negative

C1 to C20 represent TCS from chronic carriers; N1 to N4 are TCS from normal unvaccinated control individuals. The values given are per cent suppression of HBsAb synthesis. NS, non-significant suppression; ND, not done; PWM, pokeweed mitogen. Concentrations of stimulants (ng ml^{-1}): PWM, 2000; HBsAg, 10; PWM + HBsAg, 50 + 10. Experiments 1 and 2 indicate retesting of TCS on PBMC from different vaccinees.

lated with PWM + HBsAg and HBsAg alone, whereas the synthesis of total IgM was greater than IgG in cultures stimulated with PWM alone (Table 3).

For purposes of comparison, total IgG synthesis upon stimulation with PWM + HBsAg was considered to be 100% (235 ng ml^{-1}). T-cell supernatants from four carriers did not show any suppression of total IgG production. On the contrary, addition of TCS from carriers C7, C16 and C12 enhanced IgG synthesis by 125%, 302% and 263% (295, 710 and 620 ng ml^{-1} respectively); only TCS from one carrier (C13) had no effect on IgG synthesis (230 ng ml^{-1}). Total IgM synthesis by PWM + HBsAg (23 ng ml^{-1}) was not suppressed by any of the four TCS tested. Enhancement of IgM synthesis over the PWM + HBsAg-stimulated cultures was as follows: C7, 43 ng ml^{-1}, 186%; C13, 40 ng ml^{-1}, 173%; C16, 33 ng ml^{-1}, 143%; and C12, 26 ng ml^{-1}, 113%. This enhancement was seen consistently even on testing with different vaccinees.

HBV viral sequences in T lymphocytes

Hepatitis B virus sequences were demonstrable in T cells of 12 of 14 carriers, either by Southern blot (5/6) or dot-blot (7/8) analysis. The T-cell DNA from two controls (N3 and N4) was also negative for HBV

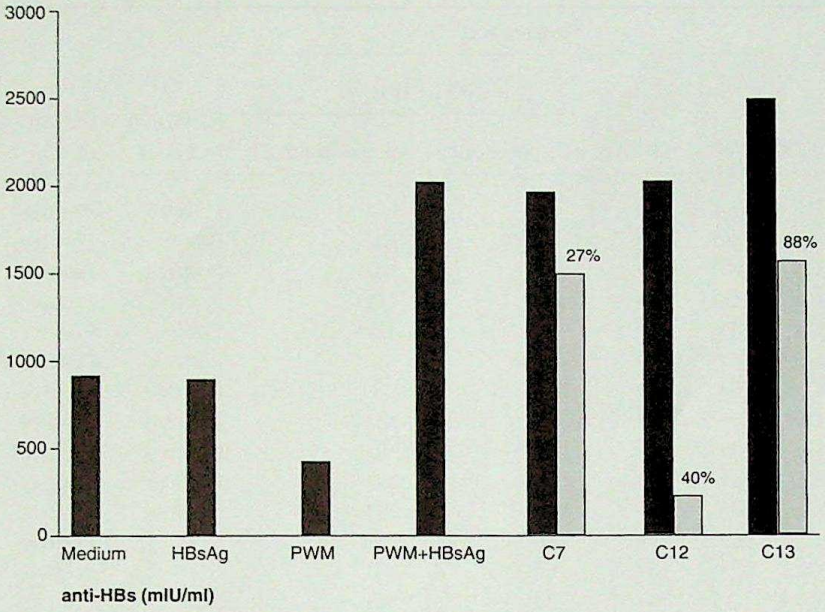

Fig. 1 Kinetics of *in vitro* antibody suppression. Experiment 1: the cultures were incubated for the first 8 h with stimulants (PWM + HBsAg) and later with a 1:10 dilution of TCS. Experiment 2: the cultures were incubated for the first 8 h with a 1:10 dilution of TCS and later with the stimulants (PWM + HBsAg). The cultures were washed on day 3 and incubated for a further 9 days. The HBsAb in the culture supernatant was estimated by Biotin-Avidin ELISA and the results were expressed as mIU ml^{-1}. HBsAg (10 ng ml^{-1}), PWM (50 ng ml^{-1}), HBsAg + PWM (10 ng ml^{-1} + 50 ng ml^{-1}) were used as stimulants. ■, experiment 1; □, experiment 2.

sequences. DNA from T cells of five chronic carriers and two control individuals, analysed by Southern hybridization (Fig. 2 a & b), showed the presence of HBV DNA sequences only in the five carriers. DNA from carrier C1 showed a band at 6.5 kb and DNA from carrier C18 showed bands at 11 kb, 4 kb and 3.2 kb; DNA from carriers C7, C8 and C9 showed a 3.2 kb band. No signals were observed in the two DNA samples from normal T lymphocytes (N1 and N2). The non-specific radioactive signal in N2 at 9.4 kb was not observed after an extra high-stringency wash of the membrane. Genomic DNA from all T cells, except from C15, were positive for HBV viral sequences as shown by dot-blot hybridization (Fig. 2c). The presence of viral sequences was considered to correlate with suppressor activity because TCS of two chronic carriers (C15 and C20), whose T cells did not have HBV DNA, also failed to show suppressor activity. Of the 18 TCS that showed suppressor activity, six were not tested for HBV DNA. Unvaccinated control subjects had neither HBV DNA nor suppressor activity (Table 2).

Hepatitis B surface antigen in TCS

The TCS from the carriers showing HBsAb suppression were further analysed, for HBsAg, by SDS–PAGE and Western blotting (Fig. 3). The HBsAg band at 43×10^3 MW was seen in all the 18 supernatants tested. No band was seen in TCS from the four unvaccinated control subjects.

Table 3 *In vitro* total IgG and IgM synthesis by peripheral blood mononuclear cells, of vaccinees, on stimulation, as estimated by ELISA

Stimulant	*n*	IgG* (ng ml^{-1})	$P^{\dagger}$	IgM* (ng ml^{-1})	$P^{\dagger}$
Medium	8	6 ± 3		15 ± 5	
PWM + HBsAg	8	553 ± 246	<0.05	152 ± 46	<0.01
PWM	8	126 ± 26	<0.0005	449 ± 164	<0.01
HBsAg	5	500 ± 190	<0.05	170 ± 63	<0.01

* Mean ± SEM.
† Wilcoxon's rank sum test.
HBsAg; hepatitis B surface antigen; PWM, pokeweed mitogen.

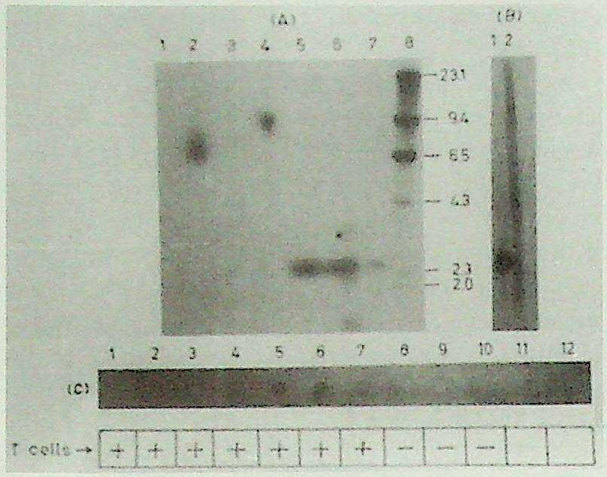

Fig. 2 Southern blot analysis of T-cell DNA from HBV carriers. (a) Southern blot analysis. Lane 1, PBR322 vector; lane 2, DNA from C1; lanes 3 & 4, DNA from N1 and N2; lanes 5–7, DNA from C7, C8 and C9; lane 8, molecular weight marker (λ *Eco*RI digest). (b) Southern blot analysis. Lane 1, DNA extracted from HBsAg-positive serum; lane 2, DNA from C19. (c) Dot-blot hybridization analysis of genomic DNA from T cells for HBV DNA sequences. Dots 1–10 correspond, respectively, to the DNA from C2, C3, C4, C5, C6, C10, C11, C15, N3 and N4.

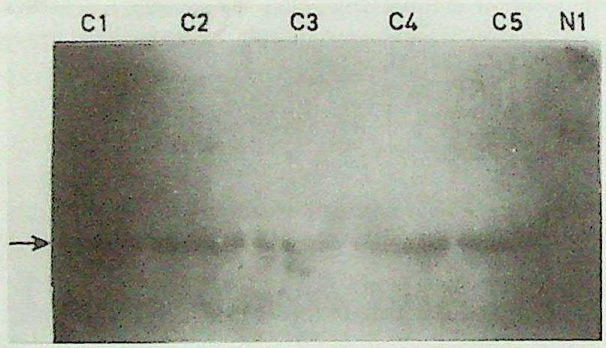

Fig. 3 Western blot analysis of TCS for HBsAg. The 43×10^3 MW HBsAg band from C1, C2, C3, C4, C5 and N1 is shown.

DISCUSSION

Our results demonstrate, for the first time, that HBsAg secreted by T cells of chronic HBV carriers is capable of suppressing *in vitro* HBsAb production, and that these T cells are infected with HBV and then infected with transcriptionally active HBV.

As PBMC from normal individuals are not capable of producing HBsAb, we used, in our experiments, PBMC from fully vaccinated immune individuals who had high titres of *in vivo* HBsAb; we stimulated these PBMC with either PWM, pure HBsAg, or a combination of both, to produce HBsAb *in vitro* in a 12-day culture system as previously described [17–19]. The optimal combination of HBsAg and submitogenic doses of PWM, which could induce high levels of HBsAb, was selected after a series of standardization experiments. Although we found that HBsAb production on stimulation with HBsAg + PWM was similar to that of HBsAg alone or PWM (mitogenic dose) alone, we conducted further studies using all three stimulants to look for any variation in the pattern of suppression of antigen-stimulated and mitogen-stimulated antibody production.

T cells of carriers have been shown previously to suppress directly *in vitro* HBsAb synthesis [1], as well as polyclonal IgG synthesis by normal PBMCs [20]. Although suppression was attributed to soluble factors [21], we thought that the designs of the above experiments [1,20] did not obviate the possibility of a direct suppressive effect by cells themselves. We therefore used cell-free supernatants, rather than T cells, in our study. We observed suppression of HBsAb synthesis on addition of carrier supernatants to cultures stimulated with PWM alone (8/8), HBsAg alone (4/5) or a combination of HBsAg + PWM (14/16). Only two of the TCS (C15 and C20) did not suppress HBsAb synthesis. The TCS (C15) that did not suppress the PWM + HBsAg-stimulated HBsAb synthesis was not able to suppress HBsAb even in cultures stimulated with HBsAg alone. Therefore, 90% (18/20) of T-cell supernatants from carriers showed suppression of HBsAb production and this was irrespective of whether the antibody production was induced by HBsAg, HBsAg + PWM, or PWM (mitogenic dose). HBsAb synthesis, on the other hand, was not suppressed by the TCS isolated from four unvaccinated control subjects. The cell viability in all cultures at the end of the 12-day suppression experiment was comparable, thereby confirming that the low HBsAb levels were caused by active antibody suppression and not by cell death.

Our further studies to assess the dynamics of TCS-mediated suppression showed that no suppression of HBsAb occurred in cultures incubated with stimulants before addition of TCS; suppression of HBsAb occurred when cultures were incubated with TCS before addition of stimulants to the same extent as on concomitant addition of TCS with stimulant. These results suggest that suppression is an active process mediated within

the first 8 h of contact of TCS with the cell, as suppression could not be reversed by a later addition of stimulant. TCS did not have any effect on cells once they had been activated.

We observed that IgG synthesis was greater than IgM synthesis in cultures stimulated with PWM + HBsAg and HBsAg alone, whereas the total IgM synthesized was greater than IgG in cultures stimulated with PWM. This interesting new observation suggests that HBsAg and a combination of HBsAg + submitogenic dose of PWM preferentially stimulates IgG response. It is not clear why TCS of three carriers (C7, C12, C16) enhanced IgG synthesis and, of four carriers, also enhanced IgM synthesis over the parallel PWM + HBsAg-stimulated cultures. This enhanced total IgG and IgM response might be a result of other spontaneously secreted growth factors (IL-4 or IL-6) present in the TCS, which favour the polyclonal antibody response.

We believe that our data conclusively demonstrate that TCS of chronic carriers have an antigen-specific suppressive effect on *in vitro* HBsAb synthesis because TCS of four carriers showed suppression of HBsAb synthesis but did not show suppression of IgG or IgM production. The suppression, however, is not caused by direct lymphoid cell lysis, because antibody-producing cultures had 8%–60% viability at the end of 12 days. Suppression caused by HBsAg–HBsAb complexes is unlikely as the antibody-secreting cultures were from normal donors and were washed thoroughly on day 3 to remove all traces of added TCS and antigen and then incubated for a further 11 days for antibody production. Hepatitis B virus is known not to be directly cytopathic. Yamouchi *et al.* [22] had previously shown suppression by T-cell supernatants; however, the study design and the conclusions drawn by these workers deserve further comment. Whereas these workers demonstrated antigen-specific suppression quite elegantly, their efforts to show the nature of suppressive factor are less convincing. Their claim that they could adsorb out the suppressor activity of TCS on a HBsAg-specific column is difficult to accept; they have also not explained how T-cell derived products could be adsorbed out by an antigen-specific column. A more plausible explanation for their findings is that the suppressor activity was non-specifically adsorbed out or diluted during chromatography, or the suppressor factor was HBsAg, produced by T cells, which could have got bound to the HBsAg column by interaction through albumin, a well-known phenomenon [23].

As virally derived proteins have been previously shown to mediate suppression [24], our further efforts were directed at demonstrating HBV within the T cells. We tested T lymphocytes of 14 carriers for the presence of HBV DNA using either Southern or dot-blot hybridization and demonstrated its presence in 12 carriers. Nine of the 15 B-lymphocyte samples and three of the eight monocyte samples tested were also positive for HBV DNA (data not shown). Four of the 12 T-lymphocyte samples were analysed by Southern blot; one of the four showed a band at 6.5 kb, indicating integrated HBV sequences. In the other three T-lymphocyte samples, free extrachromosomal HBV DNA (band at 3.2 kb) was detected. No HBV DNA was detected from normal T cells. HBV DNA was present in T cells of all the carriers whose T-cell supernatants had shown suppressor activity. Several recent reports have highlighted the presence of HBV DNA at extrahepatic sites including PBMC [10,22,25–27]; transcriptionally active HBV DNA has been previously demonstated in PBMC of patients [28–30].

All the eighteen TCS, which showed suppression, also contained a 43×10^3 MW HBsAg. The higher molecular weight of HBsAg in these samples might be a result of the variation in the glycosylation pattern of this protein in T cells. As T-lymphocyte-derived HBsAg has been demonstrated to suppress *in vitro* HBsAb synthesis, similar effects can be implicated *in vivo*. In addition, HBV DNA was also seen in B cells and monocytes and these infected cells present in the microenvironment could modify T cell and T–B cell interactions to bring about *in vivo* suppression of the HBsAb response.

Different suppressive circuits have been proposed to explain induction of antigen-specific suppression by high concentrations of antigen [31–34]. While a subimmunogenic dose of antigen suppresses the immune response, the contrasuppression circuit is stimulated by immunogenic doses of antigen, which inhibit the initial circuit and promote an immune response. A third suppression circuit is elicited by high concentrations of antigen that inactivate the contrasuppression and inhibit the immune response. Although the presence of human T-suppressor cells is still controversial, it can be proposed that direct HBsAg-mediated suppression could occur through such circuits. The *in vitro* suppression that we have found with TCS may thus reflect the third situation where the

excess HBsAg in TCS is directly suppressive. A similar analogy can be drawn *in vivo* where soluble HBsAg from T cells, in the microenvironment of immunological interactions, could mediate suppression. Such a possibility, however, does not exclude a direct down-regulation of HBsAg-specific B lymphocytes by excess HBsAg.

ACKNOWLEDGEMENTS

Dr K. Nagaraju was supported by a Senior Research Fellowship and Research Associateship from the Human Resource Development Group, Council of Scientific and Industrial Research (CSIR), N. Delhi. We are grateful to Mr D. Lambert, Pasteur Merieux, France, for providing HBsAg purified from human plasma.

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Indian J Med Res 108, September 1998, pp 80-84

Lack of *in vitro* lymphoproliferative response to hepatitis B surface antigen in healthy vaccine recipients

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Accepted August 8, 1998

A majority of HBsAg vaccine recipients show good anti-HBs antibody responses but poor antigen specific lymphoproliferative responses. We investigated the basis for this poor *in vitro* antigen specific proliferative responsiveness in vaccinees who had received the standard three dose schedule (0,1 and 6 months) of plasma derived HBsAg vaccine. Peripheral blood mononuclear cells (PBMC) from 26 of 29 (89.7%) vaccinees failed to show lymphoproliferative responses to HBsAg in spite of having a very good anti-HBs antibody response (geometric mean titer 3154 IU/l). The mitogen (phytohaemagglutinin, PHA) and antigen (purified protein derivative, PPD) driven lymphoproliferative responses in these individual where normal. Addition of exogenous recombinant interleukin-2 (rIL-2) along with HBsAg had no effect on the response to HBsAg in six of nine vaccinees who were tested six months after the third vaccine dose or on four unvaccinated controls. However, in three vaccinees who did not have lymphoproliferative response to HBsAg alone, addition of exogenous rIL-2 resulted in a synergistic response. These data suggest that HBsAg reactive cells are few in the peripheral circulation of a majority of individuals following the standard three dose schedule of vaccination and addition of exogenous rIL-2 induces a response only in a subgroup of individuals. The inability of HBsAg to induce a T cell proliferative response may have implications for the maintenance of protective immunity and immunological memory following vaccination.

Key words Hepatitis B virus - immune suppression - lymphoproliferative responses - vaccination

Vaccination against hepatitis B virus (HBV) infection using surface antigen of the virus (HBsAg) is very successful since the standard vaccination protocol induces a high anti-HBs antibody response in up to 96 per cent of vaccinees[1]. The lack of T cell responses to the surface antigen in vaccinees is of relevance since there has been a number of recent reports of S gene mutants (vaccine escape mutants) of HBV among vaccinated populations in endemic regions[2-4]. It is unlikely that the surface antigen based vaccine would protect against infection with these mutants since the mutations are generally in the virus neutralization site. Humoral response following vaccination is a result of activation of T lymphocytes which provide help for specific antibody production and generate antigen specific memory cells[5]. However, even in the presence of a high anti-HBs titer, the HBsAg induced lymphoproliferative response has either not been demonstrated *in vitro*[6,7] or has been demonstrated only in a small proportion of vaccine recipients[8,9]. The reasons for this poor T cell response in vaccinees have not been investigated. It would have important bearings on the maintenance of immune memory and the decline of antibody titers

in vaccine recipients. We therefore investigated the reason for the lack of response *in vitro* by assessing the ability of antigen reactive peripheral blood mononuclear cells (PBMC) to proliferate in response to a combination of exogenous recombinant interleukin-2 (rIL-2) and HBsAg, since Il-2 is known to induce T lymphocyte proliferation[10].

Material & Methods

Study population : Twenty nine apparently healthy hospital workers (14 women, 15 men, age range 21 - 51 yr) undergoing routine vaccination against hepatitis B virus (HBV) volunteered for the study. They were all seronegative for HBsAg by ELISA (Enzygnost-HBsAg Micro-Hoechst, Behring, Germany) and received three intramuscular doses (20 µg) of hepatitis B vaccine [Heptavax(R) Korean Green Cross Corp., Seoul, Korea) at 0,1 and 6 months. All 29 vaccinees had high titers of anti-HBs antibody (geometric mean titer 3154IU/l) 4 wk following the third dose as tested by a quantitative ELISA (Enzygnost anti-HBs Combipack, Behring, W. Germany). Eight healthy unvaccinated persons (4 women and 4 men, mean age 28 + 6.2 yr) who were seronegative for HBV markers were selected as controls.

Antigens and mitogens : HBsAg subtype adw purfied from human plasma was obtained from Pasteur Merieux, France, purified protein derivative (PPD) 289, from the Ministry of Agriculture, Fisheries and Food, Weybridge Central Vet Lab, UK, and phytohaemagglutinin (PHA), keyhole limpet haemocyanin (KLH) and rIL2 from Sigma Chem. Co. St. Louis, USA.

Lymphoproliferation assay : This was performed by the method previously reported[11]. In brief, PBMC were separated from heparinized blood by density gradient centrifugation[12]. 1×10^6 cells/ml were cultured in triplicate in 200 µl of complete RPMI 1640 (cRPMI) containing 10 per cent foetal calf serum (Biological Industries, Israel), 2 m*M* L-glutamine, 1 m*M* sodium pyruvate, 25 m*M* Hepes and antibiotic (100 U/ml penicillin, 100µg/ml streptomycin, Gibco Labs, NY, USA). Cultures were set up with and without stimulating agent; all dilutions were made in cRPMI. The cells were incubated at 37° C in 5 per cent carbon dioxide and 95 per cent air under humidified atmosphere. The cultures were incubated for 3 days in case of PHA and for 6 days in case of antigen stimulated cultures (HBsAg, PPD and KLH). The cells were pulsed with one uCi (specific activity 6500 mci/mmol) of tritiated thymidine [Thymidine (Methyl-T)-LCT3, BARC, Mumbai] for the last 18 h of the culture. Thymidine uptake was measured in liquid scintillation counter (LKB, Sweden) and results were expressed as mean of counts per minute (cpm) of triplicate cultures. Optimal concentrations of PHA for inducing lymphoproliferation were determined in preliminary studies and was found to be 10 µg/ml for PHA. Dose response studies were undertaken in vaccinees using several doses of HBsAg (from 1 to 2500 ng/ml); time course of lymphoproliferative responses was assessed in four vaccinees at 1,2,3 and 5 wk following the third dose of vecine. PPD was used at a concentration of 10µg/ml. The antigen stimulated responses were taken as positive when the stimulation indices (SI, the ratio of mean cpm in the presence of antigen to mean cpm in the absence of antigen) was>2.5.

Lymphoproliferation with exogenous rIL-2 and HBsAg : The effect of exogenous rIL-2 on proliferative responses to HBsAg and KLH was studied six months after the third vaccine dose. Cultures were set up as described above with rIL2, HBsAg or keyhole limpet haemocyanin (KLH) alone or with HBsAG+rIL2 and KLH+rIL2 and the responses were determined in six day cultures. The results were interpreted as *additive* when AB/A+B≤1 (where A was SI of HBsAg or KLH; B was SI of rIL-2; AB was SI of the combined stimuli) and synergistic when AB/A+B>1[13].

Statistical methods : The proliferative responses to PHA among vaccinees and controls was compared using Wilcoxon's rank sum test.

Results

Lymphoproliferative responses : The lymphoproliferative responses to PHA in vaccine recipients 4 wk following the third dose of vaccine were similar to those of unvaccinated controls (Table I).

Dose response studies using graded concentrations of HBsAg ranging from 1 to 2500 ng/ml showed the maximum stimulation with 500 ng/ml of HBsAg (Fig.). At this dose an SI of more than 2.5 (4.0, 13.3,

Table I. Proliferative responses of vaccine reponders and unvaccinated controls to the mitogen, Mphytohemagglutinin (PHA)

	Vaccinees (n=29)	Controls (n=8)
Nil	730±725	978±1552
PHA	40352±28466	22205±20024

Data represents mean of counts per minute ± SD

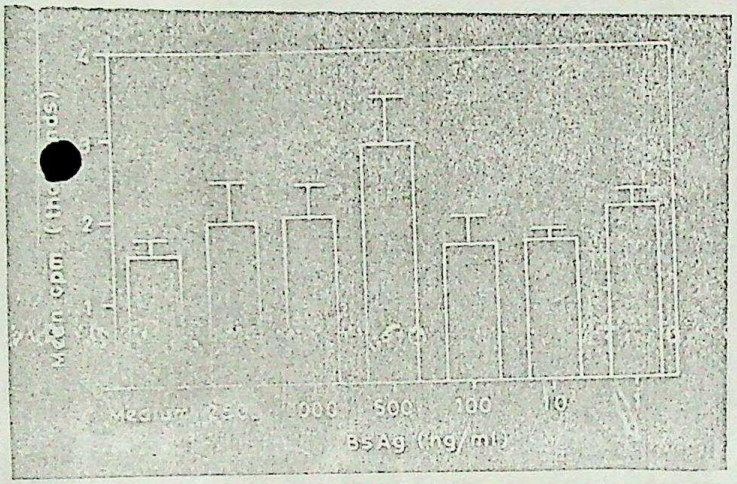

Fig. Lymphoproliferative responses of vaccine recipients to varying doses of HBsAg performed four weeks after third dose of vaccine to establish optimum antigen dose. Bars represent mean counts per minute ± SD of 11 vaccinees.

2.6) could be demonstrated in only 3 of 29 (10.3%) vaccinees; an additional two vaccinees had borderline responses of 2.5. Weekly responses in four vaccinees on the first, second, third and fifth weeks was 0.96±0.64, 1.0 ± 0.86, 0.98 ± 0.7, 1.35 ± 0.9 respectively. All vaccinees tested for lymphoproliferative responses had a good humeral response to HBsAg with anti-HBs-titre ranging from 1200 to 8500 IU/l (geometric mean = 3154 IU/l).

Eight vacciness whose PBMC showed no proliferative response to HBs Ag (mean SI 0.86 ± 0.55) were tested for their cellular responses to PPD; seven showed significant responses at an optimal concentration of 10µg/ml of PPD (mean SI 22.5 ± 31.7, SI range 3.5-94, $P<0.005$).

Effect of exogenous rIL-2 on lymphoproliferative response : Standardization experiments showed that the mean responses induced by different concentrations of rIL-2 in five individuals were as follows: 20 IU/ml - 2.26 ± 0.7; 10 IU/ml - 1.97 ± 0.82; 5 IU/ml - 1.7 ± 1.0 and 1 IU/ml - 0.9 ± 0.29. A dose of 20 IU/ml of rIL-2 was therefore selected as standard concentration for all subsequent experiments. PBMC of nine vaccinees and four unvaccinated controls were subjected to stimulation with either rIL-2, HBsAg or rIL-2+HBsAg; five of the nine vaccinees and the four controls were subjected to stimulation with an unrelated antigen KLH and rIL2+KLH. None of the nine vaccinees (SI range 0.7 - 2.3; median 1.6) or the four unvaccinated controls (SI 0.9-1.4) showed any response to HBsAg alone. Addition of 20 IU/ml concentration of exogenous rIL-2 to cultures containing HBsAg, showed an additive response in six of the nine vaccine recipients and in all four unvaccinated controls. On the other hand three of the vaccinees showed synergistic effect on addition of exogenous rIL-2, although HBsAg alone failed to induce positive proliferative response. Exogenous rIL-2 could not show induced effect on KLH stimulated proliferative response in five vaccinees and four unvaccinated controls (Table II).

Discussion

Our results demonstrate that all 29 vaccinated individuals studied had high serum anti-HBs titers, while PBMC of 26 of the 29 (89.7%) vaccinees did not show HBsAg specific lymphoproliferative

Table II. Effect of the addition of recombinant interleukin-2 (20 IU/ml) to lymphoproliferation assays using pure hepatitis B surface antigen (HBsAG) or keyhole limpet haemocyanin (KLH) as stimulant in vaccine recipients and unvaccinated controls

Stimulant	Vaccinees	Unvaccinated controls
HBsAg+rIL2		
Additive	6/9*	4/4
Synergistic	3/9	0/4
KLH+rIL2		
Additive	5/5	4/4
Synergistic	0/5	0/4

rIL2-recombinant interleukin-2
Additive effect = AB/A+B ≤ 1 and Synergistic effect = AB/A+B>1 where A is SI of HBsAg or KLH alone, B is SI of rIL-2 alone and AB is SI of the combined stimuli
*No positive / no. tested

responses. These findings corroborte earlier observations[7,6]. We have shown for the first time, that in some individuals with low lymphoproliferative responses to HBsAg (S.I ≤ 2.5), responses could be induced by the addition of exogenous rIL-2. This suggests that lack of *in vitro* lymphoproliferative responses is due either to absence of antigen reactive cells in the peripheral circulation or to an inadequate stimulus provided by HBsAg alone for IL-2 production.

We have initially demonstrated normal lymphoproliferative responses of vaccine recipients to PHA, indicating the functional competence of PBMC. Only three of the 29 veaccinees had positive proliferative response to HBsAg. This indicates that only a small proportion of vaccinated individuals had antigen reactive cells in the peripheral circulation. Eight of the 26 vaccinees who failed to show a lymphoproliferative response to HBsAG were stimulated with PPD and of these seven showed a good PPD specific proliferative response. PPD was selected as an unrelated antigen since the majority of our adult population have immunity to mycobacterial antigens either through BCG vaccination or natural exposure[14]. We have thus shown that these individuals have selective inability to respond to HBsAgin *in vitro* assays.

The factors that drive a response towards TH1 or TH2 are still not well elucidated[15]. It would seem from the present data that HBsAg when given as a protein antigen by the intramuscular route stimulates a predominantly TH2 response. It has been recently reported that intramuscular injection of naked plasmid DNA carrying the S gene generates both antibody and T cell responses[16]. The generation of T cell immunity may have bearing on the maintenance of long-term immunological memory.

Addition of exogenous rIL-2 along with HBsAg in lymphoproliferative assays demonstrated an additive effect in six vaccinees and a synergistic effect in three of the vaccinees. The individuals who showed a synergistic effect had shown positive proliferative response (S.I. of 2.5, 4 and 13.3) six months earlier. The antigen reactive cells in the peripheral circulation of those with a synergistic response may be too few to show positive proliferative response with HBsAg alone but are induced by addition of exogenous IL-2. It has been previously demonstrated that administration of rIL-2 along with HBsAg vaccine improved the antibody responses in haemodialysis patients who failed to make adequate anti-HBs response to the vaccine[17]. This effect is specific for HBsAg since none of the five vaccinees and four unvaccinated controls showed a synergistic effect when rIL-2 was added to KLH for which they were not primed. Thus a synergistic effect is observed only if antigen primed cells are present in the circulation.

It has been previously reported that stimulation of TCR alone is inadequate for T cell induction[18]. *In vitro* secondary anti-viral T cell responses to vaccinia and lymphocytic choriomeningitis viruses were absent unless IL-2 was added, confirming the crucial role of IL-2[19]. It would, therefore, seem that the majority of persons do not have primed T cells in the peripheral circulation following the standard three dose vaccination but this should not be interpreted as suggestive of a lack of cell mediated immune response to HBsAg. Although the protective role of anti-HBs is well established[20], the role of cell mediated immunity following HBsAg vaccination and its possible beneficial role to the vaccinees is not well understood. MHC restricted immunodominant T cell epitopes on HBsAg have been well described and these are important in the development of immunity against this pathogen[21]. Further work in this direction might help to shed more light on the immunogenic properties of this clinically relevant antigen and in understanding the immune response to vaccination.

Acknowledgment

The first author was supported by a Research Associateship from the Council for Scientific & Industrial Research (CSIR), New Delhi. Authors are grateful to Shri D. Lambert, Pasteur Merieux, France for providing HBsAg subtype and purified from human plasma, Dr Vijay K. Singh Additional Professor, Department of Immunology SGPGIMS, Lucknow for providing rIL-2.

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DIS 16a · 3

ORIGINAL ARTICLES

Chronic hepatitis B virus carriers have low lymphoproliferative responses to HBsAg and reduced interleukin-2 synthesis

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Background: Chronic carriers of hepatitis B virus (HBV) have impairment of lymphoproliferative responses. Recently HBV infection of peripheral blood mononuclear cells (PBMC) has been reported. The defect in the proliferative capacity of carrier PBMC has not been correlated to the presence of HBV in these cells. *Methods:* PBMC of fourteen HBV carriers and 14 healthy individuals were stimulated with phytohemagglutinin (PHA), pokeweed mitogen (PWM) or anti-CD3 for 3 days and with HBsAg and purified protein derivative (PPD) for 6 days. The supernatants of unstimulated and PHA-stimulated PBMC cultures were bioassayed for interleukin-2 (IL-2); the supernatants of unstimulated and lipopolysaccharide (LPS)-stimulated cultures were bioassayed for IL-1. DNA extracted from PBMC was hybridized with a ^{32}P-labeled HBV probe to look for HBV DNA. *Results:* HBV carriers' PBMC showed impaired responses to PHA, PWM and anti-CD3. No carrier demonstrated lymphoproliferative response to hepatitis B surface antigen (HBsAg). Seven of eight carriers with impaired HBsAg-specific proliferative responses who were tested for their response to an unrelated antigen showed a positive response to PPD. PBMC from HBV carriers produced similar amounts of IL-1 as normal PBMC on LPS stimulation; however, they produced significantly lower amounts of IL-2 as compared to normal PBMC under both spontaneous and PHA-stimulated conditions. HBV DNA was demonstrable in the PBMC of all fourteen carriers. *Conclusions:* The abnormal immune function found in chronic HBV carriers may be a consequence of replicative viral infection of the mononuclear cells.
[*Indian J Gastroenterol* 1998; 17: 83-86]
Key words: Hepatitis B immune response, cellular immune dysfunction

See editorial on page 76

Certain viruses and viral proteins induce defects of lymphocyte functions, favoring viral persistence.[1] Chronic carriers of hepatitis B virus (HBV) have, in addition to a complete lack of lymphoproliferative responses to the viral antigens, impaired lymphoproliferative responses to phytohemagglutinin (PHA) and defective interleukin-2 (IL-2) production.[2-5] Another feature is the presence of HBV DNA and HBV antigens in the peripheral blood mononuclear cells (PBMC).[6-9] No study has looked at defective lymphoproliferation in relation to infection of PBMC. We investigated the function of PBMC in HBV carriers who had HBV DNA in the PBMC.

Methods

We studied fourteen patients with chronic liver disease [12 men, 2 women; mean (SD) age 39.1 (13.1) years], who were seropositive for hepatitis B surface antigen (HBsAg) (*Enzygnost-HBsAg micro*; Hoechst, Behring, Germany) for more than one year and negative for anti-hepatitis C virus antibodies (Abbott Lab, USA). Fourteen healthy individuals [9 men, 5 women; age 35 (16) years] seronegative for HBsAg were selected as controls.

Isolation of peripheral blood mononuclear cells

PBMC were separated from venous blood by the density gradient sedimentation method.[10] The cells were washed, viability was determined by trypan blue dye exclusion and resuspended in minimal volume of complete RPMI (cRPMI) containing 10% fetal calf serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 25 mM hepes, 100 U/mL penicillin and 100 mg/mL streptomycin.

Lymphoproliferation assay[11]

In brief, 200 µL cultures were set up in triplicate with 100 µL of cells at a concentration of $1x10^6$ per well and 100 µL of either cRPMI alone in control cultures or 100 µL of stimulant resuspended in cRPMI in test cultures. The cultures were incubated at 37°C in 5% carbon dioxide and 95% air under humidified atmosphere for 3 days in case of cultures stimulated by mitogen and anti-CD3 antibody, and for 6 days in case of HBsAg- and purified protein derivative (PPD)-stimulated cultures. The mitogens, PHA and pokeweed mitogen (PWM) were used in the previously determined optimum dose of 10 mg/mL; anti-CD3 (*UCHI clone*, Dako, Denmark) was used in a dose of 15 ng/mL, HBsAg in a concentration of 500 ng/mL and PPD in a dose of 5 mg/mL. Cultures were pulsed with 1 mCi of tritiated thymidine [thymidine (methyl-T)-LCT3, BARC, Mumbai; specific activity 6500 mCi/mmol] 18 h before harvesting, and thymidine uptake was measured in liquid scintillation counter (LKB, Sweden). HBsAg-specific response was considered positive if the mean counts per minute (cpm) of stimulated cultures was ≥2.5 times that of

unstimulated cultures.

Interleukin-2 production and assay

PBMC from HBV carriers and normal subjects were stimulated with PHA (Wellcome, England) to produce IL-2. Briefly, $2x10^6$ PBMC/mL of cRPMI was incubated in sterile 24-well plates (Nunc, Denmark) with or without 1% PHA at 37°C for 48 h. The supernatants were collected by centrifugation at 1200 rpm for 10 min, filtered through 0.22 µm membranes (Advanced Microdevices, Ambala) and stored at -40°C.

IL-2 in the culture supernatant was quantitated by a method[12] which assesses its capacity to stimulate the growth of IL-2-dependent mouse T-cell line, CTLL-2. CTLL-2 was maintained in cRPMI containing 10% rat splenocyte supernatants as source of IL-2. Serial two-fold dilutions (50 µL) of sample supernatants were incubated with 50 µL of cRPMI containing $1x10^5$ CTLL-2 cells/mL (grown to log phase) for 18 h at 37°C; 10 µL of 5 mg/mL of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) was added, followed by 100 µL extraction buffer (20% sodium dodecyl sulphate + 50% dimethyl formamide, pH 4.5). All dilutions were tested in triplicate using standard IL-2 (1st International Standard for Interleukin-2 Human, WHO International Laboratory for Biological Standards, Hertfordshire, England) as reference controls. The absorbance was measured at 570 nm and the amount of IL-2 calculated from a standard graph drawn using WHO standards; dilutions of samples falling in the straight line of the graph were considered for calculation.

Interleukin-1 production and assay

PBMC of carriers and normals were cultured at $1x10^6$ cells/mL for 24 h with or without lipopolysaccharide (LPS) in a dose of 10 µg/mL to stimulate IL-1 production. The culture supernatants were harvested and filtered through 0.22 µm filters and stored at -40°C until assayed.

IL-1 was estimated using growth inhibition assay on A375, a human malignant melanoma cell line. A375 cells grown to confluence in 75 cm^2 tissue culture flasks was harvested by treatment with trypsin-EDTA, washed with RPMI 1640 and resuspended at $1x10^6$/mL. Samples and controls were diluted to 1:2, 1:10 and 1:100, and 50 µL of various dilutions of samples, controls and WHO reference IL-1 standard were added to each well along with 50 µL of cell suspension ($5x10^3$ cells/well). The plates were incubated at 37°C in CO_2 incubator for 72 h. Ten µL of MTT (0.5 µg/mL) reagent was added to each well and incubated for 4 h in CO_2 incubator; 100 µL extraction buffer was then added. Readings were taken at 570 nm and the results derived from a graph drawn using WHO IL-1 standard. The amount of IL-1 which induces 50% growth inhibition of A375 cells was taken as one unit.

Isolation of genomic DNA

For isolation of genomic DNA from PBMC, $5x10^6$ cells/mL was resuspended in 500 µL of extraction buffer (10 mM Tris.Cl pH 8.0, 0.1 M EDTA pH 8.0, 20 µg/mL pancreatic RNAse, 0.5% SDS and 100 µg/mL of proteinase K) and incubated overnight at 37°C. Extraction was done twice with phenol, once with equal volume of phenol:chloroform and once with chloroform. The upper aqueous phase was removed and DNA precipitated by adding 2.5 volumes of ethanol, 0.2 volume of 10 M ammonium acetate was added and kept overnight at -20°C; precipitated DNA was centrifuged at 12000 rpm for 20 min and the supernatant decanted. The traces of ethanol were removed by evaporation and DNA dissolved in minimal volume of Tris-EDTA buffer (pH 8.0) and kept at -20°C.

HBV DNA detection by dot blot hybridization[13]

Briefly, 25 µL (10 µg) of denatured DNA sample was mixed with 1 µL of 1% bromophenol blue in TE, pH 8.0 and loaded on to Nytran membrane (Schleicher and Schuell GmBH) using a dot blot microfiltration unit (Bio Rad, USA). Known amounts of positive and negative samples were added. The membrane was dried at 37°C before baking for 2 h at 80°C and stored in aluminum foil.

The membranes were prehybridized for 1 h and hybridized for another 16 h. After stringency washes, the membrane was developed using DIG DNA detection kit (Boehringer Mannheim). When the desired spots were observed the reaction was stopped by washing for 5 min with 50 mL TE (pH 8.0). The membranes were photographed using UVP gel documentation system (UVP, USA).

Statistical methods

Groups were compared using Wilcoxon rank-sum test for unpaired data.

Results

Lymphoproliferative responses to mitogens and HBsAg

The proliferative responses to T-cell mitogen PHA and the polyclonal B-cell mitogen PWM were significantly lower in carriers as compared to normal controls. The proliferative response to anti-CD3 was also reduced in carriers (Table 1). Proliferative response to purified HBsAg was tested using the previously determined optimal concentration (500 ng/mL) of HBsAg. Neither normal subjects nor carriers showed a positive proliferative response to HBsAg, i.e., stimulation index (SI) > 2.5.

Eight HBV carriers who did not show positive proliferative response to HBsAg were further tested for their

Table 1: Lymphoproliferative responses of normals and HBV chronic carriers to mitogens

Stimulant	Dose	Controls (n = 14)	Patients (n = 14)
PHA	10 µg/mL	90659 (5470)	9899 (1749)**
PWM	10 µg/mL	17628 (2869)	6619 (532) *
Anti-CD3	15 ng/mL	90659 (5470)	9899 (1794)**

p *<0.05, **<0.001

Results expressed as mean (SD) of counts per minute

Table 2: Interleukin-1 and interleukin-2 levels of normals and chronic HBV carriers

Cytokine	Controls (n=14)	Patients (n=14)
Spontaneous IL-1	129 (50)	156 (41)
Stimulated IL-1*	1021 (339)	1491 (615)
Spontaneous IL-2	1 65 (28)	79 (17)##
Stimulated IL-2**	321 (49)	56 (33)#

* IPS at dose of 10 µg/mL ** PHA at dose of 1%
p #<0.05, ##<0.01
Results expressed as mean (SD) in IU/mL

lymphoproliferative response to an unrelated antigen, PPD. Seven of them had positive lymphoproliferative responses (SI > 2.5) to PPD (median SI 7.9, range 3.2-280).

IL-1 and IL-2

Spontaneous and PHA-stimulated IL-2 production by HBV carriers was lower than by controls. Spontaneous and LPS-stimulated IL-1 levels were similar in the groups (Table 2).

HBV viral sequences in PBMC

HBV viral sequences were demonstrable in the PBMC in all 14 carriers. The DNA from PBMC of two normal individuals were negative for HBV viral sequences.

Discussion

We have shown that HBV carriers, all of whom had HBV DNA in their PBMC, have significantly lower lymphoproliferative responses to mitogens (PHA, PWM) and anti-CD3 than normal controls; they also failed to show HBsAg-induced lymphoproliferative responses. The capacity of the HBV carriers' PBMC to produce IL-2 both spontaneously and upon stimulation with PHA was also significantly lower than that of normal PBMC. The spontaneous and LPS-stimulated levels of IL-1 were, however, not significantly different from that of controls.

Our findings of defective proliferative responses of lymphocytes of HBV carriers to PHA and PWM support those of earlier reports.[14,15] PHA and PWM induce monocyte-dependent cellular responses; PHA preferentially activates T cells and PWM activates B cells in the presence of CD4+ helper T cells. The anti-CD3 monoclonal antibody used for stimulation of T cells activates T cells selectively through the TCR/CD3 complex. This activation is also monocyte-dependent when the antibody is used in soluble form, as in our study. Stimulation with immobilized anti-CD3, which acts on T cells through a monocyte-independent pathway, did not show abnormality in the lymphocyte responses of HBV DNA-positive carriers.[16] The combination of abnormal responses to PHA with a normal response to PMA, a known monocyte-independent T-cell activator, has been reported in carriers.[15] Hence, our findings of defective lymphoproliferation response to PHA, PWM and soluble anti-CD3 support the concept of a generalized monocyte-dependent lymphocyte dysfunction in chronic carriers. It has also been earlier shown that the poor antigen-specific lymphocyte responses in chronic carriers could be corrected by depletion of patients' monocytes and reconstitution with healthy monocytes,[17] or by increasing the ratio of monocytes to lymphocytes in cultures by *in vitro* manipulations.[18]

The proliferative response of T lymphocytes is initially dependent on monocytes for monocyte-derived IL-1 as well as co-stimulatory signals provided by cell-to-cell contact. The response is further sustained by lymphocyte-derived IL-2 and increased expression of IL-2 receptors (IL-2R) on these cells. We found normal spontaneous and LPS-stimulated IL-1 responses, but low spontaneous and PHA-stimulated IL-2 responses in chronic carriers. IL-1 levels have not been previously reported in chronic carriers. Chronic HBV carriers have been previously found to have defective capacity to produce IL-2[14,19] and reduced IL-2R expression following PHA stimulation.[15] Addition of exogenous HBsAg was found to suppress PHA-stimulated lymphoproliferation by PBMC of normal individuals negative for all serologic markers of HBV infection; these cultures also produced decreased levels of IL-2 which correlated with the decreased proliferative response.[20] Anastassakos *et al*[21] could not correct the defective T-cell responses to PHA by the addition of exogenous IL-1, IL-2 or supernatants of mixed lymphocyte cultures over a wide dose range, nor could they correct the defective T-cell response by increasing the proportion of monocytes in the system. These authors therefore implicated a primary role for T cells and not the monocytes.

Our findings of lack of lymphoproliferative responses to pure HBsAg in chronic carriers have been previously reported.[18,22,23] This is interesting in view of the finding that a majority of the chronic carriers that were studied showed a good proliferative response to PPD, an unrelated antigen. The poor response to HBsAg could occur due to inability of extraneously added antigen to bind to the TCR of HBsAg-specific T cells due to its prior occupancy, since these persons have persistent circulating antigenemia. An alternative possibility is that the recognition through the T-cell receptor *per se* is not affected in these persons but that there is a paucity of HBsAg-recognizing T cells in the peripheral circulation. This would not affect the recognition of PPD by PPD-specific T cells. A third possibility that HBsAg transduces a negative signal on receptor occupation and that this is a unique property of the antigen is supported by the ability of HBsAg to suppress responses of normal lymphocytes to mitogen PHA.[20] The defect in lymphocyte and monocyte functions is not absolute as has been shown by the impaired but not absent responses to mitogens and anti-CD3.

All our patients had HBV DNA in their PBMC. We have previously reported that the HBV DNA in this group of patients was in the transcriptionally active state.[9] It may be therefore postulated that HBV integration has modified the intrinsic functional capacity of these cells either by altering cytokine regulation or by signal transduction. HBV infection of T cells, B cells and monocytes and HBsAg on

the cell surface in variable number of PBMC of HBV carriers has been previously reported.[6,9] However, the site of viral integration is probably a random event as has been postulated for hepatic carcinogenesis.[24] HBV integration may thus vary both in extent and site and this may be responsible for differences in the response of individual patients.

The present study, for the first time, reports the immunological abnormalities in a group of chronic carriers in whom transcriptionally active HBV DNA has been demonstrated to be present in the mononuclear cells. Although the latter phenomenon has been shown for the first time almost a decade ago, its functional consequences were never demonstrated. We hypothesize that viral integration in these cells may influence the regulation of immunologically important genes, resulting in abnormal functions of monocytes and/or lymphocytes.

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Received May 12, 1997. Received in final revised form October 6, 1997. Accepted October 18, 1997

Questions and Answers

Quick Fact: Since the start of this page, over 400 individual questions have been answered. However, if you do plan on asking a question, please remember that I am NOT a physician so am unable to give any sort of medical advice.

Send your questions/comments via e-mail to me: **robert@oci.utoronto.ca**

Note: This page is intended for those who need "quick" answers to complex issues. For a more complete story, please refer to the other pages on this site. As I am **not** a physician, the recommendations I may make are **not** for use as personal medical advice. I can only urge one, if in doubt, to discuss their questions with a trained health care provider.

Commonly Asked Questions and their Answers

Is there any indication that the HBV virus can be transmitted to/from domestic (or exotic) animals or pets?

The human hepatitis B virus is only capable of infecting humans and higher primates. As such, domestic animals and pets (with the exception of those such as chimpanzees) would not be able to contract or pass on the disease as a human carrier would. However, the virus is able to linger on surface it can come in contact with. (See Epidemiology) A surface could be anything from a countertop to an animal's fur or skin. As virtually all bodily fluids of an acutely infected individual can contain virus, it may be possible to transmitt the virus indirectly through casual contact with pets, especially if the pets are exposed to

the blood of an infected person. The blood of an infected individual contains the highest titre of the virus.

As an aside, I have not actually read of any studies done on this mode of transmission probably due to its unlikeliness.

What are the treatments available for early stage HBV infection?
That's a simple question to answer. There are none. However, this should not cause alarm. Contrary to what some may say, over 90% of those infected with hepatitis B recover. What infected individuals need is support and to definitely stay away from alcohol and other substances which make the liver work harder than it needs to.

Chronic hepatitis B infection is another story. Though there is no cure for the disease, there are a variety of treatments available for the chronic carrier. (See Treatments)

Can HBV be transmitted through the saliva?
From my understanding based on readings so far, hepatitis B viral particles can be found in all bodily fluids including saliva. However, the highest concentrations of viral particles are in the blood. Yet, due to eating, brushing, etc. the saliva of an infected individual may contain some blood (perhaps this is why it can be detected in the saliva). As such, there is a risk, though probably quite low. (See Epidemiology)

When in the course of HBV should screening for HCC begin, and how often screening should take place?
As far as I have read currently, there is no regime for screening patients infected with chronic HBV infection for HCC. Typically, individuals found to have chronic hepatitis B infection are monitored and treated with various therapies such as interferon-alpha treatment. As HCC does not develop in all infected individuals, it is not common to screen them for cancer. It is more like that they would suffer from cirhossis later in infection. Then again, my knowledge in the development of HCC is also limited at this point in time (which is also why the page for hepatocellular carcinoma on my web site is not posted yet.)

1. I received the HBV vaccine probably 15 years ago and at that time I only received 2 or the 3 injections. Do you think I have any immunity remaining?
From what I have read, some recommend having a booster injection 5 - 7 years after the first vaccination schedule. Others say that 10 years is sufficient. It is comforting to know that patients who have been vaccinated had not contracted hepatitis B even after being followed for 10 years. It is hard to say whether one has immunity remaining or not, but a trip to the doctor and a blood test could verify whether or not your body is still producing antibodies against the HBs protein.

2. Should adults receive the injections and if so how often?
Adults should be vaccinated. The vaccines (Recombivax and Engerix-B) are safe to administer to most people (unless they have reactions versus yeast proteins). It is always better to be safe rather than sorry. (See Prevention)

3. Do most pediatrician offices promote HBV injections by the time children are 10-11? Should they?
I do not know about "most" pediatricians. However, I have read studies on children being immunized against the hepatitis B virus. If you fear your children are at righer risk, it may be wise to get them vaccinated.

Have you heard of the Delta virus? Do you know its affect on the hepatitis B virus?
The Delta virus (also known as hepatitis D virus) is a satellite virus of the hepatitis B virus. Simply put, the Delta virus cannot replicate in a patient unless that individual is infected with hepatitis B. It appears that the delta virus infection can be reactivated by HIV infection. Typically, delta infection is indistinguishable from hepatitis B infection alone. However, chronic delta virus infection leads to more serious complications than simply hepatitis B virus alone. As soon as I "finish" updating the pages to a decent level (ie. removing all those 'More to come shortly" statements), I shall be adding a section on hepatocellular carcinoma (liver cancer) and the Delta virus (since it is related to HBV).

How infectious is this disease? Can it be transmitted through general use of same objects being used by the infected person and non-infected persons?
The Hepatitis B virion is a relatively infectious virus. It can be found within blood and other bodily fluids and is capable of surviving lingering on surfaces for over a week. (See Epidemiology) However, the primary route of transmission is through blood contact. This could be anything from cuts to needles and pin pricks. Even shared razors, toothbrushes, gorged mosquitoes may harbor the hepatitis B virus, thus increasing the likelihood of transmitting the virus though the significance of these modes of spread are still under debate.

What would make a blood donor who does not use drugs, not had sexual relations come up positive for hepatitis b antigens?
Though blood and sexual contact is the most likely route of transmission for HBV, it is by no means the only route. Some studies add the term "household contact" onto the list of possible routes of transmission. Contact with blood (perhaps if dealing with someone with HBV who was cut) can lead to viral transmission. Also, saliva has been reported to carry some hepatitis B virus. One does not need to use intravenous drugs or be involved in sexual activity to contract HBV. (See Epidemiology)

Does this mean they have hep b?
Most likely, but not necessarily. If a person had been recently vaccinated, the hepatitis B surface antigen may be present in the blood at detectable levels (depending upon the type of assay used to detect them) (See Diagnosis)

And if the person does have this what steps would be next?
The next steps would be to verify the results of the first test. One could also have a physician do blood work looking for the HBe antigen in the blood. If the infected individual shows no symptoms of infection, that person is likely able to clear the virus. Most people with HBV infections manage to fully recover. (Last report quoted about 95% infected recover after mild symptoms) However, if jaudice or other forms of complications arise, it may become necessary to do a needle biopsy of the liver to examine and verify the extent of liver damage.

HEPATITIS B VACCINATION

Safe and effective vaccines are now available for protection against hepatitis B, a serious liver infection that can result in cirrhosis and liver cancer.

The Centers for Disease Control and the American Academy of Pediatrics recommend that all newborns, infants and children, especially sexually active teenagers be vaccinated against hepatitis B.

Vaccination is also recommended for individuals at high risk of being infected with the hepatitis B virus (HBV). These include:

- Health care workers, including doctors, dentists, nurses, blood and lab technicians;
- Emergency workers - including paramedics, fire fighters and police;
- Hemodialysis patients;
- Military personnel;
- Morticians and embalmers;
- Patients and staff of institutions for the mentally handicapped, inmates of long-term correctional institutions;
- Ethnic groups with a high rate of hepatitis B including Chinese, Koreans, Indochinese, Filipinos, Alaskan Eskimos, Haitians, and American Indians;
- People with multiple sexual partners;
- Intravenous drug users;
- Recipients of certain blood products;
- Household contacts and sex partners of hepatitis B carriers;
- International travelers

Those who are already infected will not benefit from vaccination. However, infants born of mothers who are carriers of the hepatitis B virus can be protected. A simple blood test can determine whether someone is a hepatitis B carrier.

Immunization requires three doses of vaccine according to the following schedule:

- 1st dose: For infants born to infected mothers - within 12 hours.
  For infants born to mothers who test negative - within one to two months following delivery.
- 2nd dose: 1 month later
- 3rd dose: 6 months after the first dose.

Administration is by intramuscular injection in the thigh or upper arm.

Hepatitis B is caused by a virus and is spread through blood, other body fluids and contaminated needles.

In the United States, there are about 1,000,000 carriers, who have no symptoms but can pass the infection on to others, and an estimated 300,000 new cases a year.

A significant number of people with hepatitis B have no symptoms. Others may have flu-like symptoms: fever, fatigue, muscle or joint pain, appetite loss, nausea and vomiting. Twenty-five to thirty-five percent have symptoms such as jaundice, a yellowing of the

skin and eyes, that indicates liver damage.

Five to ten percent of hepatitis B young adult victims become chronic carriers, often without knowing it. Nine of ten infants infected become chronic carriers. They are at increased risk of developing cirrhosis and liver cancer.

The vaccines provide immunization in about 90% of recipients.

TEST RESULTS AND INDICATIONS FOR VACCINATION

Checking To See If The Patient Needs Hepatitis B Vaccine. One must use a combination of two tests to truly determine if a patient is a carrier, already immune or still susceptible to the hepatitis B virus. The physician can use **HBsAg** and Anti-**HBc** or **HBsAg** and Anti-**HBs.**

HBsAg
Anti-HBc
positive
positive
the patient is a carrier. **DOES NOT NEED THE HEPATITIS B VACCINE.**

HBsAg
Anti-HBc
negative
positive
the patient has been exposed and has probably developed natural immunity. Alternatively, he may be an individual with an isolated Anti-HBc result (HBsAg negative, Anti-HBc positive and Anti-HBs negative). **DOES NOT NEED THE VACCINE.**

HBsAg
Anti-HBc
negative
negative
the patient is susceptible to hepatitis B. **GIVE THE FULL VACCINE PROTOCOL.**

HBsAg
Anti-HBs
positive
negative
the patient is infected with hepatitis B and is probably a carrier. **DOES NOT NEED THE HEPATITIS B VACCINE.**

HBsAg
Anti-HBs
negative
positive
the patient has already been exposedand has developed natural immunity or has been successfully vaccinated. **DOES NOT NEED THE VACCINE.**

HBsAg
Anti-HBs
negative
negative
the patient is susceptible. **SHOULD RECEIVE THE VACCINE.**

The American Liver Foundation is the only national voluntary health organization dedicated to preventing, treating, and curing hepatitis and all other liver and gallbladder diseases through research and education.

American Liver Foundation
1425 Pompton Avenue, Cedar Grove, NJ 07009
1-800-223-0179

http://www.gastro.com

Prevention

As the hepatitis B virus (HBV) is found in most bodily fluids, especially blood, universal precautions should be taken when handling any human blood, blood product or fluids. As a general rule, all blood and human bodily fluids should be treated as if they contain various infectious agents such as HIV and HBV. Suspected contaminated surfaces should be disinfected and cleaned.

Currently, the best method to prevent HBV infection is through vaccination. The most common vaccine on the market is derived from a recombinant yeast source. The small hepatitis B surface protein (SHBs) is generated by yeast cells. Expression of this protein by yeast results in SHBs particle formation. However, particles are not secreted by the yeast. Disruption of yeast cells is performed in order to liberate the produced spheres into solution. These particles are then purified through clarification, ultrafiltration, chromatography and ultracentrifugation. The purified particles are then adsorbed onto aluminum hydroxide to which thimerosal is added to preserve the solution.

The two yeast-derived vaccines licensed in most countries are Engerix-B (SmithKline Beecham, Philadelphia, PA) and Recombivax HB (Merck & Co., West Point, PA). Both products are structurally and chemically similar with less than 2% yeast protein remaining in solution. Recombivax HB, however, is treated with formaldehyde before its adsorption onto alum. As both are yeast-derived, the S-protein is not glycosylated (as yeast does not possess the correct post-translational machinery to do so). Both, thankfully, appear to be

quite effective as vaccines, allowing for immunization against the various forms of HBV. The vaccines, however, should not be frozen as this appears to be deleterious to its immunogenicity. Studies have shown that freezing of these vaccines results in lower immune response.

There are also some other forms of immunization and vaccines, but the ones mentioned above generally appear to be the most effective and the most widely used.

Typical vaccination schedules are 0,1 and 6 months or 0, 1, 2 and 10 months. The 0, 1 and 6 month vaccination schedule is preferred for routine pre-exposure prophylaxis. The four-dose schedule may be preferred, however, for immuno-compromised patients or for postexposure prophylaxis. It has also been recommended that a booster shot be given every 5 to7 years after the initial vaccination. Infants may also be vaccinated this way.

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DIS 16.16

Epidemiology of Hepatitis B Virus

The hepatitis B virus is globally distributed among humans. Despite reports showing HBsAg present in other primates, humans remain the principal reservoir. In more developed countries, the prevalence of hepatitis B virus infection has been decreasing likely due to changes of life-style in high risk groups, availability of HBV vaccines and screening of blood donors to name a few.

The primary source of HBV is the blood. However, the virus has been detected in a variety of bodily fluids such as saliva/ nasopharyngael fluids, semen and menstrual fluids. The virus has not been detected in feces, likely due to viral inactivation by enzymes found within the intestinal mucosa or bacterial flora. It is safe to assume that the virus is present in all fluids of an infected patient. With virus titres as high as 10 billion virions per millilitre of infected blood in an HBe-Ag-positive carrier which can linger on dry surfaces for at least one week, transmission of HBV is quite simple if care is not taken.

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HepTeach on the Web !!

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New Java Enabled Version The latest version of HepTeach encorperates some Java elements for ease of site navigation. The site is only suitable for Java enabled browsers (certian Netscape and Internet Explorer versions 2 and most versions above).
FTP Version This version is a compressed file in Microsoft Word format. Once downloaded the file will need to be uncompressed using a suitable utility such as WinZip (339 KB).

Prevalence of hepatitis B virus infection in healthy persons in North India

M. IRSHAD, Y. K. JOSHI, S. K. ACHARYA, B. N. TANDON

ABSTRACT

Background. There is scant information on the main methods through which hepatitis B virus infection is transmitted in India. We, therefore, studied the prevalence of hepatitis B surface antigen and antibody to hepatitis B surface antigen in voluntary blood donors as well as in those healthy groups who have a high risk of contracting this infection.

Methods. The groups at risk studied included commercial sex workers (635), eunuchs (28), truck drivers (217), professional blood donors (1117) and health care workers (1313). In addition, 20 435 voluntary blood donors were also studied.

Results. Hepatitis B surface antigen (and its antibody) was positive in 2.6% (14%) of voluntary blood donors, 3.6% (19%) of commercial sex workers, 5% (16%) of truck drivers, 12% (9%) of professional donors, 1.4% (19%) of health care workers and none (18%) of the eunuchs. Except professional donors and truck drivers, none of these groups had a higher positivity than the normal population (2.6%).

Conclusions. Our results indicate that in India the so-called high risk groups, other than truck drivers and professional blood donors, are unlikely to represent major sources of infection.

Natl Med J India 1994;7:210–12

INTRODUCTION

There are two main modes of transmission of the hepatitis B virus (HBV). The vertical transmission is from mother-to-infant while horizontal transmission occurs through parenteral exposure (needle-prick injury, blood transfusion and sexual contact). Though it has been reported that vertical transmission accounts for about one-third of the hepatitis B surface antigen (HBsAg) carriers,[1] this may vary from country to country and also between communities. Some recent reports,[2–4] have suggested that frequent sexual contact with multiple partners is also an important route of HBV transmission. The relative roles of the possible modes of spread of HBV infection vary from place to place and in order to plan any community-based strategy for prevention of HBV infection, it is important to evaluate the importance of each of these modes of HBV transmission. Since no data on this aspect are available from India, we planned the present study to determine the HBV status of different healthy groups to assess the possible modes of transmission of HBV infection and to suggest a strategy for prevention of this infection in our country.

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SUBJECTS AND METHODS

The major groups included in this study were commercial sex workers (635), eunuchs (28), truck drivers (217), professional blood donors (1117) and health care workers (1313). The main characteristics of these groups are given in Table I. None of them had a past history suggestive of liver disease, they were not intravenous drug users and were negative for HIV antibodies. They all lived in Delhi or close to it. Among the professional donors and truck drivers, 70% were alcoholics but none of the subjects in the other groups were. Commercial sex workers (CSWs), eunuchs and truck drivers represented the groups at high risk for HBV infection due to their frequent sexual contact with many partners. Professional blood donors, who mostly belonged to areas outside Delhi, sold their blood to different hospitals and private clinics in Delhi and faced the risk of being pricked by contaminated needles. Health care workers included doctors, nurses, laboratory personnel and ward attendants working at the All India Institute of Medical Sciences (AIIMS), New Delhi. For comparison, a large group of healthy voluntary blood donors (20 435) were also studied. In each group, there was a random selection of study subjects without any consideration of sex, religion, region and caste. However, all of them were adults. Both HBsAg and antibody to HBsAg (anti-HBs) were tested in the sera of these groups by modified ELISA techniques[5,6] using kits (Abbott Laboratories, USA). The HIV antibody test was done using an ELISA kit (Wellcome Laboratories, UK).

Statistical analysis was done using the chi-square test.

RESULTS

HBsAg was detected in 2.6% and anti-HBs in 14% of healthy voluntary blood donors with an equal distribution amongst both sexes. These data were compared with the results obtained from the high risk groups. The prevalence of HBsAg and anti-HBs in two other groups—CSWs and eunuchs—who were at high risk due to their sexual behaviour was not significantly different (Table II). However, truck drivers had higher levels of HBsAg positivity (5%) while eunuchs had lower positivity (0%). In pro-

TABLE I. Characteristics of different groups

Group	*n*	Mean age (years)	Sex	Socio-economic status	Sex habit	Sexual partners
Voluntary blood donors	20435	28±8	1:1	low to high	Heterosexual	Single
Commercial sex workers	635	26±4	All females	low	Heterosexual	Multiple
Eunuchs	28	34±3	–	low	Homosexual	Multiple
Truck drivers	217	26±6	All males	medium	Homo and heterosexual	Multiple
Professional blood donors	1117	30±8	All males	very low	Heterosexual	Single
Health care workers	1313	37±12	1:1	medium to high	Heterosexual	Single

There were no intravenous drug abusers and none of the subjects was HIV positive

TABLE II. Prevalence of HBsAg and anti-HBs in the different groups

Group	HBsAg status			Anti-HBs status		
	n	% positive	p value	*n*	% positive	p value
Voluntary blood donors	20435	2.6	–	253	14	–
Commercial sex workers	635	3.6	ns	203	19	ns
Eunuchs	28	0	<0.01	28	18	ns
Truck drivers	217	5	<0.01	184	16	ns
Professional blood donors	1117	12	<0.001	278	9	ns
[redacted]h care workers	1313	1.4	<0.01	1313	19	ns

HBsAg and anti-HBs positivity in voluntary blood donors were used as reference values for comparison ns not significant

fessional blood donors, HBsAg positivity was 12% which is higher and anti-HBs positivity was 9% which is lower than in healthy individuals. Screening of a large group of health care workers working at the AIIMS demonstrated a low HBsAg prevalence (1.4%) with no difference in anti-HBs positivity (19%) compared to the voluntary blood donor group. Further, the prevalence of these two markers in different categories of health care workers (Table III) showed no significant difference.

TABLE III. Comparative status of HBV markers in different categories of health care workers

Group	HBsAg status		Anti-HBs status	
	n	% positive	*n*	% positive
Physicians	190	1.1	190	17
Surgeons	124	1.6	124	16
Obs/Gynae	96	2.1	96	17
Dentists	15	–	15	20
Radiologists	40	–	40	28
Ophthalmologists	36	2.8	36	19
Nurses	500	1	500	17
Laboratory staff	256	2.3	256	19
Administrative staff	56	–	56	21
Total	1313	1.4	1313	19

DISCUSSION

A study from the Phillippines suggests that in developing countries an HBsAg carrier pool is created mainly by vertical transmission from mother-to-child and not by the horizontal route.[1] The major groups where conventional preventive measures are rarely adequate or effective and thus immuno-[redacted]ylaxis becomes necessary, include spouses of HBsAg carriers, sexually promiscuous persons, eunuchs and health care workers. There are several reports from other countries indicating high carrier rates in these groups.[7] Thus, they require a special effort to prevent HBV infection.

We selected two distinct groups, one where multi-partner sexual contact[7] was common, and the other, where frequent exposure to HBV positive patients blood or their body secretions and contaminated instruments, were presumed to be the major modes of transmission.[7] The first group included CSWs, eunuchs and truck drivers whereas the persons studied under the second group were health care workers and professional blood donors. Besides, a large number of healthy people were also screened for baseline data from the population.

Our results show that, compared with control subjects, the HBsAg carrier rates in CSWs were similar, in truck drivers they were higher and in health care workers they were lower. The carrier rate was almost five times higher in professional blood donors. The low HBsAg positivity in eunuchs is difficult to explain. Anti-HBs positivity was similar in all the groups except in professional donors where it was low. HBsAg and anti-HBs positivity was similar in all the different groups of health workers.

We expected CSWs, eunuchs and truck drivers to have a high prevalence of HBV markers as they generally do not use condoms during sexual intercourse.[2–4] However, our data show that only truck drivers had a high HBsAg positivity. This suggests that sexual contact may not be an important mode of HBV spread in India.

It has already been established that professional blood donors are a very important source of HBV infection.[8,9] We found HBsAg positivity in 12% and anti-HBs in 9% cases in this group. Both these figures are higher than those in healthy voluntary blood donors. Whereas high HBsAg positivity in them was attributed to repeated needle pricks, a low anti-HBs level indicates that few persons can mount an effective immune response after infection. Though, it is difficult to explain, yet suppressed immune competence due

to undernutrition or immunotolerance produced by frequent exposure to low level HBsAg, may be the reason for the low anti-HBs levels.

An important group, both for transmitting as well as acquiring infection are health care workers.[8-11] On screening them, we found that both HBsAg and anti-HBs levels in them were similar to those in the general population and the HBsAg positivity was lower. Anti-HBs positivity was the same as in the general population which again suggests that a higher risk of exposure in this group is unlikely. Further analysis of the HBsAg and anti-HBs status of those health workers who had been in the profession for more than 10 years against those less experienced showed no difference in prevalence rates either between themselves or against our control values. The low prevalence of HBV related markers may be due to their awareness of potential HBV infection and taking precautions while working.

These results support our previous findings which clearly indicate that blood transfusion from professional blood donors and vertical transmission are important modes of spread of HBV infection in India.[12-15] The so-called high risk groups are not always at high risk and thus may not require mass immunoprophylaxis, if they follow standard preventive measures. A mass immunization policy may not be cost beneficial and immunization should be restricted to only infants of HBsAg positive mothers.[15] Immunoprophylaxis in health care personnel should be limited to only those groups who show high prevalence of HBV markers on repeated screening.

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Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attractions of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

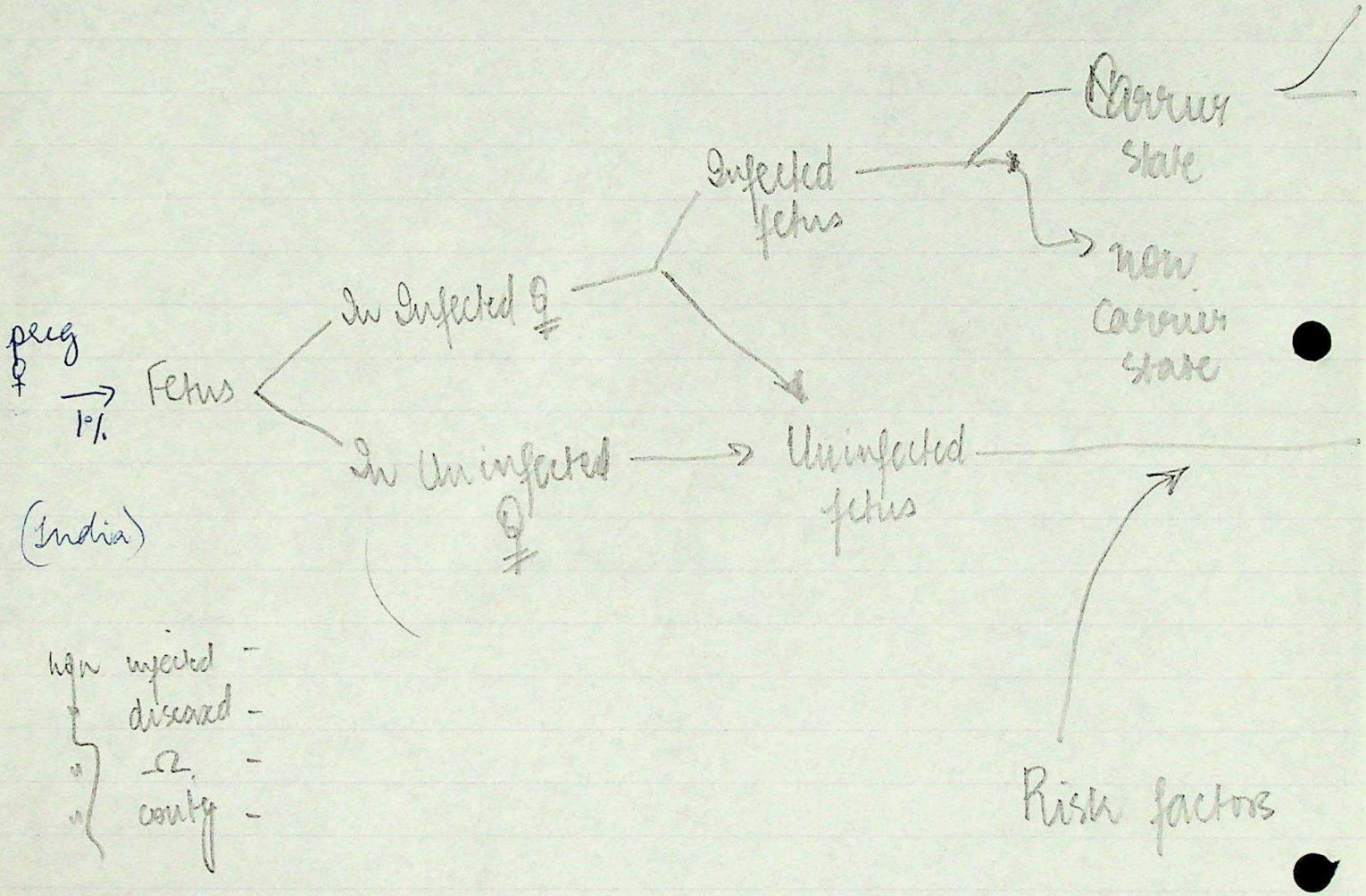
The National Medical Journal of India wishes to recognize the efforts of these doctors in a new section 'Obituaries'. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his education and training and highlight the achievements as well as the disappointments. A photograph should accompany this article.

—*Editor*

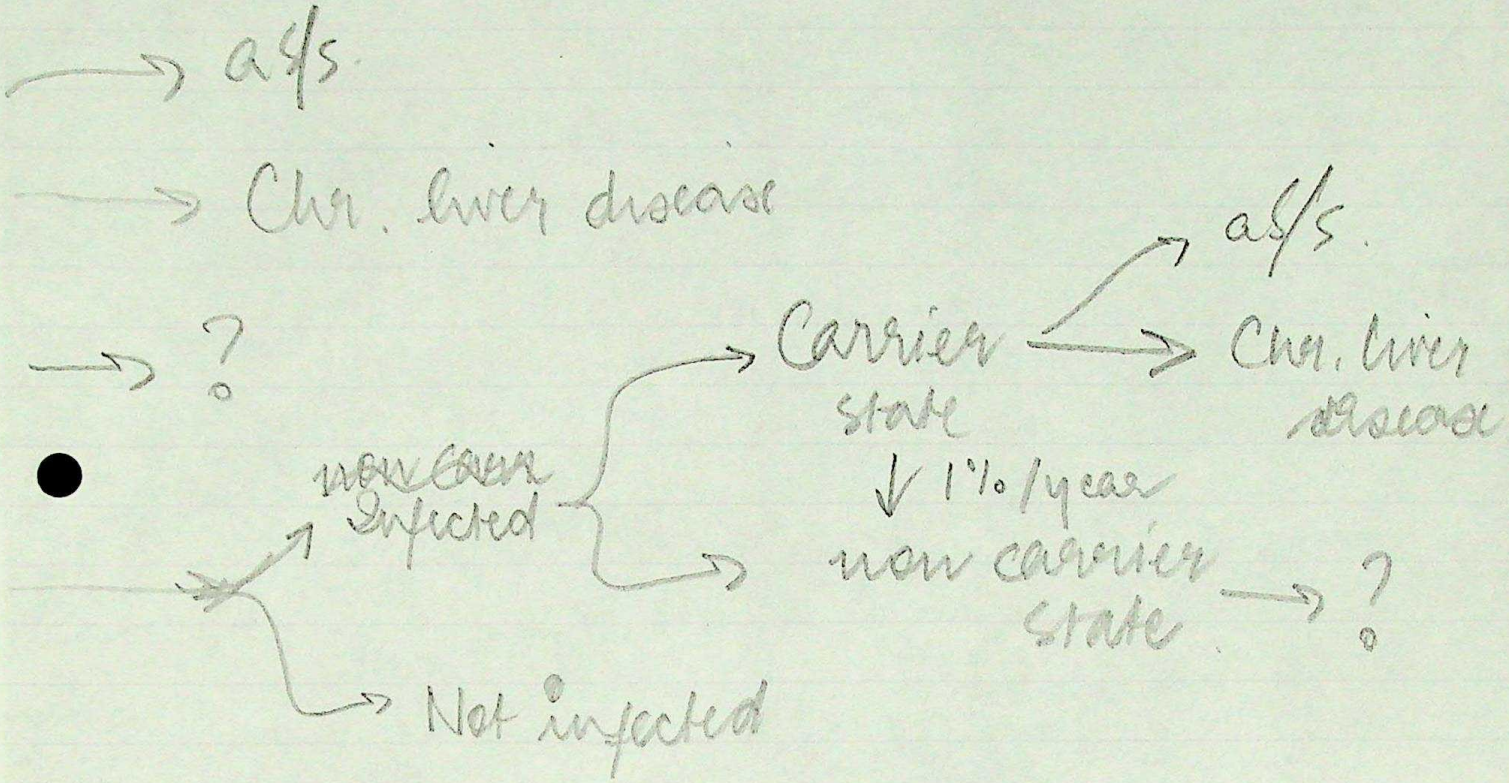
POSSIBLE INTERVENTIONS

(1) No known treatment available
Vaccination - 3 inj over six months. < plasma derived / genetically engineered.
95-98%.

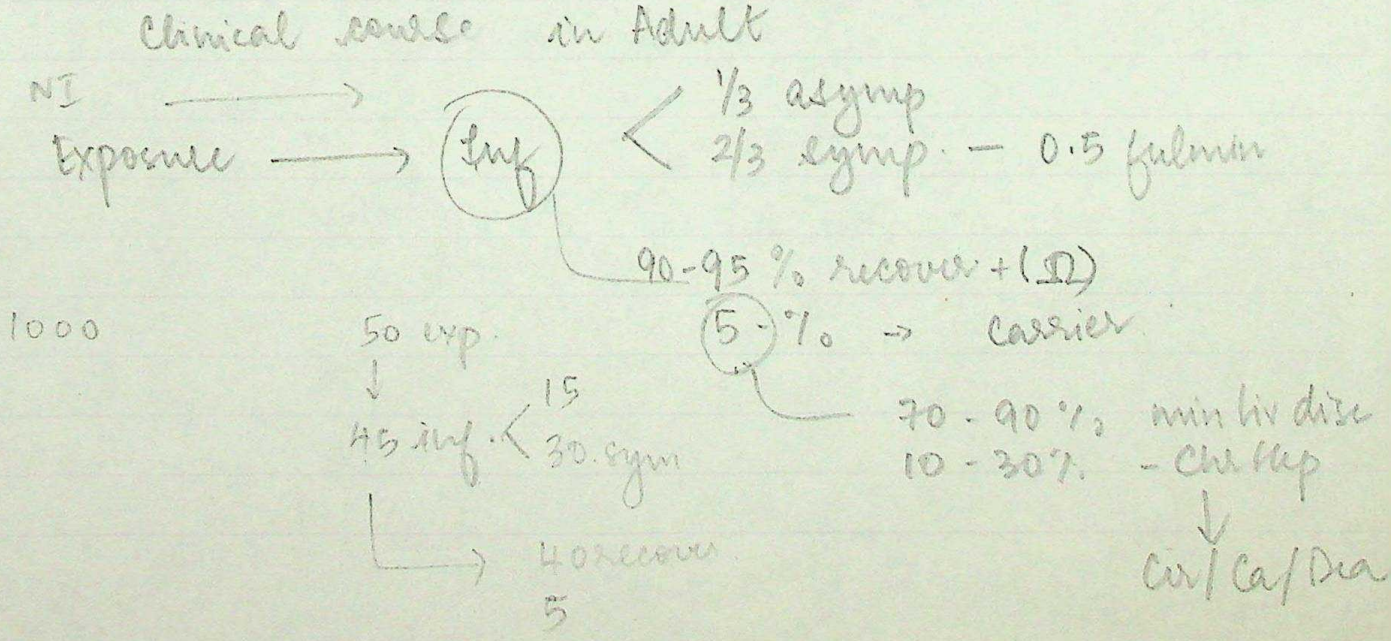
VACCINE Very effective (no figures) [D1 - D30 - D180]
2-8°C
<10 yrs - 10 M in .5 ml (single dose vial)
>10 yrs 20 M in 1 ml



INDIA - 2.5 - 3 lakh casualties each year by perinatal transmission


a/s.
Chr. liver disease
?
Carrier state
a/s.
Chr. liver disease
1%/year
non carrier state
?
now carrier infected
Not infected

+
+/-
~~+~~ ?
~~+~~ +/-


Clinical course in Adult
NI
Exposure
Inf
1/3 asymp
2/3 symp. — 0.5 fulmin
90-95 % recover + (Ω)
1000
50 exp.
45 inf.
15
30. sym
4 recover
5
5 %
carrier
70 - 90 %
10 - 30 %
min hv dise
- Chr Hep
Cir/Ca/Dea

PROBLEM

(1) 1/20 people are Hep virus carriers (<5%) – [Vol 7 Issue 5 NMJI 1994 216-220]

High risk all medical/paramedics/homo/CSW/promisc heterosexu
IV drug users // Tatooing / contact sports
People in need of reg Blood transfusions / dialysis
infants to Hep B mothers · & Family mem of Hep B car

(2) >10% of popln may suffer CLD from Hep B
3.8 - 4.2 %

? percentage in gen popln of
- Acute hepatitis / fulminant
- Chronic hepatitis
- ~~Cirrhosis~~ / chronic liver disease
- Ca liver

HbV – 60 - 70 %. acute hep – adults
20 - 22 % Children
50 %. CLD
60 - 70 Chr. hepatitis
20 - 30 %. fulminant
80 %. Hep CA in children

} So what

(Who are these women / old people ??)

World - 370 million Indian - 45 million (4.7 carrier rate)

(3) WHO 1996 2000,000,000 infected → 350 million carriers
↓ 2 million die

India 45 million get
257 million die

In High Risk Gp - HbV inf is 12-74 %.
of

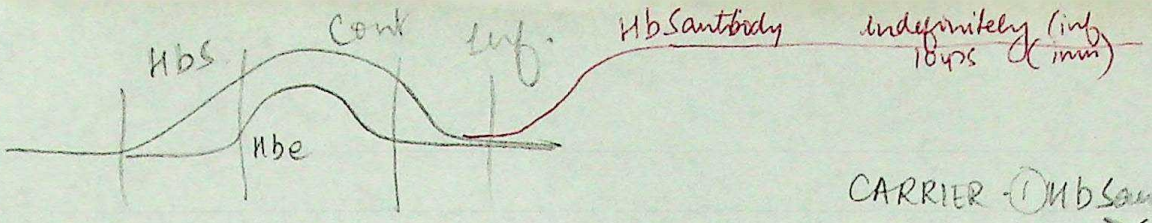
(4) Taiwan - 22,707 persons followed over 3yrs
⇒ 3000 HbsAg +ve → 49 Ca liver
158 HbsAg +ve mothers - 40 % positive for HbsAg

7. Adults Annual incidence of inf - 2.7 %

China - vertical transmission → high incidence
→ due to clustering in families

40-50,000 new cases of C. liver disease / each year
Ca liver

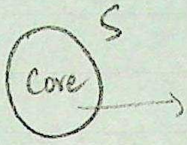
60% due to hepatitis B.



CARRIER - ① HbSantigen >6 mths
② HBe (infectivity)
③ HbC viral replication
HbC antibody (IgM) ↑ in window period
HbC antibody (IgG) (chronic / past.

EPIDEMIOLOGY

(2) DNA virus



DNA polymerase
core antigen
e antigen

5-14 % of total Hb inf are due to mutants (not detectable serologically) no vaccine protection

Human reservoir only

Modes of trans — Mother — Parenteral — Sexual trans

(In late perinatal per or delivery/ BF / handling) → Fetus

Horizontal transmission (Close contact)

In 50% of cases → NO h/o CONTACT ELICITED.

VER → Carrier pool 50 % is thru horizontal tran
40 % efficacy of vertical transmission
90 % if mother is HBe +
90 % of infected at birth → chronic carrier
25 % of these → Cirrhosis / Ca liver in 2nd - 4th decade of life

I → 3 - 20 % efficacy of transmission
Recommend - Soap + water wash
HbIg + Stdr Vacc regime
Transmission thru bl products - 90 %

25 % of infections follow family clustering

Carrier pool
50 % ? horizontal
50 % ? vertical.

50 % carria → CLDisea

INDIA - 9 % of pregnant women (2.8 %) HBsAg +

HBeAg (4 - 68.7 %)

Course

Children – younger ↑ carrier state chance
mild hepati

Adults — Acute hepatitis — 10% → chr carriers
↓ 1-2 %
fulminant hepatitis
↓ some (?)
Ca Liver / liver disease after decades

40% lifetime risk of Ca / Cirrhosis in chr carrier
- 8th most imp worldwide carcinogen 2nd to tobacco
- Highly infectious - 100 times >>> HIV

DIS 16a .57

CLINICAL SPECTRUM OF HEAPATITIS - B

Natural infection with heaptitis B virus has different course in children as compared to adults. Earlier the age at which it occurs, milder is the clinical course and higher is the chance of becoming a chronic carrier. In Fact, new borns infected perinatally rarely develop clinical disease but their chances of becoming carrier are as high as 90% if mother is Hbe Ag positive and 22-30% if she is Hbe Ag negative. Many of these carriers will develop chronic liver disease and some would go on to develop carcinoma of liver in their second to forth decade of life.

Adults infected with HBV suffer from acute hepatitis and 10% become chronic carriers. Some would develop chronic liver disease and CA liver after a decade or two. If the adult with acute HBV hepatitis has marginally raised liver enzymes then the chances of becoming chronic carriers are high are compared to those with markedly raised enzymes. Fulminant hepatitis with HBV occurs in 1-2% of cases.

ACUTE VIRAL HEPATITIS

Acute viral hepatitis occurs after an incubation period of 4-12 weeks.

Prodromal symptoms

* Anorexia * Nausea and vomiting * Fatigue * Malaise

* Arthralgia * Myalgias * Headache * Protophobia

* Cough and Coryza.

may precede the onset of jaundice by 1 or 2 weeks.

Dark urine and clay coloured stools may be noticed by the patient from 1 to 5 days prior to the onset of clinical jaundice with the onset of clinical jaundice, the constitutional prodromal symptoms usually diminish but in some patients mild weight loss is common. The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort. Infrequently , patients present with a cholestatis picture, suggesting extra hepatic biliary obstruction. Rarely, a few spider angiomas appear during the icteric phase and disappear during convalescence.

Recovery Phase : Constitutional symptoms disappear, but usually some liver enlargement and abnormalities in biochemical tests of hepatic function are still evident. Complete clinical and biochemical recovery is to be expected 3 to 4 months after the onset of jaundice in 90% of uncomplicated cases. In the remainder, biochemical recovery may be delayed. It is important to note that a substantial proportion of patients with viral hepatitis never become icteric.

Diagnosis : The serum aminotransferases AST and ALT show a variable increase during the prodromal phase and precede the rise in bilirubin level. An acute level of these enzymes, however,

does not correlate well with the degree of liver cell damage, peak levels vary from 400 to 4000 IU or more; these levels are usually reached at the time the patient is clinically icteric and diminish progressively during the recovery phase of acute hepatitis. The diagnosis of anicteric hepatitis is difficult and requires a high index of suspicion. It is based on clinical features and on aminotransferase elevations, althrough mild increases in conjugated bilirubin also may be found. Occassionaly, a prolonged prothrombin time (PT) may occur with only mild increases in the serum bilirubin and aminotransferase levels. The serum bilirubin typically rises to levels ranging from 85 per mol/1 to 340 per mol/1 (15 to 20mg/dl). The serum bilirubin may continue to rise despite falling serum aminotransferase levels. Bilirubin levels above 340 per mol/1 (20 mg/dl) extending and persisting late into the course of viral hepatitis are more likely to be associated with severe disease. Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis.

A diagnosis of HBV infection can usually be made by detection of HBs Ag in serum. In some cases were levels of HBs Ag are too low, the diagnosis can be established by the presence of IgM anti HBs. Alternatively, denovo appearance of anti - HBC and anti HBs during illness and convalescence may support the diagnostic impression.

MANAGEMENT :

REST : Is mandatory if transminases, serum bilirubin and prothrombin time show upward trend. Hospitalisation is rarely required.

DIET : High carbohydrate diet is advisable as it is more palatable. Proteins in adequate amounts are to be supplemented as they are essential for hepatic regeneration, with early signs of hepatic precoma protein is withheld. Parenteral feeding may be required when the patients has severe nausea or vomiting and food intake is not possible.

VITAMIN : Vit K 10mg daily is given if the prothrombin time is prolonged.

CORTICOSTEROIDS : Must not be used as they increase the relapse rate. It is also known to impede hepatic regeneration and help viral replication.

ANTIVIRAL AGENTS : Use not justified.

COMPLICATIONS AND SEQUALAE : The most feared complication of viral hepatitis is fulminant hepatitis (Massive hepatic necrosis) ; fortunately, this is a rare event. Patients usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The liver is usually small and the prothrombin time exces-

sively prolonged the combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the prothrombin tim, together with clinical signs of confusion, disorientation, somnolence, ascitis and oedema, indicates that the patient has hepatic failure with encephalopathy. Cerebral oedema is common, brain stem compression, gastrointestinal bleeding, sepsis, respirator failure, cardio vascular collapse, and renal failure are terminal events.

The mortality is exceedingly high (> than 80% in patients with deep coma), but patients who survive may have complete biochemical and histologic recovery.

ASYMPTOMATIC CARRIERS : Can be detected by the presence of HBs Ag and anti HBC or anti - HBC.

LOW - GRADE CHRONIC PERSISTANT HEPATITIS : In CPH, a mononuclear inflammatory infiltrate expands, but is localised to and contained within portal tracts. The "limiting plate" of periportal hepatocytes is intact, and there is no extension of the new inflammatory process into the liver lobule. A "Cobble stone" arrangement of liver cells, indicative of hepatic regeneration actively, is a common feature and minimal periportal fibrosis may be present.

As a general rule patients with chronic persistent hepatitis are asymptomatic or have relatively mild constitutional symptoms (fatigue, anorexia, nausea), have normal physical findings, except, perhaps for liver enlargement, without the usual stigmata of chronic liver enlargement and have modest devation of amino-transferase activities. Progression to more severe lesions (Chronic active hepatitis or cirrhosis) is very unlikely especially in patients with autoimmune or idiopathic chronic persistent hepatitis, however, progressive disease has been recognised in patients with chronic persistent viral hepatitis and in those with chronic persistent hepatitis following spontaneous or therapeutic remission of anti immune chronic active hepatitis.

CHRONIC ACTIVE HEPATITIS : Characterised clinically by continuing hepatic necrosis, portal/peri portal and, to a lesser extent, lobular inflammation and fibrosis. Chronic active hepatitis is recognised to be a progressive disorder that can lead to cirrhosis, liver failure and death.

MORPHOLOGICAL CHARACTERISTIC OF CAH :

1. A dense mononuclear infiltrate of the portal tracts, which is substantially expanded into the liver lobule.

2. Destruction of the hepatocytes at the periphery of the lobule, with erosion of the limiting plates of hepatocytes surrounding the portal triads (so called peice meal necrosis).

3. Connective tissue septa surrounding portal tracts and extending from the portal veins into the lobule, isolating parenchymal cells into clusters and enveloping bile ducts.

4. Evidence of hepatocellular regeneration - "rosette" formation, thickened liver cell plates and regenerative "pseudo lobules". This process may be patchy or may be diffuse. Histologic evidence of single - cell coagulative necrosis, Councilman or acidophilic bodies, appear in the periportal areas.

Piecemeal necrosis is the minimal histolgic requirement to establish a diagnosis of chronic active hepatitis.

A more severe lesion, bridging hepatic necrosis (subacute hepatic necrosis) characterises a more severe and progressive form of chronic active hepatitis.

Complications of cirrhosis occur in end-stage chronic active hepatitis and include ascities, oedema, bleeding oesophageal varices, hepatic encephalopathy, coagulopathy or hypersplenism.

LAB FEATURES :Moderate elevations in serum bilirubin (3-10 mg/dl) occur. Hypoalbuminemia and prolongation of the prothrombin time occur in severe or end stage cases. Viral markers observed are HBs Ag, IgG anti-HBC, HBeAg, HBV DNA.

MANAGEMENT :

Fulminant Hepatitis : Goal of therapy is to support the patient by maintence of fluid balance, support circulation and respiration, control of bleeding, correction of hypoglycaemia, treatment of other complications of the comatose state in anticipation of liver regeneration and repair.

Protein intake should be restricted and oral Lactulose or Neomycin administered. Meticulous intensive care is the one factor that does appear to improve survival.

When affordable, orthotopic (grafted into its normal anatomical position) liver transplantation is resorted to with increasing frequency with excellent results.

CHRONIC PERSISTANT HEPATITIS : Symptomatic and supportive therapy is essential.

A 40% sero conversion from replicative (HbeAg & HBV DNA detectable in serum) to nonreplicative (anti-HB detectable) HBV infection, with a concommitant improvement in liver histology and an approximately 10% chance of loosing detectable HBsAg is observed with treatment with anti viral drugs and Interferon.

Immuno-suppressed patients with chronic Hepatitis B do not appear to be responsive to Interferon therapy.

CHRONIC ACTIVE HEPATITIS : Same as above.

In patients with end stage chronic hepatitis B, liver transplantation is the only potential life saving intervention.

Antiviral drugs like Levamisole and Ribavarin have been tried with mixed results.

VIRAL MARKERS OF HEPATITIS - B

MARKER	INTERPRETATION
HBs Ag after(Serum, Secretions tissue fluids).	Appears within weeks to months exposure. Persistance for more than 6 months is an indication of chronic carrier state.
HBe Ag (Serum)	It appears along with or shortly after the appearance of HBs Ag. In acute self limiting cases it disappears. Shortly after the peak duration of transminases. Its disappearance precedes that of HBsAg. It's presence signifies on going viral replication and high degree of infectivity.
HBc Ag (liver detected staining)	Its presence supports viral replication.
Anti HBs (Serum)	Protective antibody appears in serum as HBs Ag declines following an acute infection and for atleast 10 years following effective immunisation.
Anti HBc (Serum)	Initially following acute infection, IgM anti-HBc appears in serum and then IgG antiHBs makes its appearance. IgM antiHBs is useful in the diagnosis of HBV infection during the Window period. IgG antiHBC suggests the diagnosis of past or chronic infections.
AntiHBe (Serum)	It correlates with period of reduced infectivity.

Routine Serology in HBV infection :

SGOT and SGPT helps in diagnosis of acute hepatitis though not in differentiating amongst various viruses causing hepatitis. These levels are raised manifold during acute hepatitis. However in severe fulminannt hepatitis the levels of these enzymes could be paradoxically low or may drop suddenly.

Persistance of elevation in their levels could also be pointer to the presence of chronic liver disease.

If the elevations in levels is minimal during presentation as acute hepatitis, it carries higher chances of development of chronic liver disease later on.

Interpretation of Results : Table - I

Acute infection - Table - II

Chronic infection - Table III

Post exposure - Table IV.

Recommendations for post exposure prophylaxis:

The type of exposure that are believed to warrant immunoprophylaxis include perinatal, percutaneous perhaps sexual contact.

a. Neonates of HBs Ag positive mothers :

For neonates of HBV infected mothers who are HBsAg positive at delivery, passive immunisation with HB Ig within hours of birth

appears to reduce the risk, specially, if the mother fails to resolve the infection. So HB Ig should be given in a dose of 0.5 ml as soon as possible after birth and then again at 3 months and 6 months. At the same time HBV vaccine in appropriate dose should be given at birth and at one and 6 months. This regimen is effective in preventing infection to the neonates in upto 95% of the cases.

b. Needle - prick exposure

For the protection of health care workers exposed to accidental needle stick of HBsAg positive material or by mucosal contamination of infections body secretions, early administration of HB Ig is recommended considering the exposure of the product, the following protocol has been suggested.

1. Known HBs Ag positive source :

Immediate administration of HB Ig (0.06ml/kg) intramuscular, along with HBV vaccine within 7 days is recommended. Following this, the recipient sample is tested for anti HBs. No further treatment is required if anti HBs exceeds 10 MIU/ml. In such cases, a single booster dose of vaccine is all that is needed. If anti HBs is absent or less than 10 MIU/ml, anti HBs testing is conducted. If this is also negative a second dose of HB Ig at one month interval and two doses of HBV vaccines at 1 and 6 months should be administered.

ii. Known source ; unknown HBs Ag status :

If the source is a recognised, high risk individual, like a homosexual man, drug abuse, a patient on dialysis the donor and the recipient blood sample should be obtained immediately and a dose of HB Ig (0.06 ml/kg) should be administered as soon as possible. If donor is HBs Ag negative, discontinue therapy. If donor is HBs Ag positive, the protocol mentioned earlier should be followed. If the same is low risk, Prophylaxis is optional.

iii. Sources of HBs Ag status unknown :

The same protocol is recommended as that suggested for a high risk sources exposure.

DIS 16a. 28

ADMIN@leo.ilban.ern, 01:33 PM 2/3/99, Campaign against misuse of Hep

From: ADMIN@leo.ilban.ernet.in
To: @ilban.ernet.in, il-health@unv.ernet.in
Date: Wed, 3 Feb 1999 13:33:06
Subject: Campaign against misuse of Hepatitis-B vaccination succesful!
Reply-to: admin@leo.ilban.ernet.in
CC: il-environment@unv.ernet.in
Priority: normal
Organization: ESG , BANGALORE

Dear Friends,

Recently, various medical professionals and NGOs of Bangalore initiated a campaign against the misinformation and misuse of the Hepatitis B Vaccination Programme engaged by various commerical organisations including MNCs.

The organisations involved in the campaign included Drug Action Forum, Environment Support Group, Community Health Cell, St. John's Medical College Hospital, and Sanmathi. Dr. Shrdi Prasad Tekur, Dr. Prakash Rao (DAF-K) and Dr. Sebastian (CHC) very actively involved.

A Press Conference was held and the Press Release that documents the issues involved, and concerns raised is enclosed below. The media reported the Conference very widely.

The Government which had not taken any action on the ongoing abuse for several months, was presurised by the Campaign to come out with clear steps. In a most significant development, Karnataka Health Minister Dr. Mahadevappa ordered an high level enquiry into the entire matter, with the involvement of the Health Secretary, Director Drug Control Authority, and several other senior officers. The commission of enquiry has been ordered to submit a report within a month's time.

In light of such abuse, the Health Minister has also called for a National Policy on Immunisation.

Based on this initiative, it is hoped that groups across the country can press for immediate action against such misuse in their regions, and press for similar enquiries from their Health Minister. Also it might aid to pressurise Health Ministers of every State to write to the Cental Health Minister/Prime Minister for a National Immunisation Policy, that is not susceptible to the pressures of various business interests.

It might also be of interest to list members, that subsequent to the

enquiry ordered, Smithkline Beecham, the MNC manufacturing the vaccine against Hep B and who held the patent till last year, flew a doctor from Zurich, who has been addressing the Press on the need for NRI's to go for Hepatitis Vaccinations!! This report is also enclosed.

Best regards

Leo F. Saldanha
Coordinator
Environment Support Group

{ESG is a research, training and advocacy initiative working on various issues of concern relating to environmental justice, public health, planning, citizen engagement, etc.)

Press Release

Ongoing Vaccination Campaign against Hepatitis - B Unjustified Causing Needless Alarm

13 January 1998

There is a major ongoing campaign initiated by some commercial agencies towards Hepatitis-B vaccination through vaccination camps, by providing injections of such vaccines as Engerix-B, Shanvac-B and Hepavac. These are being conducted along with very wide publicity by non-professional agencies exploiting the ignorance of well-meaning social organisations. The claims made by these agencies certainly do not present an accurate picture of the incidence of this disease, nor the imperative for such a massive vaccination programme.

As such campaigns are continuing without any intervention whatsoever from the relevant Health agencies, and there have been reported instances of excessive indulgence in making money by exploiting the ignorance of the public, the undersigned wish to make the following statement in the wide public interest. We take strong objection to such developments and aim to awaken the relevant Health authorities, Local and State Governments, and public interest agencies and public-spirited individuals to join us in evolving a relevant and rational policy of immunisation.

Hepatatis-B is only one form of Jaundice, and not the most widely communicable or of immediate public health importance. For instance, there are various other types of viruses that cause jaundice, spread

through water and foodstuffs, which affect the public more, e.g., Hepatitis A, C, D, E and G. Other diseases of the liver also cause jaundice for instance when there is obstruction to bile flow. Hepatitis-B is transmitted in a manner very similar to AIDS transmission, i.e., through blood and blood products, injections, sexual activity, and from an infected mother to her child.

Hence, the needless alarm created by the mass vaccination drive and associated information disseminated by the various agencies involved is wholly unjustified in its proportion and not relevant at all from the public health point of view. The ignorance of the people is being exploited, spreading fear and a wrong impression about the disease as well as the effectiveness of the vaccine.

Unfortunately, people have been led to believe that the vaccine guarantees protection against all forms of "jaundice" and "cancer" of the liver. Dissemination of such misguided opinion gravely limits possibilities of effective community intervention for even more serious diseases prevalent in our society. For instance, TB, Malaria, Typhoid, Measles, Polio and other such diseases that take a heavier toll are being ignored to the detriment of the public health.

The introduction of these vaccines is highly questionable considering that there is no evidence based on community studies to justify the same on a mass scale in Indian conditions. Studies quoted in justification of the present campaign are extrapolations of very limited research based on hospital data, largely supported by drug companies with vested interests. Further, any documented evidence in our context has not proved the extraordinary claims that are being made about the effectiveness of the vaccine. On the contrary, small local studies negate the claims to efficacy of the vaccine.

The Department of Health has been shockingly silent on the essential facts relating to the disease, quality of the vaccine, the cost of the product and the manner in which the vaccines are being promoted. This silence has been significantly exploited to the detriment of the public. In fact, people feel swindled by the varying costs of the different vaccines at different camps. Most dangerously, there is no legal and medical responsibility being taken in case the vaccines react adversely or if the vaccination is ineffective, as should be the case.

Such gross mis-information which are half-truths, unwarranted, unscientific and unethical and which unnecessarily scare the general public into vaccination for all, is highly condemnable, and should be stopped immediately.

Considering the gravity of the situation, we demand the following

action with immediate effect:

1. Stop the mass vaccination that is being introduced in schools, at public camps and to non-risk groups.
2. The drug control authorities and relevant government agencies should immediately step in to take corrective action against the prevailing vaccination campaign and involve in a mass information dissemination exercise presenting the facts of the disease in arriving at a rational disease control approach.
3. The vaccination programme should only be conducted under proper medical supervision and not at all for profit, as is presently the case.
4. The Government must take the responsibility of constituting a committee of experts to prepare Guidelines for the prevention of the disease and introduce vaccination only where needed.
5. The Government should step in to subsidise the cost of the vaccine so that high risk groups such as health care workers, high-risk adults including sex workers, street children, pourakarmikas, fire-force and police personnel, house-hold contacts of Hepatitis B patients, those given to cultural rituals such as tatooing, etc., are protected from contracting this disease or spreading it to others.

In short, this statement is being made in the public interest to prevent confusion in the public mind over the disease and the exaggerated need for vaccination. This is also a strong entreaty to the Government to end its ambivalent attitude to the ongoing campaigns, and prevent exploitation of the public by the vested interests. Finally, this is an initiative to inform the public to be guarded against the ongoing campaign and approach the relevant authorities and other sources for accurate information on the disease and its control.

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Tel: 3379016

In consultation with:

Community Health Cell, 367, Srinivasa Nilaya, Jakkasandra, 1st Main, 1st Block Koramangala, Bangalore 560 034 Tel: 5531518

Dr. Harshad Devarbhavi, and Dr. Philip, Gastroenterologists, St.

John's Medical College Hospital, Bangalore.

Supporting organisations:

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Fact Sheet about Hepatitis-B and the Vaccine

About the disease:

Hepatitis B (HB) is caused by a virus and is only one form of Jaundice, others being A, C, D, E and G. HB is several times more infectious than AIDS, and very much like AIDS only prevention works as there is no cure.

HB transmission is strikingly similar to the transmission of AIDS, i.e. through blood and blood products, injections, sexual activity and from an infected mother to her child. Transmission of HB infection through mosquito bites is unknown.

Some estimates put the quantum of disease carriers in India at about 4 crores (40 million), though this evidence is not based on large-scale community studies. 90% of those infected will recover, whilst 10% may remain as highly infectious carriers. Only 1% of these develops Fulminant Hepatitis. Chances of an infection at birth are high and directly related to the number of injections received (as quoted from WHO report No WHO/EPI/GEN/88.5). The chances diminish such that at 12 months age, it is the same as in adults. The incidence of HB virus is highest in blood donors, frequent Intravenous users, health care workers, sexually promiscuous adults, and children born to infected mothers.

HB is one of the top 10 causes of liver cancer (ibid.). 80% of liver cancers are attributable to HB infection. However, liver cancers form only 1.4% of all cancers.

World Health Organisation recommends that "in countries with chronic carrier rates of hepatitis B of over 2%, HB immunisation should be introduced as an integral part of existing childhood immunisation programmes as quickly as resources permit. Efforts to use this vaccine in ways which do not strengthen existing programmes should

not be encouraged."

Though the cost of childhood immunisation in India against HB is only Rs. 500 crores, the Government has not yet included this vaccination in its immunisation programmes. On the contrary, the Government's ambivalent attitude in addressing the problem has given rise, unfortunately, to misuse of the public ignorance creating a scare amongst them and promoting unnecessary vaccination camps.

About the vaccine:

The Hepatitis B vaccine is among the best ever developed against any disease. It is seen is as the first and effective major cancer vaccine. The current price is the only major deterrent towards launching a mass immunisation programme.

The vaccine is stable and effective only if kept at temperature ranging between 20 to 80 Centrigrade. It should not be frozen or exposed to higher ambient temperature ranges.

The vaccine is most effective when first given within 48 hours of birth, and the scheduled repeat dosages are completed depending on the type of vaccine given. If the repeat dosages are not complete, then the immunity of the individual to the disease reduces significantly.

The effectivity of the vaccination above 1 year of age is the same as for adults. Thereby, from a public health point of view childhood immunisation is extremely important and the adults who need this vaccination on a priority basis are only from high-risk groups. Such high-risk adults are medical personnel, rescue workers (police, fire-force, military), pourakarmikas (municipal waste collectors), street children, sex workers and people with multiple sex partners, patients on haemodialysis or those receiving blood and blood products, frequent intravenous (IV) users, house-hold contacts and sex partners of HB patients and international travelers.

Vaccination must necessarily be given under medical supervision. Proper records of vaccination must be maintained for future reference.

Very little is known about the long-term effects of the vaccine. In India very little evidence is available about the efficacy and any other effects of the vaccination programme as no community surveys have been conducted on a significantly large scale.

Issued in the public interest by:

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'NRIs Visting Country need to be immunised'

The Hindu, Bangalore. 03 February 1999

Bangalore, Feb 2. Non Resident Indians visiting the country after long years need to be immunised against diseases as has been the case with foreign tourists visiting India, according to Dr.Robert Steffen, Head, Division of Communicable Diseases and Director of Travellers' Health Institute, University of Zurich, Switzerland. The NRI's coming home on a holiday should take shots against tetanus, polio, diptheria, hepatitis A and B and typhoid and prophylactics against malaria, he said.

The NRIs should also follow the advice often given to foreign tourists coming to India. "Never drink water unless it is mineral water in bottles". Even drinking whisky with ice cubes could result in serious infections from viruses used in the water for the ice, the Swiss medical expert said.

Dr. Steffen, who is visiting India to give a series of lectures on the Hepatitis A vaccine, told The Hindu that the vaccine had few side effects. Some pain in the inoculated spot, soreness and a few days of fever were likely in some persons. The vaccine for children has been introduced in India by SmithKline Beecham Pharmaceuticals, and 30 million doses have been used worldwide with no serious side effects.

The hepatitis A virus was identified in the Eighties and an inactivated virus was developed into vaccine some years ago. The vaccine has been found to be safe and effective with no case of hepatitis infection reported in those vaccinated and there was long term immunity. Dr. Steffen said. The vaccine was introduced in Europe in 1992.

When children contracted hepatitis A, they usually recovered faster and the fatality rate in children was around 0.1 per cent. The infection was more serious later in life with fatality of around 2 per cent or higher. THe infectiion was more serious later in life

with fatality of around 2 per cent or higher. The infection did not usually recurr. Vaccinating children was found to be the most effective way to control the spread of the virus. Vaccinatino also reduced the number of "carriers" who could infect others.

A fullblown hepatits infection could destroy most of the liver and there was till now no medication in Western medicine which acted on the liver, Dr. Steffen said. Persons from the more affluent sections of society were more in danger from hepatitis. THose from poor families often had the virus in a milder form as young children and then developed immunity.

In regard to travel medicine, he said that with more people travelling around the world now immunisation was necessary. Work on developing a malaria vaccine had been going on for some years with some Swiss and US pharmaceutical companies engaged in research. The results so far had been unsatisfactory. Dr. Steffen said "No vaccine against malaria was likely to be developed in the next few years".

For typhoid (called enteric fever by our doctors) two types of injectible vaccines and one oral vaccine were available. A mixed vaccine for hepatitis A and B was a distinct possibility in the next few years, Dr. Steffen said. HE is giving talks on the hepatitis A vaccine to audience of doctors in Calcutta, Mumbai, Hyderabad, Delhi and Kochi.

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DIS 16a.

Medline Search - Hepatitis B + India + Epidemiology
14/12/98

Gut 1996;38 Suppl 2:S56-9

Epidemiology of hepatitis B virus infection in India.

Tandon BN, Acharya SK, Tandon A

Pushpawati Singhania Research Institute for Liver and Digestive Diseases, New Delhi, India.

The average estimated carrier rate of hepatitis B virus (HBV) in India is 4%, with a total pool of approximately 36 million carriers. Wide variations in social, economic, and health factors in different regions may explain variations in carrier rates from one part of the country to another. Professional blood donors constitute the major high risk group for HBV infection in India, with a hepatitis B surface antigen positivity rate of 14%. Blood transfusions represent the most important route of HBV transmission among adults. However, most of India's carrier pool is established in early childhood, predominantly by horizontal spread due to crowded living conditions and poor hygiene. Acute and subacute liver failure are common complications of viral hepatitis in India and HBV is reckoned to be the aetiological agent in 42% and 45% of adult cases, respectively. HBV is reported to be responsible for 70% of cases of chronic hepatitis and 80% of cases of cirrhosis of the liver. About 60% of patients with hepatocellular carcinoma are HBV marker positive. Small numbers of patients have been reported to be infected with the pre-core mutant virus but none with the S mutant. Coinfection with hepatitis C virus or hepatitis delta virus is comparatively uncommon. In conclusion, hepatitis B is a major public health problem in India and will continue to be until appropriate nationwide vaccination programmes and other control measures are established.

Bull World Health Organ 1997;75(5):463-8

Epidemiology of endemic viral hepatitis in an urban area of India: a retrospective community study in Alwar.

Singh J, Prakash C, Gupta RS, Bora D, Jain DC, Datta KK

National Institute of Communicable Diseases (NICD), Delhi, India.

In a community study during a reference period of 1 year, 192 cases of jaundice were detected in an urban population of 69,440 in Alwar, Rajasthan. Detected by paramedics and confirmed by physicians, these cases gave an annual incidence of 2.76 (95% CI: 2.37-3.15) per 1000 population. At least one of these patients died, giving a case fatality ratio of 0.6%. The jaundice cases occurred in all areas investigated, and affected all socioeconomic strata. About 94% of the affected families had only single cases. Although cases occurred throughout the year, more than 59% occurred during June-September, which are the summer and monsoon months. The incidence was highest (5.23 per 1000) among under-5-year-olds and declined progressively and significantly thereafter. Males had a higher incidence than females at all ages; the differences were not significant. Blood samples from 56 cases who had jaundice in the last 3 months of the reference period were tested for markers of viral hepatitis. Of these, 18 (32.1%), 1 (1.8%), 0, 2 (3.6%), and 4 (7.1%) were found to have hepatitis A, B, C, D and E, respectively. The etiology of the remaining 31 cases (55%) could not be established; previously, they would have been included in the NANB (non-A, non-B) category, inflating its proportion. Hepatitis A (HA) was the predominant type; being comparatively mild, it is perhaps underrepresented in hospital-based data. Many HA cases were in adults, which may be the beginning of an age shift of HA to the right owing to improvements in living standards of the study population. Five cases were carriers of hepatitis B virus (HBV), indicating the importance of HBV infection in India as well. Finally, the study found the annual incidence of laboratory-supported cases of viral hepatitis to be 1.24 (95% CI: 0.98-1.5) per 1000 population, which suggests that it is a major public health problem in India.

Indian J Gastroenterol 1998 Jul-Sep;17(3):100-3

Epidemiology of digestive tract cancers in India. III. Liver.

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Liver cancer or hepatocellular carcinoma (HCC) is the fourth commonest cause of cancer deaths in the world. The condition is extremely common in Southeast Asia and Africa. In this report the available data on the epidemiology of HCC from India are summarized. We estimate that 12,750 new patients will be diagnosed to have HCC in India in the year 2001; this will comprise 1.6% of all incident cancers. Published studies from India and those involving Indian immigrants to other countries suggest that the prevalence of HCC is relatively lower in Indians than in most parts of the world. This contrasts with the widespread contamination of foods with aflatoxin and the moderately high prevalence of hepatitis B (HBV) and hepatitis C (HCV) virus-related chronic liver disease in India. There are no studies available to explain this observation. There are several articles on HBV and HCC in India but there is a paucity of analytical epidemiological data on HCV and HCC from India. Published studies indicate HBV to be the single most important etiologic association, with HCV playing a lesser but important role. About 80% of Indian patients with HCC have hepatitis virus-associated liver disease. Multicenter epidemiological studies are needed to solve some of the enigmas and observations peculiar to India.

Indian Pediatr 1998 Feb;35(2):105-9

Acute sporadic viral hepatitis in urban population of a tribal district in Madhya Pradesh.

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OBJECTIVE: To estimate the incidence of acute sporadic viral hepatitis and describe its epidemiology in an urban population.
DESIGN: A retrospective community survey for jaundice cases. SETTING: Headquarter town of a tribal district, Bastar, in Madhya Pradesh state, India. METHOD: Trained paramedics surveyed about 51,643 population to detect cases of jaundice which occurred in the past one year. Cases were examined to collect clinical and epidemiological data. blood samples were drawn from all cases who had jaundice in the past 3 months for testing them for markers of viral hepatitis.
RESULTS: Study estimated the annual incidence of jaundice cases as 244 (95% CI 201-287) per 100,000 population. Almost 95% jaundice cases occurred in summer and monsoon months. People from all socio-economic strata were affected. The incidence of jaundice was found to be the highest in children below 15 years of age (3.7 per 1000) which declined significantly with the increase in age ($p = 0.0000$). The overall incidence in two sexes was not different statistically ($p = 0.7$). Of 57 cases who had jaundice in the past 3 months, 19 (33%) were confirmed as having viral hepatitis. Hepatitis A and E combined together contributed 68% (13/19) of acute sporadic cases of viral hepatitis, whereas hepatitis B, C and D accounted for the remaining 32% of the cases.
CONCLUSION: The study found the annual incidence of laboratory supported cases of viral hepatitis to be 81 (95 CI 57-106) per 100,000 population, which suggests that it is an important public health problem in India. Hepatitis A was much more prevalent than hepatitis E. Etiology of almost two-thirds of jaundice cases could not be established which require further community studies.

Gut 1996;38 Suppl 2:S39-42

Importance of perinatal versus horizontal transmission of hepatitis B virus infection in China.

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China has one of the highest rates of hepatitis B virus (HBV) endemicity in the world. In a survey of five provinces, the overall HBV infection rate in the general population was found to be 42.6%, with 10.3% testing positive for hepatitis B surface antigen (HBsAg). Higher rates were found in rural than in urban areas. The prevalence of HBsAg among children under 1 year of age is quite low but increases rapidly thereafter, reaching a peak among 5 to 9 year olds. The pattern of age distribution suggests that horizontal transmission is an important route of HBV infection during early childhood, and the proportion of chronic HBsAg carriage attributable to perinatal transmission has been estimated at only 13-20%. Contact with infected family members probably accounts for much of the horizontal transmission in children. In a nationwide survey, 27.2% of families were found to have one or more HBsAg positive members and a strong tendency for family clustering has been identified. The strategy for prevention of HBV infection includes vaccination of all newborns, whether their mothers are HBsAg positive or negative, together with vaccination of high risk populations, and improved control measures in clinics and blood transfusion centres.

Gut 1996;38 Suppl 2:S43-7

Epidemiology and control of hepatitis B infection: a perspective from the Philippines, Asia.

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The prevalence of chronic hepatitis B virus (HBV) infection in the Philippines, as indicated by hepatitis B surface antigen (HBsAg) positivity, ranges from 2% to 16.5%, with an average of 12% in a study of rural villagers. Although mother to child transmission is a major route of HBV infection, other routes (particularly child to child transmission) play an important part after the first year of life. In a study assessing the feasibility and effectiveness of incorporating hepatitis B vaccine into the national Expanded Programme on Immunisation, the coverage rate for fully immunised 1 year olds ranged from 80.9-84% and anti-HBs seroconversion rates ranged from 72-88%. In countries where HBV is not endemic, high risk groups included commercial sex workers (CSWs) and intravenous drug users (IVDUs), who generally have higher HBsAg positivity rates than the general population. In countries with a high HBV endemicity, carrier rates may be only slightly higher among CSWs, suggesting that other modes of transmission are more important in those regions. CSWs who are also IVDUs are at even greater risk. If HBV infection is to be controlled, innovative education and screening programmes are needed, together with the mass immunisation of neonates now started in many countries around the world.

Trop Gastroenterol 1989 Apr-Jun;10(2):106-10

Etiologic spectrum of acute sporadic viral hepatitis in children in India.

Panda SK, Datta R, Gupta A, Kamat RS, Madangopalan N, Bhan MK, Rath B, Guha DK, Nayak NC

The relative magnitude by hepatitis A virus (HAV), hepatitis B virus (HBV) and hepatitis Non-A, Non-B virus (HNANBV) was determined in 496 children from three different parts of India suffering from acute viral hepatitis by tests for specific IgM class anti-HAV and anti-HBV antibodies in the serum. HAV, HBV

and NANB infections accounted for 55.8 per cent, 20.2 per cent and 23.2 per cent of cases respectively. Hepatitis A largely (59.5%) affected younger children of 1-5 yr. Nearly a third of children affected by NANB hepatitis were additionally positive for HBsAg. The proportions of HAV and HBV infected cases respectively decreased and increased with increasing age whereas the incidence of HNANBV infection remained almost constant throughout childhood. Acute NANB hepatitis, a major health problem in the adults of India is also common throughout childhood. This study suggests that this infection does not impart long lasting protective immunity.

Gut 1996;38 Suppl 2:S5-12

The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and subtropical Africa.

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There are approximately 50 million chronic carriers of hepatitis B virus (HBV) in Africa, with a 25% mortality risk. In sub-Saharan Africa, carrier rates range from 9-20%. Many studies have suggested that HBV transmission in Africa occurs predominantly in childhood, by the horizontal rather than the perinatal route. The exact mode of transmission is uncertain but probably involves percutaneous infection through saliva or traces of blood, as well through unsterile needles, tribal scarification, and other possible vehicles. Compared with adult HBsAg carriers in the Far East, those in Africa have a low rate of HBeAg positivity, which may account for the relatively low rates of perinatal infection. It is also possible that African infants are less susceptible to perinatal HBV infection compared with their Asian counterparts. Alternatively, it may be that African infants are indeed infected with HBV at birth but, for genetically determined reasons, have persistently negative tests for a number of years until the virus is reactivated. In view of the high HBV carrier rates in the general population, universal immunisation of all infants is recommended. Ways of incorporating the hepatitis B vaccine into the Expanded Programme on Immunisation in each country are being evaluated.

Scand J Infect Dis Suppl 1990;69:43-7

Epidemiology of hepatitis B virus (HBV) infections with particular regard to current routes of transmission and development of cirrhosis and malignancy.

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The majority of hepatitis B virus (HBV) carriers world-wide becomes infected by transmission from asymptomatic carrier mother to infant, so-called "vertical" transmission, or early person to person so-called "horizontal" transmission, but sexual transmission is also important, especially in low endemicity areas. The histopathological findings at liver biopsies of these HBV-carriers vary from almost normal to severe chronic active hepatitis (CAH) with cirrhosis, and especially cirrhosis is associated with the development of HBV-related liver cancer. The reported annual incidence/100,000 of HBV-induced CAH in north-western Europe is 0.1-0.6 while the burden of the important chronic stages of hepatitis B is manyfold this in most developing countries.

JAMA 1996 Sep 18;276(11):906-8

Seroepidemiology of hepatitis B virus infection in children: Ten years of mass vaccination in Taiwan.

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Department of Pediatrics, National Taiwan University Hospital, Taipei.

OBJECTIVE: To study the seroepidemiology of hepatitis B virus (HBV) infection in children 10 years after a mass hepatitis B vaccination program was begun in Taiwan. DESIGN: Cross-sectional seroprevalence survey.
SETTING: Cheng-Chung/Chung-Cheng District, Taipei, Taiwan, 1994. SUBJECTS AND METHODS: Serum samples from 1515 healthy children younger than 12 years were tested for HBV markers. The results were compared with a baseline seroepidemiologic study conducted just before the vaccination program was launched in 1984 and with a subsequent study in 1989 in the same area. MAIN RESULTS: Eighty-seven percent of the children had received at least 3 doses of HBV vaccine. The overall prevalence rate of hepatitis B surface antigenemia decreased from 9.8% in 1984 to 1.3% in 1994. A statistically significant decrease was observed in every age group from 1 to 10 years. The overall prevalence rate of hepatitis B core antibody was 26% in 1984, 15% in 1989, and 4.0% in 1994. This suggests that the risk of horizontal HBV infection has decreased over time, not only because of the protective effect of the vaccine but also because the infection source has diminished. A high prevalence rate of hepatitis B surface antibody (79%) was noted in 1994 as anticipated.
CONCLUSIONS: The Taiwanese mass vaccination program has protected most children younger than 10 years from becoming carriers, reducing both perinatal and horizontal HBV transmission. Mass HBV vaccination has proved to be a successful method to control HBV infection in this hyperendemic area.

Comments:
Comment in: JAMA 1996 Dec 11;276(22):1802-3

Vaccine 1990 Mar;8 Suppl:S18-20; discussion S21-3

Hepatitis B: global importance and need for control.

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International Task Force on Hepatitis B Immunization, Seattle, WA.

Hepatitis B is a disease of global importance, with greater than 300 million carriers of the virus world-wide. Hepatitis B virus (HBV) is the cause of up to 80% of cases of primary liver cancer, the single most important cause of mortality globally. In countries where HBV carrier rates reach 10%, HBV infection may account for 3% of total mortality, a level which exceeds polio-related mortality before the introduction of polio vaccine. The only means by which hepatitis B can be eventually eliminated is mass vaccination of infants with hepatitis B vaccine as part of the Expanded Programme on Immunization (EPI) in areas of the world where the HBV carrier rate exceeds 2.5%. With recent dramatic increases in hepatitis B vaccine production and decreases in per-dose price, there are grounds for optimism that global HBV infection rates may be reduced by as much as 90% over the next 10 years.

Semin Liver Dis 1991 May;11(2):84-92

Hepatitis B: evolving epidemiology and implications for control.

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Control and the possible elimination of transmission of HBV infection is possible with the appropriate use of hepatitis B vaccines. The prevention of chronic HBV infection has the potential of reducing the association burden of chronic liver disease and primary hepatocellular carcinoma. Worldwide, strategies for the effective use of hepatitis B vaccine have been developed and are being implemented in those areas

where childhood transmission is the predominant source of chronic HBV infections. However, in the United States and other areas with "low" rates of HBV infection, current vaccination strategies have not been effective and have not fully taken into account the multifaceted epidemiology of HBV infection in those areas. Unfortunately, the majority of infections occur among adults who have been the most difficult to access, who acquire infection before they realize they are at risk, and where the changing epidemiology of HBV infections among the various risk groups only emphasizes the problems of vaccine delivery. In addition, the majority of persons receiving vaccine as a result of the current strategy to immunize adult high-risk groups have been persons who acquire HBV infection through occupational exposure, a group that accounted for no more than 5% of cases even before vaccine was introduced. The failure of the current immunization strategy to prevent a disease with significant health care and economic consequences is beginning to cause a reevaluation of this approach. A comprehensive approach to eliminating HBV transmission must address infections acquired during early childhood as well as those acquired by teenagers and adults. 77

J Trop Pediatr 1995 Dec;41(6):328-9

Pattern of hepatitis A and hepatitis B virus markers in cases of acute sporadic hepatitis and in healthy school children from north west India.

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The pattern of viral markers in acute sporadic hepatitis in 329 children and those in 334 healthy school children from North West India were studied. Hepatitis A was found to be the commonest infection in sporadic cases (78 per cent). Of these, 86 per cent were under 10 years and 50 per cent less than 5 years of age. Hepatitis B was positive in 8 per cent, non-A non-B in 13 per cent, A as well as B in 1 per cent, and none had Delta virus infection. Viral markers in healthy school children showed anti-HAV IgG positivity in 96 and 85 per cent in those belonging to low and high socio-economic groups, respectively, indicating past infection. HBsAg was positive in 1 per cent of cases. Viral hepatitis is an important public health problem in children and warrants active immunization.

Indian J Med Sci 1995 Oct;49(10):227-30

Prevalence of hepatitis A, B, C & D in Ludhiana.

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172 sera were tested for serological markers of hepatitis A, hepatitis B, hepatitis C and hepatitis D to define the aetiology of acute viral hepatitis by Enzyme immunoassays. The viral aetiology could be decided in 60.5% (104/ 172) of patients. Hepatitis B infection was present in 34.9%, hepatitis A in 10.5%, hepatitis C in 9.3% and hepatitis D in 5.8% of cases. Delta hepatitis associated with HBsAg positive hepatitis was detected in 10% (6/60) of the patients. The aetiology remained undecided in 39.5% of patients.

Am J Epidemiol 1991 Sep 15;134(6):641-50

Transmission of hepatitis B and hepatitis delta viruses in the households of chronic hepatitis B surface antigen carriers: a regression analysis of indicators of risk.

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To evaluate whether clinical and laboratory features of a hepatitis B surface antigen (HBsAg) carrier can predict risks of infection, its chronicity, and the development of liver disease among close contacts, the authors studied a cohort of 994 first degree relatives or cohabitants (household contacts) of 226 non-drug-addicted chronic HBsAg carriers (index cases), of whom 77% had liver disease and 26% were superinfected by hepatitis D virus (HDV). A logistic form of regression analysis was used to assess the role of each feature in the index case as predictor of hepatitis B virus (HBV)- and HDV-related outcomes among household contacts. Six models of risk, expressed as odds ratios, were assessed by multivariate step-down analysis, with the following results.

1) Infection with HBV in the household contact was independently predicted by the index case being son, sibling, spouse, female, or HBV-DNA positive.
2) Chronic HBsAg carriage in the adult household contact was associated with female sex of the index case and with being a sibling; among young subjects, household contacts were more likely to be chronic HBsAg carriers when the index case was the mother, a sibling, or an HBV-DNA-positive subject.
3) HBV-DNA positivity in the young contact was more likely when the index case was HBV-DNA positive and when she was the mother.
4) HBV-DNA positivity in the absence of hepatitis B e antigen (HBeAg) in serum in the index case was not related to a similar pattern of infection in HBsAg-positive contacts.
5) Super-infection with HDV of an HBsAg-positive household contact was significantly predicted by female sex of the index case and by anti-HDV positivity.
6) Chronic liver disease in a contact was predicted only by HDV superinfection of the index case. We conclude that horizontal, nonparenteral transmission of HBV among siblings plays a major role in the household of HBsAg carriers from an intermediate endemicity area.

Gastroenterol Jpn 1991 Jul;26 Suppl 3:192-5

Hepatitis C virus infection is the major cause of severe liver disease in India.

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The present study describes the status of hepatitis C virus infection in 167 patients with severe forms of liver diseases in India. The anti-HCV positivity rate was recorded as 43%, 47%, and 42% in patients with FHF, SAHF, and CAH respectively. HBV and HCV coinfection was recorded in 28% of FHF, 43% of SAHF and 75% of the CAH cases. Superinfection of HCV in HBsAg carriers was recorded in the 54% cases of FHF, 60% of SAHF and 42% of the CAH. None of these 167 patients was positive of HAV-IgM. Further, 27.7% of FHF, 26.4% of SAHF and 15.2% of CAH cases were neither HBV nor HCV markers positive. These can be labelled as non-A, non-B and non-C infections.

N Z Med J 1988 Nov 23;101(858):788-90

Hepatitis B virus: the importance of age at infection.

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Recent studies have demonstrated the importance of age at infection with hepatitis B virus (HBV). Age affects whether the infection is self-limited or results in the chronic carrier state, the severity of the acute

infection, and the incidence of various sequelae of the chronic carrier state. In particular, although the acute infection is more severe in adults, infections in infants and preschool children carry much greater risks of chronic carriage which increases the risk of primary hepatocellular carcinoma and cirrhosis later in life. This has two important implications for areas where HBV is endemic. First, more impact can be gained by vaccinating infants and preschool children than by vaccinating healthy adults. Second, if funds are limited, greater impact will be gained by immunising a larger number of children with low doses of vaccine so that they are protected during the early years of life when the risk of chronic carriage is highest, rather than using the standard dose in a smaller number of children even though protection may be longer lasting with standard doses. These two considerations provide the basis for an efficient strategy for control in communities or countries where HBV is endemic or hyperendemic.

J Trop Pediatr 1998 Oct;44(5):275-8

Clinical and viral marker pattern of acute sporadic hepatitis in children in Madras, South India.

Malathi S, Mohanavalli B, Menon T, Srilatha P, Sankaranarayanan VS, Raju BB, Ramathilagam B, Thyagarajan SP

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[Medline record in process]

One hundred and twenty-seven children who presented with features of acute hepatitis during the period February 1995 to January 1996 were studied. Specific aetiologic agents were identified in 89 per cent. Of these, 67.7 per cent were due to a single virus, whereas 21.3 per cent were due to two or more hepatitis viruses. Hepatitis A virus (HAV) was the sole infecting agent in 38.6 per cent of cases, hepatitis B virus (HBV) in 13.4 per cent of cases, and hepatitis E virus (HEV) in 15.7 per cent of cases. Mixed infections were due to HAV and HBV co-infection (7.1 per cent), HAV and HEV (13.4 per cent), and the combination of HAV, HBV, and HEV (0.8 per cent). In 11 per cent, none of the markers (HAV to HEV) were identified. Acute sporadic hepatitis in children can occur due to a single hepatitis virus type or, at times, due to co-infection with a combination of two enterally transmitted viruses or enteral and parenterally transmitted viruses. Improving personal hygiene and active immunization are essential in the prevention of these viral illnesses. This study was done in a referral centre and hence we report a higher morbidity (13.4 per cent) and mortality (12.6 per cent) rate in all groups of infection. Hence, apart from the viruses, factors such as the age of the child, nutritional status, and treatment taken prior to hospitalization should be taken into consideration to predict the prognosis in a given child.

J Assoc Physicians India 1989 Feb;37(2):160-1

Incidence of hepatitis B carriers in Calcutta, West Bengal.

Roychoudhury A, Bhattacharyya DK

A survey of Hepatitis B virus (HBV) carrier state of paid and voluntary blood donors in and around the city of Calcutta has been carried out. HBV carrier state is higher in paid donors (5.84%) than voluntary donors (1.79%). The nutritional status of paid donors as assessed by serum protein, immunoglobulin and cholesterol shows evidence of malnutrition and chronic infection. The socio-economic status of the prospective blood donors has an important bearing on the persistence of carrier state for HBV.

Comments:
Comment in: J Assoc Physicians India 1989 Sep;37(9):620

Eur J Epidemiol 1996 Jun;12(3):319-22

Utility of an anonymous questionnaire for the identification of a primary transmission route and possible secondary transmission in adults with acute hepatitis B virus infection.

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Sweden.

By letting adults with acute hepatitis B virus (HBV) infection answer an anonymous questionnaire covering risks associated with the acquisition and further transmission of HBV infection, we found that a likely relevant transmission route could be identified in most patients. Despite being informed of the diagnosis, 50% of the patients exposed others via sexual contact during their contagious period.

J Med Virol 1996 Mar;48(3):215-21

Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India.

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The aetiological agents responsible for, and the outcome of, acute liver failure were investigated prospectively in 44 children (29 males, 15 females) attending a tertiary health care facility in India. The children were between the ages of 2 months and 13 years. Studies for viral infections and other etiologies could be carried out in 40 patients. Specific aetiological labels were possible in 35 (87.5%) patients. Thirty (75%) had evidence of acute viral hepatitis. Acute hepatitis E virus (HEV) infection was found in a total of 18 children, with hepatitis A (HAV) in 16, hepatitis B in 5, and C in 1. Seven had isolated infection with hepatitis E, five with A, and four with B. Nine had both E and A infection. Superinfection of HEV was observed in a child with Indian childhood cirrhosis (ICC). Acute HEV infection was confirmed by immunoblot assay in all the patients and in eight of these, HEV-RNA was also detected in the serum. HAV was involved in 37.5% of cases with isolated infection in 10% (4 of 40). The aetiological factors associated with acute liver failure, apart from HAV and HEV, were other hepatotropic viruses (22.5%), Wilson's disease (5%), ICC (5%), and hepatotoxic drugs (7.5%). In five patients, no serological evidence of acute viral hepatitis could be found, neither did the metabolic screen yield any result. It was observed that enterically transmitted hepatitis viruses (HAV and HEV) were associated with 60% of acute hepatic failure in children. Mixed infection of HAV and HEV formed the single largest aetiological subgroup. In developing countries, where hepatitis A and E infections are endemic, severe complications can arise in the case of mixed infection. This may contribute to most of the mortality from acute liver failure during childhood.

J Epidemiol Community Health 1985 Jun;39(2):123-8

Hepatitis B infection in households of acute cases.

Goh KT, Ding JL, Monteiro EH, Oon CJ

Seroepidemiological studies conducted in 369 household contacts of 80 acute cases of hepatitis B in Singapore showed that asymptomatic chronic carriers of hepatitis B surface antigen (HBs Ag) are the main source of acute hepatitis B infection. The HBs Ag prevalence rate in asymptomatic household members was 20% compared with a 6% prevalence for the general population. The majority of the household carriers (60%) were highly infectious with positive hepatitis e antigen (HBe Ag). The overall prevalence of HBV infection (with at least one HBV marker) of the household contacts was 40.7%. Spouses and parents of

acute cases had a significantly higher prevalence of HBV infection than other members of the families. HBV prevalence rate showed no association with the household size. Factors associated with the risk of transmission of HBV infection included sharing of various personal and household articles, such as toothbrush, towel, handkerchief, clothing, razor, comb, bed and bedding. Sleeping in the same bedroom, eating together at meals, and sharing of eating and drinking utensils were not associated with an increased risk of transmission of infection. Follow-up studies six months later showed that 30% of the acute cases became chronic HBs Ag carriers (with 46% HBe Ag positive), thus providing an additional source of infection in the families, while 8% of the susceptible household members acquired asymptomatic HBV infection. Health education on the prevention of HBV transmission in the homes of acute cases should be based on sound epidemiological information.

Acta Gastroenterol Belg 1998 Apr-Jun;61(2):210-3

Hepatitis B: long-term outcome and benefits from mass vaccination in children.

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Hepatitis B viruses can cause chronic liver diseases in both children and adults. In hyperendemic areas, although most related complications occur during adulthood, nearly half of the primary infection in chronic hepatitis B virus carriers occurs in perinatal period through maternal transmission and the other half are from horizontal transmission mainly through intrafamilial spread or injection using unsterilized needles. Children with chronic hepatitis B virus infection are mostly asymptomatic. They are generally active and growing well with very rare exceptions. Even with acute exacerbation of liver function and active inflammation, jaundice or growth failure is uncommon. Mild histologic abnormalities in the liver begins early in life and may progress to severe liver impairment in later life. Severe liver damage, with bridging hepatic necrosis or fibrosis, or cirrhosis of the liver may occur, but is rare during childhood. Universal immunization program of hepatitis B virus has been proved to be effective in reducing hepatitis B carrier rate for more than 10 folds, and the incidence of hepatocellular carcinoma in children has also been reduced significantly.

Natl Med J India 1994 Sep-Oct;7(5):216-20

Prevention of hepatitis B infection: the appropriate strategy for India.

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Hepatitis B infection is a major global health problem with a high morbidity and mortality. With safe and effective vaccines available, it is now possible to prevent it. Many countries have started national hepatitis B control programmes but no attempt has been made to do this in our country. An analysis of the available data on the epidemiology of hepatitis B infection in India reveals that perinatal maternofoetal transmission accounts for only a minority of hepatitis B virus carriers in India. Therefore, a policy of screening pregnant mothers for the presence of hepatitis B surface antigen and selective immunization of babies born to those who are surface antigen positive will have very little effect on the hepatitis B carrier rate in our population. Universal immunization of all newborns will have a much greater impact, it will be logistically simpler and more cost-effective--the cost of preventing one hepatitis B carrier being nearly one-fourth of that with selective immunization. We recommend that hepatitis B vaccine should be included in our country's expanded programme of immunization.

DIS 16a . 29

Medline Search - Hepatitis B + India + Epidemiol
14/12/98

Gut 1996;38 Suppl 2:S56-9

Epidemiology of hepatitis B virus infection in India.

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The average estimated carrier rate of hepatitis B virus (HBV) in India is 4%, with a total pool of approximately 36 million carriers. Wide variations in social, economic, and health factors in different regions may explain variations in carrier rates from one part of the country to another. Professional blood donors constitute the major high risk group for HBV infection in India, with a hepatitis B surface antigen positivity rate of 14%. Blood transfusions represent the most important route of HBV transmission among adults. However, most of India's carrier pool is established in early childhood, predominantly by horizontal spread due to crowded living conditions and poor hygiene. Acute and subacute liver failure are common complications of viral hepatitis in India and HBV is reckoned to be the aetiological agent in 42% and 45% of adult cases, respectively. HBV is reported to be responsible for 70% of cases of chronic hepatitis and 80% of cases of cirrhosis of the liver. About 60% of patients with hepatocellular carcinoma are HBV marker positive. Small numbers of patients have been reported to be infected with the pre-core mutant virus but none with the S mutant. Coinfection with hepatitis C virus or hepatitis delta virus is comparatively uncommon. In conclusion, hepatitis B is a major public health problem in India and will continue to be until appropriate nationwide vaccination programmes and other control measures are established.

Bull World Health Organ 1997;75(5):463-8

Epidemiology of endemic viral hepatitis in an urban area of India: a retrospective community study in Alwar.

Singh J, Prakash C, Gupta RS, Bora D, Jain DC, Datta KK

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In a community study during a reference period of 1 year, 192 cases of jaundice were detected in an urban population of 69,440 in Alwar, Rajasthan. Detected by paramedics and confirmed by physicians, these cases gave an annual incidence of 2.76 (95% CI: 2.37-3.15) per 1000 population. At least one of these patients died, giving a case fatality ratio of 0.6%. The jaundice cases occurred in all areas investigated, and affected all socioeconomic strata. About 94% of the affected families had only single cases. Although cases occurred throughout the year, more than 59% occurred during June-September, which are the summer and monsoon months. The incidence was highest (5.23 per 1000) among under-5-year-olds and declined progressively and significantly thereafter. Males had a higher incidence than females at all ages; the differences were not significant. Blood samples from 56 cases who had jaundice in the last 3 months of the reference period were tested for markers of viral hepatitis. Of these, 18 (32.1%), 1 (1.8%), 0, 2 (3.6%), and 4 (7.1%) were found to have hepatitis A, B, C, D and E, respectively. The etiology of the remaining 31 cases (55%) could not be established; previously, they would have been included in the NANB (non-A, non-B) category, inflating its proportion. Hepatitis A (HA) was the predominant type; being comparatively mild, it is perhaps underrepresented in hospital-based data. Many HA cases were in adults, which may be the beginning of an age shift of HA to the right owing to improvements in living standards of the study population. Five cases were carriers of hepatitis B virus (HBV), indicating the importance of HBV infection in India as well. Finally, the study found the annual incidence of laboratory-supported cases of viral hepatitis to be 1.24 (95% CI: 0.98-1.5) per 1000 population, which suggests that it is a major public health problem in India.

Indian J Gastroenterol 1998 Jul-Sep;17(3):100-3

Epidemiology of digestive tract cancers in India. III. Liver.

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Division of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Mumbai.

Liver cancer or hepatocellular carcinoma (HCC) is the fourth commonest cause of cancer deaths in the world. The condition is extremely common in Southeast Asia and Africa. In this report the available data on the epidemiology of HCC from India are summarized. We estimate that 12,750 new patients will be diagnosed to have HCC in India in the year 2001; this will comprise 1.6% of all incident cancers. Published studies from India and those involving Indian immigrants to other countries suggest that the prevalence of HCC is relatively lower in Indians than in most parts of the world. This contrasts with the widespread contamination of foods with aflatoxin and the moderately high prevalence of hepatitis B (HBV) and hepatitis C (HCV) virus-related chronic liver disease in India. There are no studies available to explain this observation. There are several articles on HBV and HCC in India but there is a paucity of analytical epidemiological data on HCV and HCC from India. Published studies indicate HBV to be the single most important etiologic association, with HCV playing a lesser but important role. About 80% of Indian patients with HCC have hepatitis virus-associated liver disease. Multicenter epidemiological studies are needed to solve some of the enigmas and observations peculiar to India.

Indian Pediatr 1998 Feb;35(2):105-9

Acute sporadic viral hepatitis in urban population of a tribal district in Madhya Pradesh.

Singh J, Prakash C, Panda R, Bora D, Jain DC, Datta KK

National Institute of Communicable Diseases, Shamnath Marg, Delhi.

OBJECTIVE: To estimate the incidence of acute sporadic viral hepatitis and describe its epidemiology in an urban population.
DESIGN: A retrospective community survey for jaundice cases. SETTING: Headquarter town of a tribal district, Bastar, in Madhya Pradesh state, India. METHOD: Trained paramedics surveyed about 51,643 population to detect cases of jaundice which occurred in the past one year. Cases were examined to collect clinical and epidemiological data. blood samples were drawn from all cases who had jaundice in the past 3 months for testing them for markers of viral hepatitis.
RESULTS: Study estimated the annual incidence of jaundice cases as 244 (95% CI 201-287) per 100,000 population. Almost 95% jaundice cases occurred in summer and monsoon months. People from all socio-economic strata were affected. The incidence of jaundice was found to be the highest in children below 15 years of age (3.7 per 1000) which declined significantly with the increase in age ($p = 0.0000$). The overall incidence in two sexes was not different statistically ($p = 0.7$). Of 57 cases who had jaundice in the past 3 months, 19 (33%) were confirmed as having viral hepatitis. Hepatitis A and E combined together contributed 68% (13/19) of acute sporadic cases of viral hepatitis, whereas hepatitis B, C and D accounted for the remaining 32% of the cases.
CONCLUSION: The study found the annual incidence of laboratory supported cases of viral hepatitis to be 81 (95 CI 57-106) per 100,000 population, which suggests that it is an important public health problem in India. Hepatitis A was much more prevalent than hepatitis E. Etiology of almost two-thirds of jaundice cases could not be established which require further community studies.

Gut 1996;38 Suppl 2:S39-42

Importance of perinatal versus horizontal transmission of hepatitis B virus infection in China.

Yao GB

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China has one of the highest rates of hepatitis B virus (HBV) endemicity in the world. In a survey of five provinces, the overall HBV infection rate in the general population was found to be 42.6%, with 10.3% testing positive for hepatitis B surface antigen (HBsAg). Higher rates were found in rural than in urban areas. The prevalence of HBsAg among children under 1 year of age is quite low but increases rapidly thereafter, reaching a peak among 5 to 9 year olds. The pattern of age distribution suggests that horizontal transmission is an important route of HBV infection during early childhood, and the proportion of chronic HBsAg carriage attributable to perinatal transmission has been estimated at only 13-20%. Contact with infected family members probably accounts for much of the horizontal transmission in children. In a nationwide survey, 27.2% of families were found to have one or more HBsAg positive members and a strong tendency for family clustering has been identified. The strategy for prevention of HBV infection includes vaccination of all newborns, whether their mothers are HBsAg positive or negative, together with vaccination of high risk populations, and improved control measures in clinics and blood transfusion centres.

Gut 1996;38 Suppl 2:S43-7

Epidemiology and control of hepatitis B infection: a perspective from the Philippines, Asia.

Lansang MA

Research Institute for Tropical Medicine, University of the Philippines, Manila.

The prevalence of chronic hepatitis B virus (HBV) infection in the Philippines, as indicated by hepatitis B surface antigen (HBsAg) positivity, ranges from 2% to 16.5%, with an average of 12% in a study of rural villagers. Although mother to child transmission is a major route of HBV infection, other routes (particularly child to child transmission) play an important part after the first year of life. In a study assessing the feasibility and effectiveness of incorporating hepatitis B vaccine into the national Expanded Programme on Immunisation, the coverage rate for fully immunised 1 year olds ranged from 80.9-84% and anti-HBs seroconversion rates ranged from 72-88%. In countries where HBV is not endemic, high risk groups included commercial sex workers (CSWs) and intravenous drug users (IVDUs), who generally have higher HBsAg positivity rates than the general population. In countries with a high HBV endemicity, carrier rates may be only slightly higher among CSWs, suggesting that other modes of transmission are more important in those regions. CSWs who are also IVDUs are at even greater risk. If HBV infection is to be controlled, innovative education and screening programmes are needed, together with the mass immunisation of neonates now started in many countries around the world.

Trop Gastroenterol 1989 Apr-Jun;10(2):106-10

Etiologic spectrum of acute sporadic viral hepatitis in children in India.

Panda SK, Datta R, Gupta A, Kamat RS, Madangopalan N, Bhan MK, Rath B, Guha DK, Nayak NC

The relative magnitude by hepatitis A virus (HAV), hepatitis B virus (HBV) and hepatitis Non-A, Non-B virus (HNANBV) was determined in 496 children from three different parts of India suffering from acute viral hepatitis by tests for specific IgM class anti-HAV and anti-HBV antibodies in the serum. HAV, HBV

and NANB infections accounted for 55.8 per cent, 20.2 per cent and 23.2 per cent of cases respectively. Hepatitis A largely (59.5%) affected younger children of 1-5 yr. Nearly a third of children affected by NANB hepatitis were additionally positive for HBsAg. The proportions of HAV and HBV infected cases respectively decreased and increased with increasing age whereas the incidence of HNANBV infection remained almost constant throughout childhood. Acute NANB hepatitis, a major health problem in the adults of India is also common throughout childhood. This study suggests that this infection does not impart long lasting protective immunity.

Gut 1996;38 Suppl 2:S5-12

The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and subtropical Africa.

Kiire CF

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There are approximately 50 million chronic carriers of hepatitis B virus (HBV) in Africa, with a 25% mortality risk. In sub-Saharan Africa, carrier rates range from 9-20%. Many studies have suggested that HBV transmission in Africa occurs predominantly in childhood, by the horizontal rather than the perinatal route. The exact mode of transmission is uncertain but probably involves percutaneous infection through saliva or traces of blood, as well through unsterile needles, tribal scarification, and other possible vehicles. Compared with adult HBsAg carriers in the Far East, those in Africa have a low rate of HBeAg positivity, which may account for the relatively low rates of perinatal infection. It is also possible that African infants are less susceptible to perinatal HBV infection compared with their Asian counterparts. Alternatively, it may be that African infants are indeed infected with HBV at birth but, for genetically determined reasons, have persistently negative tests for a number of years until the virus is reactivated. In view of the high HBV carrier rates in the general population, universal immunisation of all infants is recommended. Ways of incorporating the hepatitis B vaccine into the Expanded Programme on Immunisation in each country are being evaluated.

Scand J Infect Dis Suppl 1990;69:43-7

Epidemiology of hepatitis B virus (HBV) infections with particular regard to current routes of transmission and development of cirrhosis and malignancy.

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The majority of hepatitis B virus (HBV) carriers world-wide becomes infected by transmission from asymptomatic carrier mother to infant, so-called "vertical" transmission, or early person to person so-called "horizontal" transmission, but sexual transmission is also important, especially in low endemicity areas. The histopathological findings at liver biopsies of these HBV-carriers vary from almost normal to severe chronic active hepatitis (CAH) with cirrhosis, and especially cirrhosis is associated with the development of HBV-related liver cancer. The reported annual incidence/100,000 of HBV-induced CAH in north-western Europe is 0.1-0.6 while the burden of the important chronic stages of hepatitis B is manyfold this in most developing countries.

JAMA 1996 Sep 18;276(11):906-8

Seroepidemiology of hepatitis B virus infection in children: Ten years of mass vaccination in Taiwan.

Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, Chen DS

Department of Pediatrics, National Taiwan University Hospital, Taipei.

OBJECTIVE: To study the seroepidemiology of hepatitis B virus (HBV) infection in children 10 years after a mass hepatitis B vaccination program was begun in Taiwan. DESIGN: Cross-sectional seroprevalence survey.
SETTING: Cheng-Chung/Chung-Cheng District, Taipei, Taiwan, 1994. SUBJECTS AND METHODS: Serum samples from 1515 healthy children younger than 12 years were tested for HBV markers. The results were compared with a baseline seroepidemiologic study conducted just before the vaccination program was launched in 1984 and with a subsequent study in 1989 in the same area. MAIN RESULTS: Eighty-seven percent of the children had received at least 3 doses of HBV vaccine. The overall prevalence rate of hepatitis B surface antigenemia decreased from 9.8% in 1984 to 1.3% in 1994. A statistically significant decrease was observed in every age group from 1 to 10 years. The overall prevalence rate of hepatitis B core antibody was 26% in 1984, 15% in 1989, and 4.0% in 1994. This suggests that the risk of horizontal HBV infection has decreased over time, not only because of the protective effect of the vaccine but also because the infection source has diminished. A high prevalence rate of hepatitis B surface antibody (79%) was noted in 1994 as anticipated.
CONCLUSIONS: The Taiwanese mass vaccination program has protected most children younger than 10 years from becoming carriers, reducing both perinatal and horizontal HBV transmission. Mass HBV vaccination has proved to be a successful method to control HBV infection in this hyperendemic area.

Comments:
Comment in: JAMA 1996 Dec 11;276(22):1802-3

Vaccine 1990 Mar;8 Suppl:S18-20; discussion S21-3

Hepatitis B: global importance and need for control.

Maynard JE

International Task Force on Hepatitis B Immunization, Seattle, WA.

Hepatitis B is a disease of global importance, with greater than 300 million carriers of the virus world-wide. Hepatitis B virus (HBV) is the cause of up to 80% of cases of primary liver cancer, the single most important cause of mortality globally. In countries where HBV carrier rates reach 10%, HBV infection may account for 3% of total mortality, a level which exceeds polio-related mortality before the introduction of polio vaccine. The only means by which hepatitis B can be eventually eliminated is mass vaccination of infants with hepatitis B vaccine as part of the Expanded Programme on Immunization (EPI) in areas of the world where the HBV carrier rate exceeds 2.5%. With recent dramatic increases in hepatitis B vaccine production and decreases in per-dose price, there are grounds for optimism that global HBV infection rates may be reduced by as much as 90% over the next 10 years.

Semin Liver Dis 1991 May;11(2):84-92

Hepatitis B: evolving epidemiology and implications for control.

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Control and the possible elimination of transmission of HBV infection is possible with the appropriate use of hepatitis B vaccines. The prevention of chronic HBV infection has the potential of reducing the association burden of chronic liver disease and primary hepatocellular carcinoma. Worldwide, strategies for the effective use of hepatitis B vaccine have been developed and are being implemented in those areas

where childhood transmission is the predominant source of chronic HBV infections. However, in the United States and other areas with "low" rates of HBV infection, current vaccination strategies have not been effective and have not fully taken into account the multifaceted epidemiology of HBV infection in those areas. Unfortunately, the majority of infections occur among adults who have been the most difficult to access, who acquire infection before they realize they are at risk, and where the changing epidemiology of HBV infections among the various risk groups only emphasizes the problems of vaccine delivery. In addition, the majority of persons receiving vaccine as a result of the current strategy to immunize adult high-risk groups have been persons who acquire HBV infection through occupational exposure, a group that accounted for no more than 5% of cases even before vaccine was introduced. The failure of the current immunization strategy to prevent a disease with significant health care and economic consequences is beginning to cause a reevaluation of this approach. A comprehensive approach to eliminating HBV transmission must address infections acquired during early childhood as well as those acquired by teenagers and adults.

J Trop Pediatr 1995 Dec;41(6):328-9

Pattern of hepatitis A and hepatitis B virus markers in cases of acute sporadic hepatitis and in healthy school children from north west India.

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The pattern of viral markers in acute sporadic hepatitis in 329 children and those in 334 healthy school children from North West India were studied. Hepatitis A was found to be the commonest infection in sporadic cases (78 per cent). Of these, 86 per cent were under 10 years and 50 per cent less than 5 years of age. Hepatitis B was positive in 8 per cent, non-A non-B in 13 per cent, A as well as B in 1 per cent, and none had Delta virus infection. Viral markers in healthy school children showed anti-HAV IgG positivity in 96 and 85 per cent in those belonging to low and high socio-economic groups, respectively, indicating past infection. HBsAg was positive in 1 per cent of cases. Viral hepatitis is an important public health problem in children and warrants active immunization. ZZZZZZZ

Indian J Med Sci 1995 Oct;49(10):227-30

Prevalence of hepatitis A, B, C & D in Ludhiana.

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172 sera were tested for serological markers of hepatitis A, hepatitis B, hepatitis C and hepatitis D to define the aetiology of acute viral hepatitis by Enzyme immunoassays. The viral aetiology could be decided in 60.5% (104/ 172) of patients. Hepatitis B infection was present in 34.9%, hepatitis A in 10.5%, hepatitis C in 9.3% and hepatitis D in 5.8% of cases. Delta hepatitis associated with HBsAg positive hepatitis was detected in 10% (6/60) of the patients. The aetiology remained undecided in 39.5% of patients.

Am J Epidemiol 1991 Sep 15;134(6):641-50

Transmission of hepatitis B and hepatitis delta viruses in the households of chronic hepatitis B surface antigen carriers: a regression analysis of indicators of risk.

Craxi A, Tine F, Vinci M, Almasio P, Camma C, Garofalo G, Pagliaro L

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To evaluate whether clinical and laboratory features of a hepatitis B surface antigen (HBsAg) carrier can predict risks of infection, its chronicity, and the development of liver disease among close contacts, the authors studied a cohort of 994 first degree relatives or cohabitants (household contacts) of 226 non-drug-addicted chronic HBsAg carriers (index cases), of whom 77% had liver disease and 26% were superinfected by hepatitis D virus (HDV). A logistic form of regression analysis was used to assess the role of each feature in the index case as predictor of hepatitis B virus (HBV)- and HDV-related outcomes among household contacts. Six models of risk, expressed as odds ratios, were assessed by multivariate step-down analysis, with the following results.

1) Infection with HBV in the household contact was independently predicted by the index case being son, sibling, spouse, female, or HBV-DNA positive.
2) Chronic HBsAg carriage in the adult household contact was associated with female sex of the index case and with being a sibling; among young subjects, household contacts were more likely to be chronic HBsAg carriers when the index case was the mother, a sibling, or an HBV-DNA-positive subject.
3) HBV-DNA positivity in the young contact was more likely when the index case was HBV-DNA positive and when she was the mother.
4) HBV-DNA positivity in the absence of hepatitis B e antigen (HBeAg) in serum in the index case was not related to a similar pattern of infection in HBsAg-positive contacts.
5) Super-infection with HDV of an HBsAg-positive household contact was significantly predicted by female sex of the index case and by anti-HDV positivity.
6) Chronic liver disease in a contact was predicted only by HDV superinfection of the index case. We conclude that horizontal, nonparenteral transmission of HBV among siblings plays a major role in the household of HBsAg carriers from an intermediate endemicity area.

Gastroenterol Jpn 1991 Jul;26 Suppl 3:192-5

Hepatitis C virus infection is the major cause of severe liver disease in India.

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The present study describes the status of hepatitis C virus infection in 167 patients with severe forms of liver diseases in India. The anti-HCV positivity rate was recorded as 43%, 47%, and 42% in patients with FHF, SAHF, and CAH respectively. HBV and HCV coinfection was recorded in 28% of FHF, 43% of SAHF and 75% of the CAH cases. Superinfection of HCV in HBsAg carriers was recorded in the 54% cases of FHF, 60% of SAHF and 42% of the CAH. None of these 167 patients was positive of HAV-IgM. Further, 27.7% of FHF, 26.4% of SAHF and 15.2% of CAH cases were neither HBV nor HCV markers positive. These can be labelled as non-A, non-B and non-C infections.

N Z Med J 1988 Nov 23;101(858):788-90

Hepatitis B virus: the importance of age at infection.

Pearce N, Milne A, Moyes C

Department of Community Health, Wellington School of Medicine.

Recent studies have demonstrated the importance of age at infection with hepatitis B virus (HBV). Age affects whether the infection is self-limited or results in the chronic carrier state, the severity of the acute

infection, and the incidence of various sequelae of the chronic carrier state. In particular, although the acute infection is more severe in adults, infections in infants and preschool children carry much greater risks of chronic carriage which increases the risk of primary hepatocellular carcinoma and cirrhosis later in life. This has two important implications for areas where HBV is endemic. First, more impact can be gained by vaccinating infants and preschool children than by vaccinating healthy adults. Second, if funds are limited, greater impact will be gained by immunising a larger number of children with low doses of vaccine so that they are protected during the early years of life when the risk of chronic carriage is highest, rather than using the standard dose in a smaller number of children even though protection may be longer lasting with standard doses. These two considerations provide the basis for an efficient strategy for control in communities or countries where HBV is endemic or hyperendemic.

J Trop Pediatr 1998 Oct;44(5):275-8

Clinical and viral marker pattern of acute sporadic hepatitis in children in Madras, South India.

Malathi S, Mohanavalli B, Menon T, Srilatha P, Sankaranarayanan VS, Raju BB, Ramathilagam B, Thyagarajan SP

Department of Digestive Health and Diseases, Government Peripheral Hospital, Anna Nagar, India.

[Medline record in process]

One hundred and twenty-seven children who presented with features of acute hepatitis during the period February 1995 to January 1996 were studied. Specific aetiologic agents were identified in 89 per cent. Of these, 67.7 per cent were due to a single virus, whereas 21.3 per cent were due to two or more hepatitis viruses. Hepatitis A virus (HAV) was the sole infecting agent in 38.6 per cent of cases, hepatitis B virus (HBV) in 13.4 per cent of cases, and hepatitis E virus (HEV) in 15.7 per cent of cases. Mixed infections were due to HAV and HBV co-infection (7.1 per cent), HAV and HEV (13.4 per cent), and the combination of HAV, HBV, and HEV (0.8 per cent). In 11 per cent, none of the markers (HAV to HEV) were identified. Acute sporadic hepatitis in children can occur due to a single hepatitis virus type or, at times, due to co-infection with a combination of two enterally transmitted viruses or enteral and parenterally transmitted viruses. Improving personal hygiene and active immunization are essential in the prevention of these viral illnesses. This study was done in a referral centre and hence we report a higher morbidity (13.4 per cent) and mortality (12.6 per cent) rate in all groups of infection. Hence, apart from the viruses, factors such as the age of the child, nutritional status, and treatment taken prior to hospitalization should be taken into consideration to predict the prognosis in a given child.

J Assoc Physicians India 1989 Feb;37(2):160-1

Incidence of hepatitis B carriers in Calcutta, West Bengal.

Roychoudhury A, Bhattacharyya DK

A survey of Hepatitis B virus (HBV) carrier state of paid and voluntary blood donors in and around the city of Calcutta has been carried out. HBV carrier state is higher in paid donors (5.84%) than voluntary donors (1.79%). The nutritional status of paid donors as assessed by serum protein, immunoglobulin and cholesterol shows evidence of malnutrition and chronic infection. The socio-economic status of the prospective blood donors has an important bearing on the persistence of carrier state for HBV.

Comments:
Comment in: J Assoc Physicians India 1989 Sep;37(9):620

Eur J Epidemiol 1996 Jun;12(3):319-22

Utility of an anonymous questionnaire for the identification of a primary transmission route and possible secondary transmission in adults with acute hepatitis B virus infection.

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Sweden.

By letting adults with acute hepatitis B virus (HBV) infection answer an anonymous questionnaire covering risks associated with the acquisition and further transmission of HBV infection, we found that a likely relevant transmission route could be identified in most patients. Despite being informed of the diagnosis, 50% of the patients exposed others via sexual contact during their contagious period.

J Med Virol 1996 Mar;48(3):215-21

Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India.

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Department of Paediatrics, All India Institute of Medical Sciences, New Delhi, India.

The aetiological agents responsible for, and the outcome of, acute liver failure were investigated prospectively in 44 children (29 males, 15 females) attending a tertiary health care facility in India. The children were between the ages of 2 months and 13 years. Studies for viral infections and other etiologies could be carried out in 40 patients. Specific aetiological labels were possible in 35 (87.5%) patients. Thirty (75%) had evidence of acute viral hepatitis. Acute hepatitis E virus (HEV) infection was found in a total of 18 children, with hepatitis A (HAV) in 16, hepatitis B in 5, and C in 1. Seven had isolated infection with hepatitis E, five with A, and four with B. Nine had both E and A infection. Superinfection of HEV was observed in a child with Indian childhood cirrhosis (ICC). Acute HEV infection was confirmed by immunoblot assay in all the patients and in eight of these, HEV-RNA was also detected in the serum. HAV was involved in 37.5% of cases with isolated infection in 10% (4 of 40). The aetiological factors associated with acute liver failure, apart from HAV and HEV, were other hepatotropic viruses (22.5%), Wilson's disease (5%), ICC (5%), and hepatotoxic drugs (7.5%). In five patients, no serological evidence of acute viral hepatitis could be found, neither did the metabolic screen yield any result. It was observed that enterically transmitted hepatitis viruses (HAV and HEV) were associated with 60% of acute hepatic failure in children. Mixed infection of HAV and HEV formed the single largest aetiological subgroup. In developing countries, where hepatitis A and E infections are endemic, severe complications can arise in the case of mixed infection. This may contribute to most of the mortality from acute liver failure during childhood.

J Epidemiol Community Health 1985 Jun;39(2):123-8

Hepatitis B infection in households of acute cases.

Goh KT, Ding JL, Monteiro EH, Oon CJ

Seroepidemiological studies conducted in 369 household contacts of 80 acute cases of hepatitis B in Singapore showed that asymptomatic chronic carriers of hepatitis B surface antigen (HBs Ag) are the main source of acute hepatitis B infection. The HBs Ag prevalence rate in asymptomatic household members was 20% compared with a 6% prevalence for the general population. The majority of the household carriers (60%) were highly infectious with positive hepatitis e antigen (HBe Ag). The overall prevalence of HBV infection (with at least one HBV marker) of the household contacts was 40.7%. Spouses and parents of

acute cases had a significantly higher prevalence of HBV infection than other members of the families. HBV prevalence rate showed no association with the household size. Factors associated with the risk of transmission of HBV infection included sharing of various personal and household articles, such as toothbrush, towel, handkerchief, clothing, razor, comb, bed and bedding. Sleeping in the same bedroom, eating together at meals, and sharing of eating and drinking utensils were not associated with an increased risk of transmission of infection. Follow-up studies six months later showed that 30% of the acute cases became chronic HBs Ag carriers (with 46% HBe Ag positive), thus providing an additional source of infection in the families, while 8% of the susceptible household members acquired asymptomatic HBV infection. Health education on the prevention of HBV transmission in the homes of acute cases should be based on sound epidemiological information.

Acta Gastroenterol Belg 1998 Apr-Jun;61(2):210-3

Hepatitis B: long-term outcome and benefits from mass vaccination in children.

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Hepatitis B viruses can cause chronic liver diseases in both children and adults. In hyperendemic areas, although most related complications occur during adulthood, nearly half of the primary infection in chronic hepatitis B virus carriers occurs in perinatal period through maternal transmission and the other half are from horizontal transmission mainly through intrafamilial spread or injection using unsterilized needles. Children with chronic hepatitis B virus infection are mostly asymptomatic. They are generally active and growing well with very rare exceptions. Even with acute exacerbation of liver function and active inflammation, jaundice or growth failure is uncommon. Mild histologic abnormalities in the liver begins early in life and may progress to severe liver impairment in later life. Severe liver damage, with bridging hepatic necrosis or fibrosis, or cirrhosis of the liver may occur, but is rare during childhood. Universal immunization program of hepatitis B virus has been proved to be effective in reducing hepatitis B carrier rate for more than 10 folds, and the incidence of hepatocellular carcinoma in children has also been reduced significantly.

Natl Med J India 1994 Sep-Oct;7(5):216-20

Prevention of hepatitis B infection: the appropriate strategy for India.

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Hepatitis B infection is a major global health problem with a high morbidity and mortality. With safe and effective vaccines available, it is now possible to prevent it. Many countries have started national hepatitis B control programmes but no attempt has been made to do this in our country. An analysis of the available data on the epidemiology of hepatitis B infection in India reveals that perinatal maternofoetal transmission accounts for only a minority of hepatitis B virus carriers in India. Therefore, a policy of screening pregnant mothers for the presence of hepatitis B surface antigen and selective immunization of babies born to those who are surface antigen positive will have very little effect on the hepatitis B carrier rate in our population. Universal immunization of all newborns will have a much greater impact, it will be logistically simpler and more cost-effective--the cost of preventing one hepatitis B carrier being nearly one-fourth of that with selective immunization. We recommend that hepatitis B vaccine should be included in our country's expanded programme of immunization.

Disease Control Priorities in Developing Countries

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Published for the World Bank
Oxford University Press

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Hepatitis B

Mark Kane, John Clements, and Dale Hu

Hepatitis B, one of the main diseases of mankind, is now preventable with safe and effective vaccines—the first vaccines against cancer. More than 2 billion individuals alive today have been infected at some time in their lives with the hepatitis B virus (HBV), and approximately 350 million are chronically infected carriers of this virus. These carriers are at high risk of serious illness and death from cirrhosis of the liver and primary liver cancer, diseases that kill more than 1 million carriers per year (Maynard, Kane, and Hadler 1989). Primary liver cancer caused by HBV infection is one of the top three causes of cancer death in much of Africa, Asia, and the Pacific Basin (Parkin 1986). In addition, these carriers constitute a reservoir of infected individuals who perpetuate the infection from generation to generation.

Most people in Africa, eastern Asia, Southeast Asia, the Pacific Basin, the Amazon Basin, and parts of the Middle East become infected with this virus during childhood, either from an infected mother (perinatal transmission) or from another child. Infection during childhood is especially likely to lead to the chronic carrier state. In Europe, North America, much of Latin America, and Australia, hepatitis B infection is an important sexually transmitted disease and a significant cause of morbidity for health care personnel and certain other groups defined by lifestyle and occupation (CDC 1990).

Hepatitis B (HB) vaccines, if given prior to infection, can prevent disease and the carrier state from developing in almost all individuals. These vaccines have been used in more than 100 million persons and have proven to be among the safest, most immunogenic, and most effective vaccines yet developed. The vaccines are most effectively used as a routine part of the infant immunization schedule, although they can be used at any age.

Recent dramatic decreases in vaccine cost in developing countries (from $20 to $1–$2 per pediatric dose) have allowed public health officials to consider the mass use of these vaccines in infant immunization programs (Kane, Ghendon, and Lambert 1990), but it is still considerably more expensive than the other routine childhood vaccines. Although these vaccines have been widely used by health care workers in industrial countries and as a routine infant immunogen in countries with relatively more resources but in which the disease is endemic, international agencies and donors have not made the vaccines available to developing countries who are dependent on donors for the vaccines. An analysis of the reasons for this may shed light on the future of immunization as a viable public health strategy.

History and Epidemiology of HBV Infection

Hepatitis B virus infection leads to one of three outcomes in humans. An infected individual may die of fulminant hepatitis within days or weeks of clinical onset of disease, may recover after symptomatic or asymptomatic acute infection and develop lifelong immunity, or may become a chronic carrier, harboring a persistent infection which usually lasts for life. The age of infection is the primary factor in determining the outcome of HBV infection.

Approximately 25 percent of chronic carriers will die from cirrhosis or primary hepatocellular carcinoma (PHC), also called primary liver cancer (Beasley and Hwang 1984). Cirrhosis is usually preceded by chronic active hepatitis, which can cause years of morbidity and significant work loss. Death from cirrhosis and PHC usually occurs during the third to sixth decade of life, during the peak years of adult productivity.

Geographical Distribution

Hepatitis researchers have divided the world into areas of "high," "intermediate," and "low" HBV endemicity, basing this division on the prevalence of HBV markers and on the primary modes of HBV transmission. Areas of high endemicity include those in which most of the population becomes infected with the virus, usually during the perinatal period or during childhood. Various authors have used figures of 5 percent to 10 percent to define the lower limit of the prevalence of HBV carriers for this category. The upper limit of the prevalence of the carrier state is about 20 percent. Most countries included in this category have a carrier prevalence of 10 to 15 percent, and 50 to 95 percent of the population have serologic evidence of prior HBV infection. Africa, Asia east of the Indian Subcontinent, the Pacific Basin, the Amazon Basin, the Arctic Rim, the Asian Republics of the Commonwealth of Independent

States (CIS), and portions of the Middle East, Asia Minor, and the Caribbean are areas of high endemicity. Parts of eastern Europe such as Bulgaria, Romania, Albania, and Moldova have a carrier prevalence of between 5 and 10 percent in the general population.

Areas of intermediate endemicity generally have an HBV carrier prevalence of 2 to 5 percent, and 30 to 50 percent of the population have serological evidence of prior HBV infection. Some parts of southern and eastern Europe, the Middle East, western Asia through the Indian Subcontinent, and parts of Central and South America are included in this category. In these areas both child-to-child and adult-to-adult transmission occur. Acute viral hepatitis with jaundice is a primary cause of morbidity because a substantial proportion of infection occurs in older adolescents and adults, who are much more likely to present with acute clinical disease.

North America, western Europe, Australia, and parts of South America are considered to be areas of low endemicity. In these areas perinatal and child-to-child transmission is relatively uncommon, and most infections occur in adults through sexual activity, needle sharing during drug abuse, or during occupational exposure to blood. Acute hepatitis B is a significant cause of morbidity in many countries in this category.

Modes of Transmission and Outcome of HBV Infections

Understanding the outcome of HBV infection in children and adults is critical to designing effective control strategies. Young children rarely develop symptomatic HBV infection with jaundice, but about 25 percent of children infected before the age of seven will become carriers. The younger the child, the more likely it is that this will occur. Many carriers who acquire infection during childhood will live long enough to develop PHC after a latency period of thirty to sixty years. After the age even, children exhibit an adult pattern of disease outcome, with about 5 to 10 percent becoming carriers. Even if the duration of protection from HB vaccines were only seven years, children immunized early in life would be protected during the most critical period of HBV infection, and significant reductions in HBV transmission, cirrhosis, and PHC would occur.

Perinatal transmission is one of the most efficient and serious modes of HBV transmission (Stevens and others 1985). Perinatal transmission occurs from mothers who are positive for both the hepatitis B surface antigen (HBsAg) and the hepatitis B "e" antigen (HBeAg). More than 90 percent of these women are chronic HBV carriers, although women acutely infected with the virus during pregnancy may also transmit to their children. Mothers who are HBeAg-positive carriers have a 70 to 90 percent chance of infecting their newborns perinatally, and almost all these infected newborns become HBV carriers. Infected newborns rarely develop acute hepatitis, although there have been several reports of fatal fulminant hepatitis. These carriers form a pool of infectious individuals who will infect others in the community and eventually their own offspring. Infants of mothers who are HBeAg-negative carriers rarely become carriers through perinatal transmission.

Transmission from child to child, often called horizontal transmission, is responsible for the majority of HBV infections and carriers. Although the relative importance of the various modes of transmission from child to child have not been established, many hepatitis researchers believe that skin lesions such as impetigo, scabies, abrasions, and infected insect bites play an important role. These lesions provide a route for the virus to leave the body of infectious children and a route for it to enter the body of susceptible children with whom they have skin-to-skin contact, such as in wrestling or sharing the same bed. Other modes of transmission include reuse of unsterile needles and other medical and dental equipment, tattooing and other scarification procedures, sharing of household items such as toothbrushes, and sexual activity. Premastication of food and insect transmission have been postulated as modes of transmission but remain unproven.

The transmission of HBV to adults is the primary mode of transmission in regions of lower endemicity where large populations of susceptible adults are found. About one-third of infected adults develop clinical hepatitis B with jaundice, and 6 to 10 percent become chronic HBV carriers with a subsequent risk of chronic active hepatitis, cirrhosis, and PHC. Sexual transmission, both heterosexual and homosexual, accounts for the majority of adult transmission. In some Western countries, needle sharing by drug abusers is also important. Hepatitis B is the main infectious occupational hazard to health care workers in areas of low and intermediate endemicity. Transmission to patients by contaminated blood product and unsterilized reused medical and dental instruments also occurs. In addition, any of the modes of transmission discussed for child-to-child transmission may occur.

Hepatitis B Vaccines

Hepatitis B vaccines are alum adjuvented highly purified preparations of hepatitis B surface antigen, the glycoprotein that forms the outer coat of the hepatitis B virus. Hepatitis B surface antigen can either be purified from the plasma of HBV carriers (plasma-derived vaccines) or produced in yeast or mammalian cells by recombinant technology (recombinant vaccines). Hepatitis B vaccines are highly immunogenic, even in newborns, and can induce protective anti–hepatitis B surface antibody in 90 to 97 percent of healthy individuals, depending primarily on the age of the recipient.

Hepatitis B vaccines have been successfully used in field trials in many parts of the world where the immunogenicity of the vaccines in infants is usually measured at 95 to 99 percent. The protective efficacy of the vaccines against the development of disease or the carrier state is often 95 to 99 percent in cohorts of immunized infants.

Plasma-Derived Vaccines

In natural HBV infections, liver cells produce much more HBsAg than is needed to coat viral particles, and the excess HBsAg forms 22-nanometer spherical and long tubular particles. Plasma-derived HB vaccines are prepared by purifying HBsAg

particles from the plasma of HBsAg-positive donors. These vaccines are inactivated to ensure that no infectious viral or other microorganisms are present, and then alum is added as an adjuvant. Plasma-derived vaccines, available since 1981, have an outstanding record of safety and efficacy and have been used in more than 70 million individuals.

Recombinant HB Vaccines

These vaccines are produced from HBsAg derived from yeast or mammalian cells in which replicating plasmids containing the viral HBsAg gene are inserted. The HBsAg forms spherical particles similar to the natural 22-nanometer spherical particle in both chemical composition and immunogenicity. Recombinant HBsAg for vaccines may be produced in almost unlimited amounts in brewery-like fermentation vats, so there need be no concern that lack of availability of antigen will compromise future vaccine supply. Manufacturers could produce tens of millions of doses in the next few years but will require firm commitments from vaccine purchasers before they make the capital investments to produce the more than 300 million doses necessary to provide this vaccine to the world's children.

HB Vaccines and Immunization

The single most important step in the global control of hepatitis B will be the integration of these vaccines into the Expanded Programme on Immunization (EPI). This integration was recommended by the Technical Advisory Group on Viral Hepatitis and the Global Advisory Group of EPI in 1987. In 1991 the Global Advisory Group set targets for the introduction of HB vaccine into national immunization programs (WHO/EPI 1992a, b, and c), and these targets were approved by the World Health Assembly in 1992. Targets call for all countries with a prevalence of carriers of 8 percent or greater to integrate HB vaccines into routine infant immunization programs by 1995: all other countries should have programs in place by 1997.

Integration of HB vaccines into routine infant immunization raises many practical questions which need to be addressed when the addition of a new antigen is considered. Hepatitis B vaccines have characteristics which make them ideal for the integration into EPI. They are flexible enough to integrate into immunization schedules without requiring additional patient visits, do not interfere with the immune response to currently used antigens, have an extremely low rate of unacceptable side effects, are immunogenic from birth with no interference from maternal antibody, and have shipping and storage characteristics similar to currently used antigens.

Compatibility with Other EPI Antigens

Coursaget and coworkers (1986, 1990) have shown that EPI antigens do not interfere with the immune response to HB vaccines, and conversely, that HB vaccines do not interfere with the response to BCG (bacille Calmette-Guérin), DPT (diphtheria-pertussis-tetanus), or inactivated polio, measles, and yellow fever antigens. Similar data are available from laboratory animal studies as well as from human trials in Italy, Senegal, Myanmar, and China.

Target Age

When HB vaccine is given to an infant of a carrier mother who is HBeAg positive, he or she has, in most cases, already been exposed to the virus, and the vaccine must provide postexposure prophylaxis. Plasma-derived HB vaccines alone have an efficacy of about 75 percent in preventing such infants from becoming carriers if the first dose is given soon after birth. This may be feasible if infants are delivered in hospitals or clinics, but it may be difficult to achieve at home deliveries unless they are attended by midwives specially trained to administer vaccine or unless there is very rapid reporting of births to vaccinators. A hepatitis B vaccine trial in Lombok, Indonesia, has successfully stimulated birth registration and achieved a high level of immunization of infants within one week from birth in an area where home delivery predominates. In another trial, in Long An County, China, midwives have been successfully trained to deliver the vaccine at the time of birth.

Infants of mothers who are not HBeAg-positive HBV carriers can receive the first dose of HB vaccine either near the time of birth with BCG, or with DPT-1, because many are protected by passive maternal antibody and because the risk of horizontal infection is low during the first few months of life.

Duration of Immunity

The duration of protection from HB vaccines is a crucial issue which will be understood only by carefully following long-term HB vaccine trials. Cohorts of immunized adults and older children followed for five to ten years show no evidence of clinical hepatitis B, antigenemia, the development of elevated liver enzymes, or the development of the carrier state, despite declining levels of serum antibodies. It is clear that protection against disease outlasts detectable serum antibody levels, although some individuals have developed antibodies to the hepatitis B "core" antigen (anti-HBc), indicating that subclinical infection has taken place.

It is unclear how long clinical protection against disease and the development of the carrier state will persist. Some experts believe that long-term, even lifelong protection against significant infection will occur following the immunologic "prime" provided by the initial vaccine series. Others think that loss of protection against significant disease will occur at some point and booster doses may be necessary. Further follow-up of immunized cohorts is indicated to answer to this question.

Number of Doses and Schedule

In early trials of HB vaccines and initial licensure of the product for adults, vaccine schedules were used that were not necessarily consistent with EPI schedules, and the vaccines were given at 0, 1, and 6 months or 0, 1, 2, and 12 months. For use in EPI, the vaccines should be given during existing visits to avoid the

expense and trouble of additional patient contacts. Fortunately, the vaccines have proven themselves to be extremely flexible and capable of retaining their immunogenicity and efficacy in virtually any EPI schedule (Hadler and others 1989). The first dose should be given with BCG near birth, if possible, or with the first dose of DPT if there is no immunization contact at birth. The second dose should be given with the next dose of DPT, and the third dose with the third dose of DPT or at the time of the measles immunization.

Low-Dose and Intradermal Administration

Studies of healthy children and young adults in certain settings have shown good immunogenicity of doses of HB vaccines substantially lower than that for which the vaccines are licensed. Although there may be some savings in using one-half or even one-quarter the manufacturer's recommended dose, there is concern that many vaccine recipients may not get an immunologically sufficient dose under conditions which may be found in developing countries. These conditions include malnutrition, immunodeficiency, less than optimal administration, missed doses, and schedules which are not maximally immunogenic.

Some investigators have attempted intradermal administration of approximately one-tenth the recommended dose of HB vaccines in healthy adults and children; they have achieved relatively good rates of seroconversion but substantially lower geometric mean titers. Intradermal administration in infants was less successful, with lower efficacy in infants of carrier mothers and reports of difficulty in administration and pain in the recipients. Additional concerns include reliability of personnel in administering intradermal injections, and the use of extremely low doses of vaccines that may vary somewhat in potency. Intradermal administration of HB vaccines is presently not recommended by EPI and the Technical Advisory Group for Viral Hepatitis.

Immune Globulin

If hepatitis B immune globulin (HBIG) is given to newborns of HBeAg-positive mothers in addition to HB vaccines, the efficacy may be increased to 75 to 95 percent. Use of HBIG adds considerably to the cost of treatment because it is expensive ($25 to $50 per child) and because it requires serologic testing of mothers to determine their HBsAg status. Such testing is itself expensive and requires laboratories and prenatal testing programs that are generally unavailable in developing countries. For these reasons it is generally accepted that it is more cost-effective to devote resources to routine infant immunization and that most developing countries will elect to forgo the use of HBIG.

Stability and Temperature Requirements

Both plasma-derived and recombinant types of hepatitis B vaccines are adsorbed on aluminium salts. As with other such vaccine preparations, they should be protected from being frozen. At temperatures of 2 to 8 degrees centigrade, the vaccines appear to be stable for many years. Some plasma- and yeast-derived products appear to be relatively stable at higher temperatures. This raises the possibility that HB vaccines could be used in the field without a cold chain, something not previously contemplated for other EPI antigens. Such a proposal needs careful field testing before widespread implementation, but it opens up the possibility that the vaccines could be carried by those attending births in the home.

Currently, EPI recommends that the vaccines be handled in the same way as triple antigen (DPT), that is, kept between 2 and 8 degrees centigrade. A temperature-sensitive marker in the vaccine vial or on the exterior of the vial would be a helpful addition to the product. The marker would indicate if the vaccine had been frozen before use. Thus, with regard to the EPI cold chain, the vaccines are easy to integrate and need no new developments or conditions.

Storage Bulk

Vaccines that are delivered in vials which contain multiple doses are less expensive per dose and require less storage space than those which are packaged with few doses per vial. Wastage rates rise with increasing number of doses per vial, however, and this becomes an important issue while HB vaccines remain more expensive than other EPI antigens. There is concern that the cold-chain storage space in some locations will be exceeded if programs adopt HB immunization plans using vials containing few doses each. However, modeling done by EPI suggests that most cold chains could accommodate the addition of HB vaccines with little or no expenditure for additional equipment. Currently available HB vaccines vary enormously in packaging volume, and the World Health Organization (WHO) is working with manufacturers to develop efficient packaging standards. Careful calculations will need to be made to estimate space requirements before introduction of the vaccines.

Equipment

Hepatitis B vaccines are given by injection in the same manner as other EPI antigens: no special equipment is needed. The use of reusable equipment will require more episodes of sterilization and the replacement of equipment sooner. If disposable needles and syringes are used, three more per child will be needed. These items will have to be budgeted for and supplied appropriately.

Future Strategies to Increase the Efficiency of HB Immunization

Drop-out rates (parents not bringing their children for scheduled immunizations) between the second and third doses of DPT are significant, and a similar drop-out rate must be expected with HB vaccines. Any strategy that might reduce this drop-out rate would be advantageous. One possibility is the development of preparations which surround the antigen with a poly-

mer which allows timed, slow release in pulses. This technology is, in theory, practical for HB vaccines and could mean that a single injection might be sufficient to immunize a child fully. Such research underlines the importance of developing a system which allows for the maximum number of antigens to be administered as early in life as possible.

Another way to increase the efficiency of immunization would be to use combined DPT and HB vaccines and DPT, IPV (inactivated polio vaccine), and HB vaccines; these are under development but will not be available for several years. Such vaccines would eliminate additional storage and delivery costs and would spare the recipient several additional injections. In Asia, an additional dose of univalent HB vaccine could be delivered at birth to prevent perinatal infection.

Strategies for Control

Recommended HB immunization strategies have differed in various regions of the world because of the different epidemiological patterns of HBV infection. When the vaccine became available in 1982, expert groups recommended universal infant immunization as the proper strategy for areas in which HBV infection was moderately or highly endemic, and immunization of "high-risk groups" as the recommended strategy for areas of lower endemicity.

Although high-risk individuals will undoubtedly benefit from immunization, there is now considerable doubt from both epidemiological and practical viewpoints that such high-risk-group strategies will ever lead to a significant reduction of HBV infection on a national or international scale. It is likely that universal infant immunization is the proper strategy for long-range control of HBV infection everywhere.

Hepatitis B Virus Control in Asia and the Pacific Basin

In the hyperendemic areas of Asia, about 7 to 10 percent of pregnant women are HBsAg-positive chronic carriers, and about 40 percent of these women are also HBeAg positive. Because the mothers of about 2.5 to 4 percent (40 percent of 7–10 percent) of Asians are HBeAg-positive carriers, and because about 10 to 15 percent of the population are carriers, it follows that 25 to 40 percent of carriers may have resulted from perinatal transmission. The majority of infection in the community and the development of the carrier state in the majority of carriers are the result of childhood infection which is not perinatal.

The need to treat infants of HBV-carrier mothers soon after birth poses a problem in areas in which there is no contact with immunization services until several weeks or months after birth. In such areas children born to carrier mothers who are HBeAg positive may not receive protection from the vaccines. Immunization programs in Asia will need to provide HB vaccines near birth to maximize the prevention of HBV-carrier children.

The problem of HBV infection and its relation to PHC is well understood by Asian health authorities, and HB control is high on their list of health priorities. Most countries in eastern Asia and the Pacific Basin have begun infant immunization programs, which are presently at various stages. Countries with more health resources have embarked on national programs, whereas those with fewer resources have begun demonstration projects in selected areas with the intention of expanding them into national programs. Countries in this region which cannot afford vaccines are looking for donor support to allow them to begin immunization.

Hepatitis B Virus Control in Africa

In Sub-Saharan Africa, about 10 to 15 percent of the population are HBV carriers, and about 70 to 95 percent of the population show serological evidence of prior HBV infection. These prevalence figures are consistent in this region, and most experts do not feel that serological studies need to be done in each country before HB vaccine programs are begun. It may be necessary, however, to do such studies to convince health authorities that their country has an HBV problem of this magnitude.

The risk of a newborn infant acquiring HBV infection perinatally in Africa is much lower than that of his or her Asian counterpart (Mariner and others 1985). Although about 10 percent of women of childbearing age in Africa are HBsAg positive, only 10 to 15 percent of them are also HBeAg positive, so only about 1 to 1.5 percent of African children are born to HBeAg-positive mothers. For this reason perinatal transmission is much less common. In contrast, 70 to 90 percent of children become infected before the age of seventeen. In many countries in Sub-Saharan Africa, PHC is the first or second cause of cancer death in males.

Because perinatal transmission is uncommon, and because most African children are passively protected by maternal antibodies for about six months, the timing of the first HB vaccine injection is not critical. About 95 to 98 percent of fully immunized children would be protected whether the first dose were given at birth or at three months of age. Several studies are in progress in Africa which are designed to examine the question of optimal timing of doses.

Hepatitis B Virus Control of Intermediate Endemicity Areas

Less attention has been paid to HBV control in areas of intermediate endemicity than in areas of higher or lower prevalence. Public health officials in these areas often believe that immunization of health care workers and maternal screening with treatment of newborns of carrier mothers make up the proper strategy for control of hepatitis B. For reasons that will be discussed below, however, immunization of all newborns with HB vaccine is probably the only strategy that will provide long-term control.

Hepatitis B Virus Control in Areas of Low Endemicity

Since the availability of HB vaccines in 1981–82, strategies for HBV control have stressed the immunization of high-risk groups and the screening of pregnant women and treatment of the

infants of HBV-carrier mothers. With few exceptions, the effect of this strategy has been the immunization of health care workers—about 85 percent of HB vaccines sold in the United States and Europe has been used in this group. Although it is certainly desirable to immunize these workers, cases of hepatitis B in health care workers represent fewer than 5 percent of reported cases in the United States, and it is unlikely that immunization of one small group will control HBV infection in the community (Alter and others 1990).

Intravenous drug abusers, those who acquire HBV infection through homosexual or heterosexual activity, and those who belong to ethnic minorities in which HBV infection has a higher-than-average prevalence are difficult to reach with health care services and are often infected before they go to any health setting where immunization could be offered (Kane and others 1989). For these reasons immunization of all infants nd, in some areas, of adolescents for an interim period is now national policy in the United States (CDC 1991), Italy, and New Zealand and is being viewed by many experts worldwide as the only strategy that will provide long-term control of HBV infection even in areas of low endemicity.

Treatment of Chronic Sequelae of HBV Infection

There is no effective treatment for PHC, which is essentially 100 percent fatal even with tertiary care in industrial countries. Death occurs within one to four months of presentation in developing countries, so PHC itself does not carry with it prolonged morbidity (Beasley 1988). Most patients who die of PHC, however, have underlying cirrhosis, and many patients have had years of morbidity from their chronic liver disease. In industrial countries, PHC patients are often treated with chemotherapy, hepatic artery embolization, or surgery. Although these measures can prolong life for several months at great expense, the cure rate is extremely low.

Alpha-fetoprotein is a host protein produced early and in high quantities by PHC tumor cells. It is detectable with sensitive assays, and trials are in progress to assess its usefulness as a screening test for early detection of PHC at a stage when the tumor may be resectable. Trials in Alaska (McMahon and others 1990) and Shanghai have met with success in screening populations with this marker and resecting patients with early tumors. Japanese gastroenterologists use yearly ultrasound examinations of the liver in cirrhotic patients in a similar attempt to find curable early PHC tumors, which they treat with either surgery or ethanol injections. Alpha-fetoprotein and routine ultrasound screening are expensive, require knowledge of who in the population are carriers, and are not practical at this time in developing countries.

There is also no practical treatment for chronic hepatitis or the carrier state in developing countries. In industrial countries, liver transplantation is sometimes attempted to prolong the life of a cirrhotic patient or one with fulminant hepatitis, but this is not a reasonable option in developing countries. Interferon treatment is being tried to alter the natural history of carriers with chronic hepatitis. Treatment may cause an early seroconversion from HBeAg to anti-HBe, which may bring about histological and biochemical improvement in chronic liver disease, but only a few patients lose their HBsAg, which defines the carrier state. It is not known whether oncogenic progression to PHC will be affected by this treatment. The treatment requires six months of thrice weekly interferon injections, is expensive ($3,000 just for the drug), causes significant side effects in most patients, and is usually ineffective if the carrier state has been present since childhood, which is the usual situation in developing countries. If a country finds it difficult to prevent the development of a carrier with vaccine for $3 per child, it will probably not be able to treat hundreds of thousands or millions of carriers for thousands of dollars each.

Cost-Effectiveness Considerations

Although there are numerous publications on the cost-effectiveness of HB immunization of health care workers and of maternal screening for HBsAg in industrial countries, there are few published studies on the cost-effectiveness of universal infant HB immunization in industrial or developing countries, and the studies which exist do not use the outcome measure of disability-adjusted life-years (DALYs). Because immunization in industrial countries is not the issue of concern in this collection, it will be mentioned but not discussed in detail.

There are no effective treatment alternatives to immunization, although in industrial countries patients with severe chronic disease or PHC may receive expensive palliative treatment or treatment designed to slow or alter progression of disease. No one would argue, from a medical, ethical, or economic point of view that we should consider not preventing this disease in favor of treating infected individuals. The effect of treatment on economic analyses is greatly to increase the cost of not vaccinating in industrial countries.

In industrial countries, with a relatively low incidence of infection and high vaccine cost, immunization of health care workers (Mulley and others 1982; Lahaye and others 1987; Koplan 1986), immunization of other high-risk groups (Adler and others 1983), screening of pregnant women, and immunization of newborns of carrier mothers (Arevalo and Washington 1988; Kane and others 1988) have been shown to be cost effective and even cost saving. The author of one study in Greece (Hatziandreu and others 1991) and the investigators of several as yet unpublished studies in the United States have examined the cost-effectiveness and cost benefit of universal HB immunization in industrial countries of low and intermediate endemicity. (Personal communications [1992] from Dr. P. Coleman, Centers for Disease Control; Dr. B. Bloom, University of Pennsylvania; Dr. R. Anderson, University of London; and Dr. G. Ginsberg, Jerusalem Ministry of Health.) Taking into consideration the high cost of treatment and medical care in these countries, those researchers who attempted to do a cost-effectiveness analysis found that the

strategy of universal immunization of infants was cost effective and cost saving if the cost of vaccine for public sector programs was less than that charged in the private sector.

In 1985 the Institute of Medicine published a comprehensive report on priorities for new vaccine development in developing countries (Institute of Medicine 1985). In its analysis, the burden of disease from HBV infection ranked second to *Streptococcus pneumoniae* among all infectious diseases considered. The researchers estimated that, in 1985, 572,650 deaths per year occurred from PHC, 246,239 deaths occurred from cirrhosis, and 3,347 deaths occurred from acute and fulminant HB infection. Unfortunately, they considered the probable cost of HB vaccine to be $30.00 per dose and did not perform a sensitivity analysis on vaccine cost. Because the cost of HB vaccine is now $0.65 to $2.00 per dose in developing countries, it would be useful to recalculate their outcome measures.

For developing countries, the authors of two cost-effectiveness studies (Maynard, Kane, and Hadler 1989; Hu 1990) have constructed decision trees to model the number of carriers and deaths from liver disease that will result from doing nothing and from integrating HB vaccines into EPI programs. These studies predict a cost per carrier prevented ranging from $65.00 to $100.00 and an undiscounted cost per death prevented ranging from $260.00 to $400.00 at a vaccine cost of $1.00 to $1.40 per dose. It is assumed in the studies that the delivery cost of the vaccine will add an additional one-sixth to the current EPI costs. In one analysis the undiscounted cost per death prevented drops to $75.00 if vaccine cost drops to $0.50 per dose, a level probably achievable now in very large purchases.

An important study of the cost-effectiveness of hepatitis B immunization in the Gambia, the only African country with routine infant HB immunization, has recently been prepared (Robertson and others 1992). The authors of this study used actual costs from the Gambian EPI program, and they used the HBV prevalence and incidence rates as measured by the Gambia Hepatitis Intervention Study. At an HB vaccine cost of $1.00 per dose, the marginal costs of adding the HB vaccine to the existing Gambian EPI averaged $4.23 per fully immunized child. The delivery costs, the cost of all inputs except vaccine, averaged only $0.28 per dose for a three-dose regimen.

The analysis revealed that at a vaccine cost of $1 per dose, the cost per carrier prevented was $30 to $40, and the undiscounted cost per death averted was approximately $150 to $200. Discounting raised the cost per death averted to approximately $1,000 to $1,400. Because the carrier state develops during early childhood in the Gambia, discounting is not a significant factor in the calculation of the cost per carrier averted. These results compare favorably with the cost-effectiveness of other vaccines in the Gambia. The authors of the study note that the cost per carrier averted is higher than the cost of preventing a case of measles or pertussis but much lower than the cost of preventing a case of neonatal tetanus, polio, or diphtheria (Robertson and others 1985). The cost-effectiveness of HB immunization in the Gambia also compared favorably with data on other EPI vaccines from other countries (WHO 1982; Barnum and others 1980).

We are aware of only one attempt at a cost-benefit analysis of HB immunization in a developing country (Zhy Yi Xu and Richard Mahoney, personal communication, August 1992). These researchers, who measured the cost benefit of routine HB immunization in China, found an extremely high benefit-to-cost ratio for vaccine use at a vaccine cost of approximately $1.00 per dose. They also calculated the cost per DALY gained for universal HB immunization in China, which they found to be $17.50 to $22.40, about one-half the cost calculated by Barnum and Greenberg (chapter 21, this collection).

There is an obvious need for additional cost-effectiveness and cost-benefit studies concerning the addition of HB vaccines to routine immunization programs in other areas of the world, and there is a need for researchers to convert their outcome measures to DALYs so that results are comparable with other interventions discussed in this collection. Nevertheless, the existing published and unpublished studies, whether based on modeling or actual country data, are quite consistent in finding that at present it costs only $20 to $60 to prevent, through a routine infant immunization program, the development of a chronic carrier of hepatitis B in countries of high endemicity. This finding, plus the cost per death prevented, discounted or undiscounted, places HB immunization among the most cost-effective health interventions available. It is equally important to realize that this intervention is possible within the existing framework of national immunization programs which are effectively delivering vaccines to 80 percent of the world's children.

Hepatitis B is a disease with a burden of morbidity and mortality comparable to measles, each having the potential to cause up to 3 percent of the mortality in a population. Hepatitis B vaccine, because it can be used at birth, is more effective than measles vaccine. Deaths from chronic hepatitis, however, usually occur during the third to sixth decade of life and are heavily discounted by the DALY method. Families in developing countries, however, might "discount" (in a noneconomic sense) the loss of a four-month-old child from measles and the death of a forty-five-year-old father in a much different way, because the loss of the father could have dire social and economic consequences for the entire family.

Hepatitis B Vaccine and Future Immunization Policy

Excellent HB vaccines have been available for ten years but are still not available to children in many developing countries. There is a serious problem in our ability to integrate a developed new vaccine into the international immunization system. The problem is not technical but relates to the willingness of donors to increase their contribution to add vaccines to national immunization programs that are dependent on donor support. A discussion of this issue must consider the economics and politics of vaccine development and delivery, and the goals and realities faced by private sector companies, interna-

tional and nongovernmental organizations, donors, and industrial and developing countries.

The Expanded Programme on Immunization is a network of international, regional, national, and local immunization programs that deliver vaccine to approximately 80 percent of the world's children. Some of these vaccines are produced by laboratories in the public sector in various countries, and some vaccines are purchased from manufacturers by national governments, but approximately 50 percent of vaccines for children are purchased from private manufacturers by the United Nations Children's Fund (UNICEF), which must raise money from donors to purchase this vaccine. The cost fully to immunize a child varies from country to country, but it averages about $15. Most of this cost goes for salaries, equipment, training, and delivery of the vaccine: the cost of the vaccines themselves is less than $1 per fully immunized child.

Most vaccines are produced by private manufacturers in dustrial countries, who are in business to make a profit. Yet prices obtained by UNICEF are only pennies per dose. How can such prices be obtained? Because manufacturers' books are not made public, the actual costs of production are proprietary information, but these prices can reflect little more than the marginal cost of production plus the cost of the vial and packaging. Some manufacturers claim that they can only provide low cost vaccine to UNICEF because they sell the same vaccine for much more in industrial countries. Indeed, in the United States and Europe, pediatric vaccines sell for between $5 and $20 per dose. A second reason for the relatively low cost is that these are older vaccines, whose costs for research, development, and capitalization have already been recovered.

Manufacturers of hepatitis B vaccine claim that this is a relatively new vaccine and that they are still recovering the very substantial costs of research, development, and marketing and the capital costs of the new production facilities. In addition, some manufacturers pay a substantial royalty per dose to other companies who developed the clones used to make the vaccine. They claim that they cannot sell this vaccine at prices comparable to the other EPI antigens. In industrial countries HB vaccine sells for between $5.00 and $20.00 per pediatric dose. In developing countries vaccine may be obtained for between $0.65 and $2.00 per dose. It is unclear how low this price would go if tenders for tens of million to hundreds of million doses were offered.

A vicious cycle exists between potential vaccine purchasers, such as UNICEF, and the manufacturers. Even at $1.00 per dose ($3.00 per child), UNICEF claims, the vaccine cost per fully immunized child would more than double and thus it cannot afford this vaccine. The manufacturers claim that without guaranteed substantial orders, they cannot make the investments to scale up production that would allow them to offer a lower price. Pooling of orders from a number of countries and competitive bidding with large orders should lead to significantly lower prices, which in turn would allow more countries to afford HB immunization. Pooled procurement would also ensure that participating countries received vaccine that met WHO requirements and that uniform shipping and storage conditions were met.

Ministry of Health officials in countries that can afford the vaccine are often confused by contradictory information from manufacturers, local experts, international agencies, and nongovernmental organizations. They are variously advised to purchase plasma-derived vaccine, purchase recombinant vaccine, import and repackage bulk vaccine, produce their own plasma vaccine or recombinant vaccine, and enter into regional production or procurement schemes. National committees are often set up and given the task of sorting these options out, but the committees are often unable to come up with acceptable recommendations even after years of deliberation.

In many developing countries, children do not get vaccine unless it is provided by donors. The newer vaccines, with HB vaccine as the prototype, will cost more per antigen than the six vaccines currently supplied to EPI. Donors and international immunization authorities must increase the resources devoted to the purchase of new vaccines and fund new vaccine development if the world's children are to benefit from these technologic advances.

Transfer of Technology

A number of countries have expressed interest in local production of HB vaccines. In theory, local production of plasma-derived vaccines and the use of a readily available local material, HBsAg-positive plasma, which is identified during blood donation and is otherwise discarded, could make vaccines available at an estimated cost of $0.10 to $0.40 per dose (Mahoney 1990). The technology to produce plasma-derived HB vaccine has been successfully transferred to China, which has produced up to 20 million doses per year. Several countries, including China, are exploring the possibility of transfer of technology to produce recombinant HB vaccines.

Critics of transfer of technology point out that there are few instances of successful transfer of technology of biologicals in the public sector. They also point out that current producers in industrial countries could produce large volumes of additional vaccine at a marginal cost that is less than the cost of putting into place new transfer of technology schemes. There is concern that although a few well-trained scientists and engineers could produce a vaccine, the overall infrastructure to ensure that high-quality vaccine is consistently produced may not exist. There may not be consistent availability of good water, electricity, trained technicians, and reagent kits for quality control. National control authorities with independent, high-quality testing facilities and trained personnel may also not be present.

Proponents of the idea argue that although efficient production by a few large producers may be a good strategy in an ideal global economy, HB vaccines have been available for ten years, and most developing countries still cannot afford them. Hard currency considerations make it such that countries that can-

not afford foreign vaccines may be willing to spend local currency to produce vaccine. Purchase from a few large producers also does nothing to reduce long-term dependence on foreign aid to supply vaccines. There has been much consolidation among large pharmaceutical firms, and vaccine production, not a very profitable enterprise compared with the production of other pharmaceuticals, could conceivably be dropped by many producers in the future.

Additional arguments in favor of transfer of technology include the economic benefits of developing a capability for production of biologicals and recombinant biotechnology. The production could be placed in the private sector, where there may be more motivation for efficient operation. Excess vaccine could be sold in the private sector or to neighboring countries to recoup part of the cost of production.

A significant obstacle to local vaccine production is the large initial cost of purchasing the technology, the equipment, and the plant. International funding agencies and donors should consider loans or grants to cover this period if an analysis of the economic aspects shows local production to be reasonable, and if competent national regulatory authorities exist to ensure that a high-quality product is consistently produced. In some countries, the level of technology and infrastructure seem adequate to produce an affordable, high-quality vaccine.

Conclusions

Hepatitis B vaccines have proved themselves to be stable, safe, immunogenic, and effective. There are no technical or scientific impediments to their immediate use. Indeed, the dimensions of the global problem of HBV infection make it clear that their use is a matter of urgency. As with all vaccines, research and development efforts must continue to improve the vaccine and its preparations, determine the most cost-effective strategies for delivering it, and lower the costs of production. The final task before us is to develop national programs and obtain financial resources to provide this important antigen to the world's children.

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WHO/EPI/GEN/88.5
ORIGINAL: ENGLISH
DISTR: GENERAL (E)

EXPANDED
PROGRAMME
ON IMMUNIZATION

Hepatitis B Immunization Strategies

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WORLD
HEALTH
ORGANIZATION

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3. HBV and HBV MARKERS

3.1 THE VIRUS

HBV is a 42 nm particle, originally known as the "Dane particle", containing double-stranded DNA and belongs to a unique virus group unofficially designated "HEPADNA". Man is its only natural host, although chimpanzees and other higher primates can be infected. It has never been cultured in vitro so detection is usually accomplished by immunologic markers.

Infection with HBV is demonstrable by five immunologic markers:

- hepatitis B surface antigen (HBsAg)
- antibody against the surface antigen (anti-HBs)
- antibody against the core antigen (anti-HBc)
- e antigen (HBeAg)
- the antibody against the e antigen (anti-HBe).

3.2 HEPATITIS B SURFACE ANTIGEN (HBsAg)

The surface antigen is found in blood as 18-22 nm spherical particles and as tubular forms. It was the first HBV marker identified, and was named Australia antigen by Blumberg who discovered it in 1967 using agar gel diffusion. Today it is usually diagnosed by passive haemagglutination (PHA), radioimmunoassay (RIA) or ELISA tests.

HBsAg is clearly the most important marker. It is the protein that makes up the virus coat and is detectable whenever there is viraemia, such as in the early phase following infection (irrespective of whether there is acute clinical hepatitis) and in the chronic carrier state. The definition of a carrier is a person whose serum is repeatedly HBsAg positive, often arbitrarily defined as over a six month period or longer.

Following infection most adults have a period of viraemia which lasts for a few days to weeks, which may or may not be accompanied by illness. A prolonged carrier state develops in less than 10% of infected adults. Once established the carrier state may last many years, even a lifetime.

3.3 ANTIBODY AGAINST SURFACE ANTIGEN (ANTI-HBs)

If the carrier state disappears it is usually followed after some weeks to months by the appearance of anti-HBs which is often detectable for the remainder of the person's life. In adulthood, however, a few persons lose their anti-HBs and are left with anti-HBc as their only residual marker of past infection. Chronic liver disease due to HBV appears only to occur in persons who become chronic HBsAg carriers.

HBV vaccine is purified HBsAg and the immune response it evokes is the production of anti-HBs. A successful immunization is marked by the presence of anti-HBs. As with

all the conventional vaccines, it is unlikely that any susceptibility test will be recommended before immunization.

3.4 ANTIBODY AGAINST CORE ANTIGEN (ANTI-HBc)

HBcAg is present in the serum of people in whom there is active viral replication, but there are no commercial tests available for this marker. Early in the acute phase of infection anti-HBc is produced, and continues to be present for many years (perhaps a lifetime) whether or not there is persistence of HBsAg. Anti-HBc is not a protective antibody and appears to play no role in the immune regulation nor in the immune pathogenesis. It is useful as a stand-in marker for HBcAg. Anti-HBc testing may be of value in programmes for older children and adults because it is the best single test to find HBV-susceptible persons, in the absence of immunization. Such screening is not needed if all individuals in a group are to be immunized, and has no place in immunization programmes for newborns because most infants possess passive maternal antibodies. Immunization with HBV vaccine does not produce an anti-HBc response, thus the presence of anti-HBc in an immunized individual suggests that at some time that person had experienced an active HBV infection, a distinction that is not important in population based immunization programmes.

* * *

3.5 e ANTIGEN (HBeAg)

HBeAg only occurs in the presence of HBsAg and is a marker of infectivity. In immunization programmes the test for HBeAg is only useful if there is a differential immunization policy in relation to the mother's HBeAg status, e.g. administration of HBIG and/or vaccine to infants whose mothers are HBeAg positive. If vaccine is to be given to all newborns or all newborns of HBsAg positive mothers then the HBeAg test need not be performed.

3.6 ANTIBODY AGAINST e ANTIGEN (ANTI-HBe)

When e antigen disappears it is usually replaced by anti-HBe. HBsAg carriers who are anti-HBe positive are much less infectious than those who have HBeAg. However, it is very unlikely that anti-HBe testing would have a place in any immunization programme.

4. EPIDEMIOLOGY

4.1 GENERAL

Hepatitis B is a global problem existing in even the most remote and isolated populations in the world. Humans are the only reservoir. The origins of the virus are unknown and there are no naturally infected wild animals, although chimpanzees and several other higher non-human primates can be infected experimentally. Although HBV is found in all populations, the frequency of infections and of the carrier state has striking geographic and ethnic variability (see table 1).

Table 1. Geographic distribution of levels of HBsAg prevalence

HBsAg prevalence	<2%	2-10%	>10%
	Low	Intermediate	High
Geographic examples	W. Europe N. America Australia New Zealand S. America (partly)	E. Europe S. Europe Middle East Japan S. America (partly)	China SE Asia Pacific Islands Africa S. America (partly)

4.2 TRANSMISSION

4.2.1 General

There are three important mechanisms of transmission of HBV:

* mother to infant in the perinatal period
* parenteral
* person to person.

The relative importance of each varies substantially from population to population around the world.

Because of the viraemia of chronic HBV infections, there has been considerable interest in the possibility that vectors might play a role in HBV transmission. Biological propagation of HBV has not been demonstrated in an arthropod, so vector transmission, if it occurs, would have to be mechanical. Epidemiological studies in various parts of the world do not suggest that vectors play an important role, if any, in HBV transmission.

4.2.2 Perinatal

Mother to infant transmission, also sometimes referred to as vertical transmission, most often occurs during the time of labour and delivery. This may occur through small leaks across the placenta, and can be precipitated by trauma associated with the birth process. It may also occur through exposure of the infant to maternal secretions in the birth canal.

Transmission in utero before the birth process is initiated appears to be unusual: only about 5% of high

risk infants have established infections when they are born. The mother continues to be infectious after delivery but post-natal infections are not common because most high risk infants have already been infected at birth.

The term vertical transmission, although widely used, should be discouraged in order to avoid confusion with its prior established usage meaning transmission through germ cell lines, which is not the case with HBV.

Perinatal infections most commonly occur from asymptomatic carrier women who have no knowledge of their carrier status, unless they have had a blood test for HBsAg. It also occurs in the rare circumstance when the the mother has acute hepatitis B during the later part of pregnancy or shortly after the birth of the child.

Regardless of the method by which the infant is infected, the result is usually an asymptomatic chronic HBV infection manifest by the carrier state which lasts for many years and often for a lifetime. The probability that an infected mother will infect her child during the perinatal period is directly related to the number of infectious virus particles in her circulation.

For reasons that are not well understood, the surface material of HBV (designated as HBsAg and manufactured in the cytoplasm of the hepatocyte), is often produced in amounts far exceeding the core material of HBV (designated as HBcAg), which is produced in the nucleus of the hepatocyte. For this reason uninfectious free HBsAg often circulates in great excess of whole virus particles.

In general the amount of infectious material is greater in acute infections and in the earlier chronic phase of the carrier state, and is almost always found in greater amounts in infants and children than in adults. Since no simple test is available to detect whole HBV particles or HBcAg, the infectivity of a carrier can be approximated by either the presence of HBeAg which is located in or near to the virus core, or by the titer of HBsAg.

Carrier mothers are highly infectious when they are HBeAg positive or when they have high titers of circulating HBsAg. Both HBeAg and HBsAg titer are good tests for predicting which HBsAg carrier mothers are likely to infect their infants and can be utilized in immunization programs, if resources are scarce and not all newborns can be immunized, to select the highest risk infants who would benefit the most from immunization.

After an incubation of 2 to 3 months, the infant who is infected becomes a source of large quantities of highly infectious material. HBsAg may be produced in huge amounts by the infant.

4.2.3 Parenteral

It has been known for many decades that HBV can be transmitted by transfusion of blood or blood products from HBV carriers or by inadequately sterilized needles and other inoculation equipment. Very large amounts of infectious material exist in the blood of some carriers so it is not surprising that parenteral transmission by inadequate sterilization of inoculation equipment may occur. It

should be noted that HBV is much more infectious than Human Immunodeficiency Virus (HIV), and remains a considerable risk in the parts of the world where many injections are given without properly sterilizing the injection equipment. At least two studies have shown a clear correlation between the number of injections received by children and the frequency of HBV infection. Ritual scarification, tattooing, and illicit drug use are other circumstances in which parenteral HBV transmission may occur.

4.2.4 Person to person

Person to person transmission, often called "horizontal transmission" (although that term is to be discouraged), of HBV infections are common in many parts of the world, although the exact mechanisms are not well understood. Close body contact with exchange of body fluids such as saliva may play an important role although this has never been proven.

4.2.4.1 Children

HBV infections among children whose mothers are not HBsAg positive are common in many parts of the world. For example, in Asia approximately 50% of HBV infections occur in persons who do not have HBsAg positive mothers. Some of these may be due to parenteral transmission but a significant proportion are probably due to person to person contact, most commonly between children, since they are often more infectious than adults. Because saliva is often HBsAg positive (albeit with a much lower titer than blood), and no other means of transmission can be identified, it is widely assumed that saliva is a common source of person to person spread of HBV. In some parts of the world adults premasticate the food of infants and this may be a common mechanism of transmission.

4.2.4.2 Adults

Adults can be infected by the same routes as children. In addition there is sexual transmission. HBV transmission between sexual partners occurs but the frequency and mechanisms are not well understood. Transmission can occur between heterosexual or homosexual partners. In many Western countries high rates of HBV infection have been demonstrated in homosexual males. It is not clear whether the transmission is via saliva, blood or genital secretions all of which often have detectable HBsAg.

In areas of the world where carrier rates are very high most people are infected before they reach sexual maturity and thus sexual transmission is probably of little importance. Few, if any, studies have been conducted of sexual partners of carriers in geographical areas where HBV infections are of intermediate frequency, however.

* * *

5. IMMUNIZING AGENTS

5.1 VACCINE

By virtually every parameter except cost, the available HBV vaccines are among the best immunogenic agents ever developed against any disease. The current price is the only major deterrent to a global programme to control one of mankind's greatest scourges. The HBV vaccine will almost certainly be the first effective major cancer vaccine. There have been well publicized efforts to improve the first generation vaccines which are derived from the plasma of human HBV carriers but the only really important improvement needed in the present HBV vaccines is a lower purchase price. The available vaccines have no important side effects. It can almost certainly be assumed that the eventual price of HBV vaccine will be less than the most expensive vaccine now being used in the EPI. It is therefore reasonable to begin planning the strategies for HBV immunization now.

5.1.1 Types of vaccine

5.1.1.1 Human plasma derived - The first generation of HBV vaccines consists of highly purified HBsAg derived from plasma of human carriers inactivated by one or more procedures to assure that no living material exists in the vaccine. Most manufacturers have achieved at least 95% HBsAg purity by two steps of ultracentrifugation, one of the major reasons for the high cost of the plasma vaccine. Various inactivation procedures have been used including formalin, heat, pepsin and urea. The extent to which inactivation alters the immunogenic properties of the vaccine have been the subject of some debate and is unresolved. This debate notwithstanding, even the most severe inactivation leaves a potent vaccines. It should be stressed that only with the plasma derived vaccines has there yet been long and widespread experience. Over 30 million doses of hepatitis B vaccine derived from human plasma have been distributed worldwide and there are now more than ten manufacturers globally. No serious problems with the use of these vaccines are recognized, and concepts of the duration of protection are primarily based on experience with the plasma vaccines.

5.1.1.2 Recombinant - DNA recombinant vaccines are purified HBsAg which are intended to be identical in composition to the first generation plasma vaccines. Both of the presently available recombinant vaccines (Merck and SKF-RIT) are derived from ordinary bread yeast. Several manufacturers are developing recombinant vaccines from mammalian cell lines which have the advantage of a high yield of HBsAg in the supernatant, which is more easily harvested. HBsAg from yeast can only be recovered after lysing the cells. In as much as the recombinant vaccines are more expensive there seems to be no advantage to their use since they appear to be equivalent to the plasma vaccines in other respects.

5.1.1.3 Polypeptide - Polypeptide vaccines are currently only experimental and their feasibility is yet to be established. Their main appeal is that they can potentially be manufactured in very large amounts at very low cost.

5.1.2 Safety

No serious side effects nor problems have occurred with any of the licensed vaccines. Fears that other viruses existing in the donors, eg. HIV, might survive the manufacturing inactivation procedures have not been substantiated, and careful follow-up of thousands of plasma vaccine recipients have not shown any increase in AIDS risk following HBV immunization. The experience to date with the plasma vaccines is now substantial and it seems likely that this is one of the safest vaccines yet developed. Although concern has been expressed that that residual components from the source materials (eg. normal human plasma protein components in plasma derived vaccines or yeast proteins in the yeast derived rDNA vaccines) could be cause problems; there are no data to substantiate this theoretical concern.

5.1.3 Immunogenicity

5.1.3.1 General - Purified aqueous preparations of HBsAg alone are poorly immunogenic, but excellent immunogenicity can be achieved by adsorption with an adjuvant, e.g. alum which is used by all current manufacturers of both plasma and recombinant vaccines. The alum is the cause of the slight fever and/or soreness at the sight of injection which occurs in about 5% of immunized persons.

Freezing will inactivate the vaccine because it causes vaccine-adjuvant dissociation.

5.1.3.2 Host factors influencing immunogenicity - The immune status of the host is the most important determinant of the ability to respond to HBV vaccine. Persons with immunological diseases or undergoing treatment which adversely influences the immune system (eg cancer chemotherapy, steroids etc) may not respond as well as otherwise healthy people.

Healthy infants and children of all races and ethnic groups respond extremely well to HBV vaccine. Females of all ages have a slightly better response than males but the difference is not great enough to necessitate differential policies for the sexes. The immune response gradually declines with increasing age for reasons that are not well understood. The effects of malnutrition on the response to HBV vaccine have not been studied.

5.1.3.3 Non-responders - Almost all healthy infants, including newborns, mount a good immune response to HBV vaccine. With increasing age the vigor of the immune response diminishes. Repeated immunizations, especially with larger doses results in sero-conversions in some of the initial non-responders.

5.1.4 Efficacy

5.1.4.1 General - The goal of every HBV immunization programme should primarily be the prevention of the HBsAg carrier state from which arises chronic liver disease including hepatocellular carcinoma. Persons who are infected with HBV but do not become HBsAg carriers are probably not at increased risk of

chronic liver disease. In numerous well designed randomized controlled trials HBV vaccine has been shown to provide excellent protection against HBV.

5.1.4.2 **Adults** - In various studies in healthy adults it has been shown that the vaccine protects against HBV infection and acute clinical manifestations of HBV hepatitis. Vaccine failures were limited to those already infected and in the incubation phase, and a small proportion of vaccinees who were non-responders. Adult vaccine recipients did not become HBsAg carriers (but in any cases that is an unusual outcome of HBV infection after childhood except in immune compromised individuals). Renal dialysis patients were not protected in one study, although they have been in others.

5.1.4.3 **Infants and Children** - Most importantly, HBV vaccine induces excellent protection of infants and children. Children have a better immune response than adults and infants. Newborns respond as well as older children.

The goal of HBV immunization is protection against the HBsAg carrier state because chronic liver disease, including HCC, only occurs in chronic carriers. Furthermore, acute clinical hepatitis B rarely occurs in infants

5.1.4.4 **Immunogenicity as an indicator of efficacy** - In infants, children and adults, full protection is achieved when any detectable anti-HBs is present. Thus efficacy can be assessed by the anti-HBs response to vaccine.

5.1.4.5 **Duration of protection** - As with all good vaccines this will be one of the last questions to be answered. As expected, anti-HBs titers decline following the peak achieved with each dose of vaccine. Following the last in the regular immunization series (third for Merck; fourth for Pasteur) anti-HBs titers decline with a projected mean extinction at about 5 or 6 years, causing some people to believe that a booster would be desirable at about the time of school entry. There is considerable individual variation in the rapidity of loss of detectable anti-HBs, and there has not been long enough follow up of enough individuals, especially infants and children, to adequately assess this issue.

5.1.4.6 **Efficacy against chronic hepatitis, cirrhosis and HCC** - The vaccine has not been in use long enough to have shown its expected long term efficacy in preventing chronic hepatitis, cirrhosis, or hepatocellular carcinoma. A study for this purpose is currently being conducted in The Gambia and results are expected in 30 to 40 years. In the mean time scientists are convinced that the clear ability of HBV vaccine to prevent the HBV carrier state, the antecedent of HBV-induced chronic liver disease, fully justifies undertaking immunization programmes.

* * *

5.1.5 Manufacturers

Plasma vaccines are manufactured and are commercially available from several countries, eg. France (Pasteur), United States (Merck), Netherlands (Red Cross), Japan (Green Cross and Kitasato), and S.Korea (Green Cross). (NB: Japan Green Cross and Korea Green Cross are different). Several other plasma vaccines have also been developed including one by the United States NIH, and by several institutions in China. The oldest and most widely used and still available are the Pasteur and Merck vaccines. There has been much less experience with the newer recombinant vaccines which are being made by several manufacturers. Yeast derived DNA recombinant vaccines are now being marketed by Merck and by SKF. Field trials are underway with recombinant vaccines from several other manufacturers as well.

5.1.6 Shipping and storage

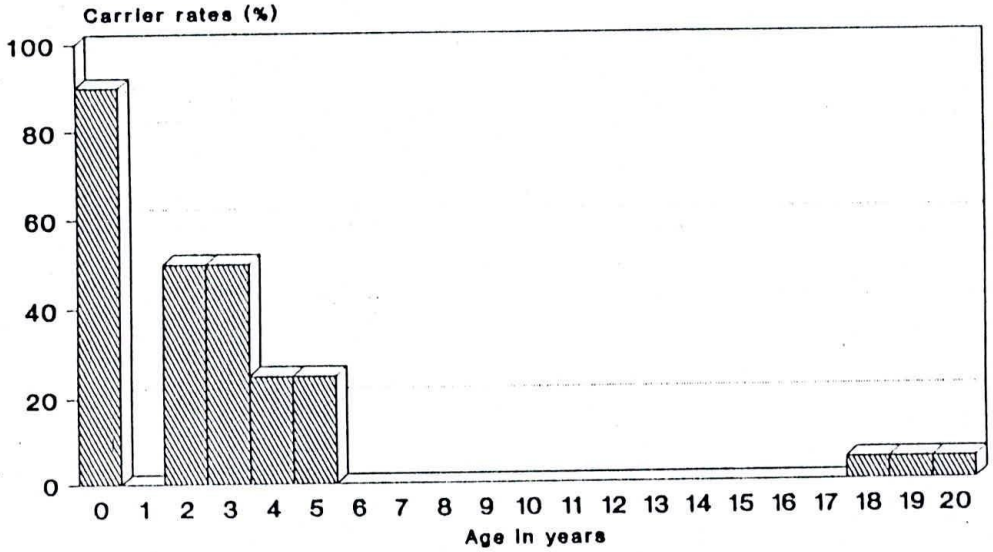
HBV vaccines are adjuvanted purified proteins derived from the surface of the virus. They are moderately stable at room temperature, but probably require cold chain protection. At 2 to 8 degrees C, the vaccines appear to be stable for many years; the upper limits of storage life have not yet been defined. Inactivation can occur at high ambient temperatures and by freezing. The stability of the vaccines at higher ambient temperature ranges is being investigated. As with DPT, HBV vaccine must not be frozen because vaccine-adjuvant dissociation. Little or no visible change occurs following freezing and it should be standard practice to include freeze indicators with all shipments. For all practical purposes the HBV vaccine should be handled in the same fashion as DPT.

Table 2. Overview of HBV vaccine manufacturers

Institution	Country	Plasma-derived		Recombinant	
		Licensed	Human trial	Licensed	Human trial
Merck	USA	yes	yes	yes	yes
Pasteur	France	yes	yes	no	?
Kitasato[1]	Japan	yes	yes	no	?
Green Cross[1]	Japan	yes	yes	no	?
Life Guard [1]	Taiwan	yes	yes	no	no
Green Cross[2]	Rep. Korea	yes	yes	no	NA
Cheil Sugar	Rep. Korea	yes	yes	NA	NA
4 Factories [2]	China	yes	yes	NA	NA
SKF-RIT	Belgium	NA	NA	yes	yes

1 Identical or very similar to Pasteur method
2 Identical or very similar to Merck method

Figure 1. Carrier rates following HBV infection at various ages.



5.1.8 Site of administration

All HBV vaccines were designated for intramuscular inoculation since it has been established that subcutaneous administration produces an inferior immune response. Recent data have revealed that adults have a better immune response following deltoid compared with gluteal administration. It has been assumed that this effect may have been because of the thickness of the layer of fatty tissue and that as a result some of the injections may not have been fully intramuscular. In most infants, especially newborns the deltoid muscle mass is too small, so almost all intramuscular injections, including HBV vaccine, are given in the anterior thigh.

Several studies have been undertaken to evaluate the immunogenicity of intradermal inoculation of the adjuvanted HBV vaccines intended for intramuscular use. Studies done with both the Pasteur and Merck vaccines using doses of 0.1 ml administered intradermally with a tuberculin syringe have yielded excellent immune responses without the severe local reactions that had been anticipated by some investigators. Cutaneous erythema is frequent but seldom severe enough to cause concern. The appeal of the intradermal approach is that there can be substantial cost reduction because it requires only about 10% the amount of vaccine to achieve the same level of antibody response

5.1.7 Dose and schedules

Higher doses of vaccine given more often achieve faster and higher antibody responses. Early studies used schedules with quantities as high as 40 µg/dose of vaccine. Because of its high cost, considerable effort has been made to determine the lowest acceptable dose.

There is no final consensus on the best schedule and number of doses. Pasteur has developed a four dose schedule while Merck and many other manufacturers use a three dose schedule. The first generation Merck vaccine (plasma) has been licensed in the United States for use in adults at 20 µg/dose, and in infants at 10 µg/dose, each given in a three dose series at times 0, 1 and 6 months.

All studies with all HBV vaccines in animals and humans indicate the need for at least three doses to establish sufficiently high levels of antibody to provide adequate duration of protection.

The third dose is needed to:

- bring about the desired high conversion rates, especially in older individuals.
- obtain high enough titers to provide long term protection.
- stimulate adequate long term immunological memory.

No studies of the efficacy against perinatal transmission of one or two dose schedules have been undertaken. But is probable that one or two doses will prevent a perinatal transmission as well as three doses, but will be insufficient to provide long term protection. It is possible that many infants receiving only two doses would have initial protection but would be subsequently infected by their still infectious mothers, older siblings, or playmates.

Two aspects of the immunology of hepatitis B infection should be considered:

* The risk of developing the carrier state drops rapidly with increasing age (Figure 1, page 16). Therefore, the value of immunization declines steadily as the child grows older and runs an ever decreasing risk of becoming a carrier, even if infected. The age at which the risk of becoming a carrier has reached its lowest level has not been established.

* Even loss of detectable antibody may not mean total loss of protection because the long incubation of HBV allows the host more time to mount a secondary immune response to infection than is the case with other viral infections. Although further studies will be needed to clarify this point, there is no clear indication that a fourth dose is needed.

induced by the intramuscular route. The great disadvantage is that it might be inadvertently given intramuscularly or subcutaneously where it would be ineffective and thus leave the child unprotected. Until further studies are done on this subject, intramuscular injection using full dosage is recommended.

5.1.9 Simultaneous administration of HBV vaccine with other vaccines

Two studies on the simultaneous administration, at different injection sites, of HBV vaccine with other EPI vaccines have been undertaken and both show that HBV vaccine neither enhances nor interferes with the immunogenic effect of BCG, DPT, OPV, or measles. Likewise, these vaccines do not effect the HBV response.

5.1.10 Combined administration of HBV vaccine with DPT

Studies of a combination DPT-HBV vaccine are being planned. Since all four immunizing agents are proteins which are adjuvanted and handled in similar fashion it is anticipated that such a combination would be feasible and would not interfere with the immunizing efficiency of any of the individual components.

Of greater concern is whether the age of DPT-1 could be lowered to coincide with HBV-1 which should be given as soon as possible after birth. Administration of DPT as early as six weeks is already advocated by EPI, and studies are now being conducted to determine the safety and immune response of DPT in newborns.

5.2 HEPATITIS B IMMUNE GLOBULIN (HBIG)

5.2.1 Source

HBIG is human immune globulin prepared from pooled human plasma by Cohn fractionation, using exactly the same procedures as for the preparation of conventional immune globulin. HBIG is, therefore, distinguished from immunoglobulin only in that the donor source is plasma from persons with high titers of anti-HBs. Originally, all HBIG was from persons who had experienced natural HBV infections from which they had recovered without becoming HBsAg carriers. A simple HBV infection rarely if ever results in the very high anti-HBs titers needed for HBIG. Therefore, most HBIG donors have to have their anti-HBs titers boosted with the new vaccine.

In addition to anti-HBs, HBIG contains other antibodies from the donor pool such as anti-HBc and anti-hepatitis A virus (anti-HAV) antibody. Some lots of HBIG have also contained antibodies against HIV although there is no evidence that HBIG has transmitted infectious HIV. Cohn fractionation probably inactivates retroviruses. It is also possible that anti-HIV in HBIG recipients is the result of antibodies stimulated in them from inactivated HIV in the HBIG.

5.2.2 Use in perinatal transmission

Although passive prophylaxis has been recommended in several exposure situations, the primary value of HBIG is for prevention of perinatal transmission of HBV. Some mothers are much more infectious than others

and they can be identified using the HBeAg test. Approximately 90% of HBeAg positive HBsAg carrier mothers infect their infants, usually during labor and delivery. In contrast, less than 5% of HBeAg negative mothers infect their babies.

5.2.3 Timing and dose

Although newborns generally mount a vigorous antibody response to HBV vaccine, it is not always early enough to protect against perinatal transmission. An intramuscular injection of HBIG administered to the infant immediately after birth will provide temporary protection until the active immune response has occurred in response to vaccine. It is particularly noteworthy that passive immunization not only provides the necessary early protection but has no inhibitory effect on active immunization. It must be stressed that, to be of value, the HBIG must be given shortly after birth. If delayed more than 48 hours it has no value at all. This fact alone will be a major deterrent to the use of HBIG in many parts of the world.

Empirically it has been determined that optimal protection can be obtained with 0.5 ml of HBIG containing at least 300 mIU and administered within the first few hours of life. Delay is only needed long enough to attend to any urgent procedures related to the delivery itself and washing the baby adequately so that the HBIG injection itself does not transmit infectious material from maternal secretions on the skin of the baby. This is followed by HBV immunization any time over the next few weeks. There is no immunological value in delaying vaccine administration, however, and since there is individual variation on both the speed of the active immune response as well as the rapidity of loss of passive antibodies, active immunization should be started within the first week of life. Occasionally it may be prudent to delay the first dose until the end of the first week where cultural groups may incorrectly attribute the administration of the vaccine to the early death of an infant.

6. IMMUNIZATION PROGRAMMES

6.1 OBJECTIVES

Prevention of chronic hepatitis, cirrhosis and hepatocellular carcinoma by prevention of the chronic HBV carrier state is the primary objective of an immunization programme using HBV vaccine. The chronic disease manifestations of HBV infection have only been identified in association with the long term carrier state and not with other serological parameters representing prior HBV infection (eg. anti-HBs, and/or anti-HBc in the absence of HBsAg).

Prevention of acute clinical hepatitis due to HBV is of secondary importance because acute clinical manifestations are relatively rare.

Prevention of infections per se is of little importance because infections which do not lead to the carrier state are rarely of clinical or public health significance.

HBV prevention programmes should therefore be targeted at infants and young children who are the group most at risk of becoming carriers. If resources are available and high risk adult populations have been identified then immunization of selected high risk adult populations may be considered.

The possible value of immunizing the mother is often raised. This, is of limited value because if the mother is already a carrier, neither HBIG nor vaccine can alter her carrier status or infectivity. If the mother is not a carrier, immunization with HBV vaccine may stimulate antibody formation or a booster response which is, of course, good and should not be discouraged if adequate resources exist, but is not likely to be an important means of preventing many HBV infections.

6.2 ESTIMATION OF LEVEL OF RISK

6.2.1 Criteria for a programme

Any country considering whether to embark on an immunization programme using HBV vaccine must determine what the level of risk in that country is before committing extensive resources.

The primary determinants of whether to mount an immunization programme in a given area or country should be:

- the HBV carrier frequency in the population,
- the proportion of carriers attributable to perinatal transmission
- the death rate from liver disease attributable to chronic HBV infection where this can be estimated.

The carrier rate indicates the magnitude of HBV as a problem and is the primary guide to the resources which should be allocated to its control. The fraction of carriers attributable to perinatal transmission will determine the extent to which an immunization programme should be targeted at newborns. Immunization safety is not an issue, so the limitation to an ideal programme will be cost and ability to reach the target populations. In considering cost it must be understood that the price of the vaccine will almost certainly be declining over the next several years and that countries will need to be readjusting their immunization strategies accordingly.

6.2.2 Seroprevalence studies

The most useful scientific guide for estimating the risk to infants is a serological survey of women of child-bearing age. If resources permit, it may be extended to include infants and children up to adulthood. The latter will give an indication of what percentage of carriers result from infection in the newborn period, and what percentage results from other routes of transmission.

To some extent, any division into high and low risk populations must be arbitrary. However, from

the knowledge of the epidemiology of HBV (see table 1) it is possible to make an attempt at categorizing areas of HBsAg prevalence, based on serum surveys.

- **A HIGH prevalence of greater than 10%** indicates that a serious problem exists, and an immediate implementation of a programme for neonates is justified.

- **An INTERMEDIATE prevalence of 2% to 10%** indicates an intermediate level of risk. It may be possible to identify some subgroups who are at much higher risk within the population. Some geographic areas in the country may be at high risk. But in general, the intermediate risk group also needs an immunization programme for neonates.

- **A LOW prevalence of less than 2%** generally indicates there is not a significant level of risk to undertake a mass immunization programme. However small subgroups within the population (for instance immigrants from high risk countries) may well need to be offered immunization.

6.2.3 Routine measurement of maternal markers

Where there is high and intermediate seroprevalence, it is unlikely to be necessary to measure the markers of every pregnant women. It may be assumed that every infant is at risk even if not all would necessarily become infected.

In areas of low risk, it may be worthwhile screening all pregnant women to indicate those at risk of perinatal transmission. However if the cost of screening is high, it may be better to commit resources only to the immunization of infants, ignoring any screening procedure.

6.3 STRATEGIES

6.3.1 General

The most effective strategy will vary from country to country with the epidemiology of HBV. The choice will also be affected by available resources. Universally, however, the first and highest priority should be given to the immunization of infants.

6.3.2 Perinatal Transmission - Carrier Rate Reduction Strategies

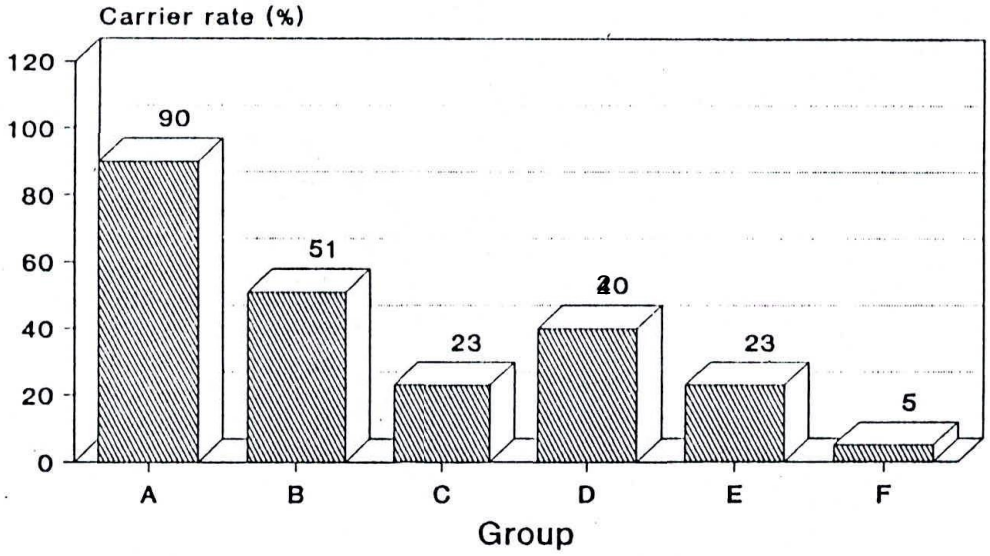
6.3.2.1 Unpreventable Intrauterine Infections

The combination of HBIG and vaccine will protect all but about 5% of high risk infants from becoming carriers. This small proportion of unprotectable infants are those who are infected in utero and already have established infections in their livers when they are born. Although there is no practical reason to do so, these infants can be identified by their high levels of HBsAg in the infant circulation at birth; cord blood testing yields unreliable results and should be discouraged. Neither passive nor active immunization of infected infants has harmful effects, such as antigen-antibody complex disease. HBsAg is produced in such large amounts in infected individuals that it is detectable even after the administration of HBIG.

6.3.2.2 Carrier Rate Reduction Strategies

The effect of five different carrier rate reduction strategies on infants of HBeAg positive mothers is illustrated in Figure 2.

Figure 2. Effect of 5 carrier rate reduction strategies.



Description of groups	
A = No prophylaxis	
B = HBIG (1 dose at birth)	- No vaccine
C = HBIG (3 doses: at birth, 3 months, 6 months,	- No vaccine
D = HBV vaccine (3 doses, first at 1 month)	- No HBIG
E = HBV vaccine (3 doses with first at 1 week)	- No HBIG
F = HBIG (1 dose at birth) AND 3 doses of HBV vaccine	

6.3.3 Selective immunization

Within the first few days of life, vaccine may be given selectively to all infants born to HBsAg POSITIVE MOTHERS. Additionally HBIG may be administered to infants whose mothers are found to be highly infectious (HBeAg positive and/or high titer HBsAg)

Selective immunization of HIGH RISK infants and children is advisable if significant amounts of non-perinatal transmission are shown to be occurring

Selective immunization of groups of high risk ADULTS may be indicated.

6.3.4 Mass immunization

The choice between immunization of selected groups or immunization of all infants will be helped by knowing the contribution perinatal maternal transmission makes to the overall carrier rate in the particular area (see table 1).

6.4 Country experiences

In Taiwan the carrier rate in the general population is about 20%, and 40-50% of this is attributable to perinatal transmission. In 1984, a step-wise island-wide programme was started. During the first two years all pregnant women attending the island's widely used prenatal clinics were screened for HBsAg. Those found positive were also tested for HBsAg titer and/or HBeAg. All newborns of HBsAg positive mothers were given HBV vaccine shortly after birth and if the mother was highly infectious the newborn was also given HBIG within the first 24 hours of life. In the first year 77% of the target population was reached. In July 1986 the programme was expanded to include HBV vaccine for all newborns. Over the next several years HBV immunization will be offered to infants and children who were born before July 1984, moving gradually upward in age until complete coverage has been reached.

In the United States, where each State Health Department develops its own policies, California has developed a programme which follows the above outline but aims at the known high risk of perinatal transmission among the large number of Asians residing there. HBsAg screening is undertaken for Asian women attending prenatal clinics and those found to be positive are tested for HBsAg and for HBeAg. Infants of all carrier mothers are given HBV vaccine. Additionally HBIG is given to those who are HBeAg positive.

In the Federal Republic of Germany, there is a nationally funded programme to screen all pregnant women and administer HBIG and HB vaccine to the infants of those found to be HBsAg positive. This country is also providing free HBV vaccine to all susceptible new persons entering the health care professions.

* * *

7. RECOMMENDATIONS

- Chronic infection with hepatitis B virus is common in developing countries. Such infection is a cause of hepatocellular carcinoma, one of the 10 most common cancers in the world. Hepatitis B vaccine is safe and effective in preventing infection. Its use early in infancy can reduce chronic carrier rates by over 75%.

- Hepatitis B immunization programmes should be considered in all population groups who have chronic carrier rates of hepatitis B virus of over 2%; they become a major public health priority for populations with carrier rates above 10%.

- In countries with chronic carrier rates of hepatitis B of over 2%, hepatitis B immunization should be introduced as an integral part of existing childhood immunization programmes as quickly as resources permit. Efforts to use this vaccine in ways which do not strengthen existing programmes should not be encouraged.

- The specific immunization schedule adopted in national programmes needs to be adapted to national circumstances, bearing in mind the usual age of hepatitis B infection and the delivery capacities of the health system. The objective is to prevent chronic carriage of hepatitis B virus. National immunization schedules should be formulated so that the use of hepatitis B vaccine minimizes extra contacts with the health system beyond those already needed for vaccines included within national childhood immunization programmes.

- A minimum of three doses of hepatitis B vaccine is recommended, given by the intramuscular route. The first dose is recommended at birth or as soon as possible thereafter. Early immunization is a special priority for those countries in which perinatal transmission is frequent. The second dose should be given 4-12 weeks after the first, timed to coincide with other routine childhood immunizations. The third dose may be given 2 to 12 months after the second, again timed to coincide with other routine childhood immunizations. At present, additional doses of vaccine are considered a low priority.

- While the use of hepatitis B immune globulin is effective in complementing the use of hepatitis B vaccine in preventing perinatal infection, its high cost and the need to administer it within hours of birth will preclude its use in most developing countries.

APPENDIX - A.

Definitions and abbreviations

HBV	Hepatitis B virus
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
Anti-HBs	Antibody to hepatitis B surface antigen
Anti-HBc	Antibody to hepatitis B core antigen without differentiation into immunoglobulin class
Anti-HBc IgG	Antibody to hepatitis B core antigen of the IgG class
Anti-HBc IgM	Antibody to hepatitis B core antigen of the IgM class
Anti-HBe	Antibody to hepatitis B e antigen
HCC	Hepatocellular carcinoma
HEPADNA	The unofficial designation for the group of viruses to which HBV belongs

APPENDIX - B.

RECOMMENDATIONS OF THE NOVEMBER 1987 HEPATITIS TECHNICAL ADVISORY GROUP

"HEPATITIS B VACCINES AND IMMUNIZATION STRATEGIES"

1. The TAG notes that over 30 million doses of plasma-derived HB vaccine have been distributed worldwide and that there are now more than 10 manufacturers of these vaccines globally. The vaccines have an impressive record of safety. In addition, several vaccines manufactured by rDNA technology are now on the market and additional manufacturers are expected to enter the market in the next two or three years. These rDNA vaccines are equivalent to plasma derived vaccines in respect to safety, immunogenicity and efficacy and neither offers any advantage over the other in these respects. Plasma-derived vaccines will continue to play an essential role in Hepatitis B control programmes worldwide for the foreseeable future.

2. There has been a dramatic decrease in the price of HBV vaccines to the level where many countries in Hepatitis B hyperendemic areas may now begin the development and implementation of large scale vaccination programmes. WHO should encourage their implementation and monitor their progress.

3. The TAG encourages the establishment of programmes and liaising with relevant groups within and without the Organization and encourages continued and increasing close collaboration between WHO and such bodies in the development and implementation of the global programme on HBV control.

4. The TAG emphatically reiterates that the most important means to control HB on a global scale and to reduce mortality due to chronic sequelae of this infection, including cirrhosis and HCC, is the large scale immunization of infants. It therefore recommends that HB vaccination be integrated into EPI as soon as possible. For incorporation into EPI, it is recommended that three doses of HBV vaccine will be given and that administration should be intramuscular into the thigh of infants. The first dose (HBV-1) should be given as soon as possible after birth. Although programmes should aim at administration of HBV-1 within the first week of life, it should be initiated at any time if it cannot be given so early. It is also desirable that HBV-1

be given simultaneously with the first EPI immunization.

The second dose (HBV-2) should be given 4 to 12 weeks after HBV-1, as it best fits into the EPI schedule of the particular Region.

A third dose (HBV-3) is currently needed to achieve high levels of antibody and prolonged protection. There is considerable latitude regarding timing of this dose. Countries can adopt schedules with 2 to 12 months following. HBV-2, at a time when it best fits into the EPI schedule of the particular Region.

HBIG may be of additional value in HB immunization programmes for infants, but cost of its inclusion into large scale immunization programmes precludes its use in most countries.

5. The TAG encourages operational research to define methods for an optimal integration of HB vaccination into EPI through the establishment of immunization projects in selected countries in hyperendemic areas of the world, and that WHO monitor the results of these projects. In particular the effectiveness of Hepatitis B vaccination in a variety of EPI settings and according to differing schedules of delivery of other EPI immunogens should be evaluated. Also thermal stability of HB vaccines should be further evaluated in order to adapt them to EPI cold chain characteristics.

Model immunization projects in Indonesia, Thailand and China are being established in collaboration with the International Task Force of Hepatitis B Immunization. These projects should be closely monitored and evaluated on an ongoing basis.

DIS 16a. 22

IMMUNOGENICITY OF SHANVAC-B (RECOMBINANT DNA HEPATITIS B VACCINE) IN INFANTS

Principal Investigators: Thomas Cherian
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Co-investigators: T. Sathish Kumar
Sukanya Raghuraman

Departments where study will be conducted:

Departments of Child Health and Clinical Virology, Christian Medical College & Hospital, Vellore.

Estimated duration of the study: 6 months

Objectives:

To determine the immunogenicity of Shanvac-B (Indigenously prepared recombinant DNA hepatitis B vaccine) in infants.

Summary of study design:

50 infants aged 6 weeks and older coming for the first dose of DPT vaccine will be recruited for the study after obtaining parental consent. Children will be given 3 doses of the vaccine (10-microgram dose)at 0, 1 and 3 months after obtaining a blood sample for hepatitis B markers. Vaccine will be given intramuscularly in the anterolateral thigh. The DPT vaccine will be administered on the opposite thigh. The children will be followed up for adverse reactions. A second blood sample will be collected 4 weeks after the third dose. The presence and titre of anti-HBs will be measured in the post-immunization sample. The seroprotection rate following 3 doses of the vaccine will be determined from the above data.

Present knowledge and relevant bibliography:

Hepatitis B virus (HBV) is a major cause of morbidity and mortality worldwide. It causes a wide spectrum of disease ranging from subclinical illness to fulminant hepatitis, cirrhosis and hepatocellular carcinoma. The hepatitis B carriage rate in India ranges from 3 to 5%, placing it the intermediate range of endemicity [1]. There are an estimated 40 million chronic HBV carriers in India [2]. Infection in children can occur either via vertical transmission from a carrier mother or via horizontal transmission during pre-school and early school years. Data from India suggests that there is a high rate of horizontal transmission of HBV infection among children in India. Unlike adults, children who are infected with HBV are at higher risk for chronic infection. Rates of chronic infection range from 90% in neonates to 30% in school going children.

In 1993, the WHO recommended that HBV vaccination should be introduced in the Expanded Programme on Immunization (EPI) of all countries with high endemicity by 1995 and in all remaining countries by 1997. One of the factors that have hindered the introduction of HBV vaccine in the EPI in India has been the high cost of the vaccine, which was imported from overseas. Recombinant HBV vaccine is now manufactured and licensed for use in India and is available at nearly half the cost of the imported vaccine. However, the immunogenicity of this vaccine in children has not been tested. This study aims to determine the immunogenicity of this vaccine, preliminary to the introduction of this vaccine in our immunization clinic.

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Detailed research plan:

Healthy infants, 6 weeks and older, attending the well baby clinic for the first dose of DPT vaccine will be recruited into the study after obtaining informed consent from the parents. All children will have a base-line physical examination. Anthropometric data such as weight, height and head circumference will be recorded at entry and at each re-visit.

The following will be excluded from the study:

1. Infants who have received hepatitis B vaccine or immune globulin at birth.
2. Infants who have received blood, blood products or immunoglobulin within the last six months or who are likely to receive them during the period of the study.
3. Infants born to HIV-infected mothers.
4. Infants with suspected or proven congenital immunodeficiency disorders
5. Infants on immune-suppressive therapy.
6. Infants who have participated in any other clinical trial 30 days before or during the period of this study
7. Infants with hypersensitivity to yeast; infants who experience hypersensitivity reaction after hepatitis B vaccine will not receive further doses of the vaccine.

The vaccine will be administered at a dose of 10 micrograms intramuscularly on the anterolateral thigh. DPT vaccine will be administered in the opposite thigh.

The second and third doses of the vaccine will be administered at 1-month intervals.

The parents will be given a card in which they will record adverse reactions such as fever, local pain and redness, irritability. The parents will also be asked to grade the reactions as mild, moderate and severe. To determine the systemic adverse reactions Over and above that caused by DPT vaccine, 50 children who receive DPT vaccine without concomitant hepatitis B vaccine will also be followed up for adverse reactions using the same Performa.

Blood will be collected by venipuncture before the first dose and 4 weeks after the third dose of the vaccine.

The pre-immunization blood will be tested for HBsAg, anti-HBc and anti-HBs.

Post-immunization blood will be tested for the presence and titre of anti-HBs.

Seroprotection will be defined as the presence of post-immunization anti-HBs titre > 10 mIU/ml.

The seroprotection rate and the geometric mean titres of anti-HBs following vaccination will be determined

Budget:

HBsAg, anti-HBs (X2) and anti-HBc test for 60 infants:	Rs. 61,800.00
Disposables (Gloves, needles, and syringes):	Rs. 1500.00
Travel allowance for study patients (for 3rd visit)	Rs. 3000.00
Stationery, Xeroxing of study forms etc.	Rs 1000.00
Data entry and analysis	Rs. 1000.00
Communications (fax, telephone etc.)	Rs. 1000.00
TOTAL	**Rs 69300.00**
10% institutional overhead	Rs 6930.00
GRAND TOTAL	**Rs 76230.00**

All the vaccine doses and funds for the study will be supplied by Shanta Biotechnics Pvt. Ltd., Hyderabad

DIS 16a-13.

HB Vac

Product Monograph

Cadila healthcare

THE ZYDUS GROUP

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1

ABOUT THE DISEASE

1.1

Hepatitis B Infection

- Hepatits B is a worldwide disease caused by the Hepatitis B Virus (HBV).
- It is a highly infectious viral infection of the liver characterised by acute hepatitis which may progress to chronic liver disease, liver cirrhosis or even liver cancer.
- Acute and chronic HBV infection are important public health problems and the disease is responsible for much morbidity, mortality, economic loss and human suffering.

1.2

Magnitude of problem

- It is estimated that more than 2000 million people have been or are affected worldwide with Hepatitis B virus.[1]
- As a result of these infections, about 350 million people worldwide are chronically infected carriers of Hepatitis B Virus (HBV) who are not only at increased risk of dying from the long term consequences of HBV infection but also act as a source of infection in the community.[1]
- It is further estimated that roughly 2 million people worldwide die each year from the consequences of Hepatitis B infection.[2]

1.3

Epidemiology of HBV infection

- The prevalence of HBV varies around the globe from 4% in countries with low endemicity to 95% in countries with high endemicity.[3]

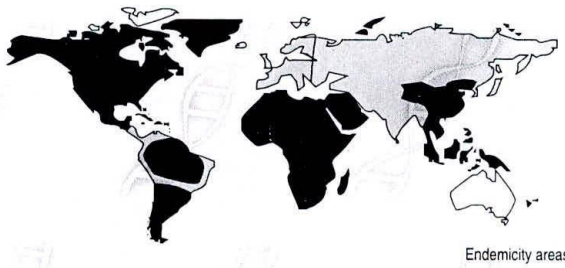


Fig. 1 : World Map of HBV endemicity

1.4

Hepatitis B : The Indian Scenario

- India comes under the "intermediate" endemicity (2-7%) zone as the mean national surface antigen carrier rate is around 4.7%.[4]
- Assuming the population of India to be around 900 million, there are an estimated 42.5 million carriers in the country.[4]
- HBV infection in select high risk group in India ranges between 12-74%.[4]
- Surface antigen positivity in children below 15 years has ranged from 1.3 - 12.7% in various studies and is not different from the adult population. Even in this age group, a large amount (27.4%) of children were infected when under 5 years of age.[4]
- 1-9% of pregnant women (weighted average 2.8%) are positive for surface antigen in various studies in India, with a very high transmission rate to the newborn.[4]

1.5

More about Hepatitis B infection

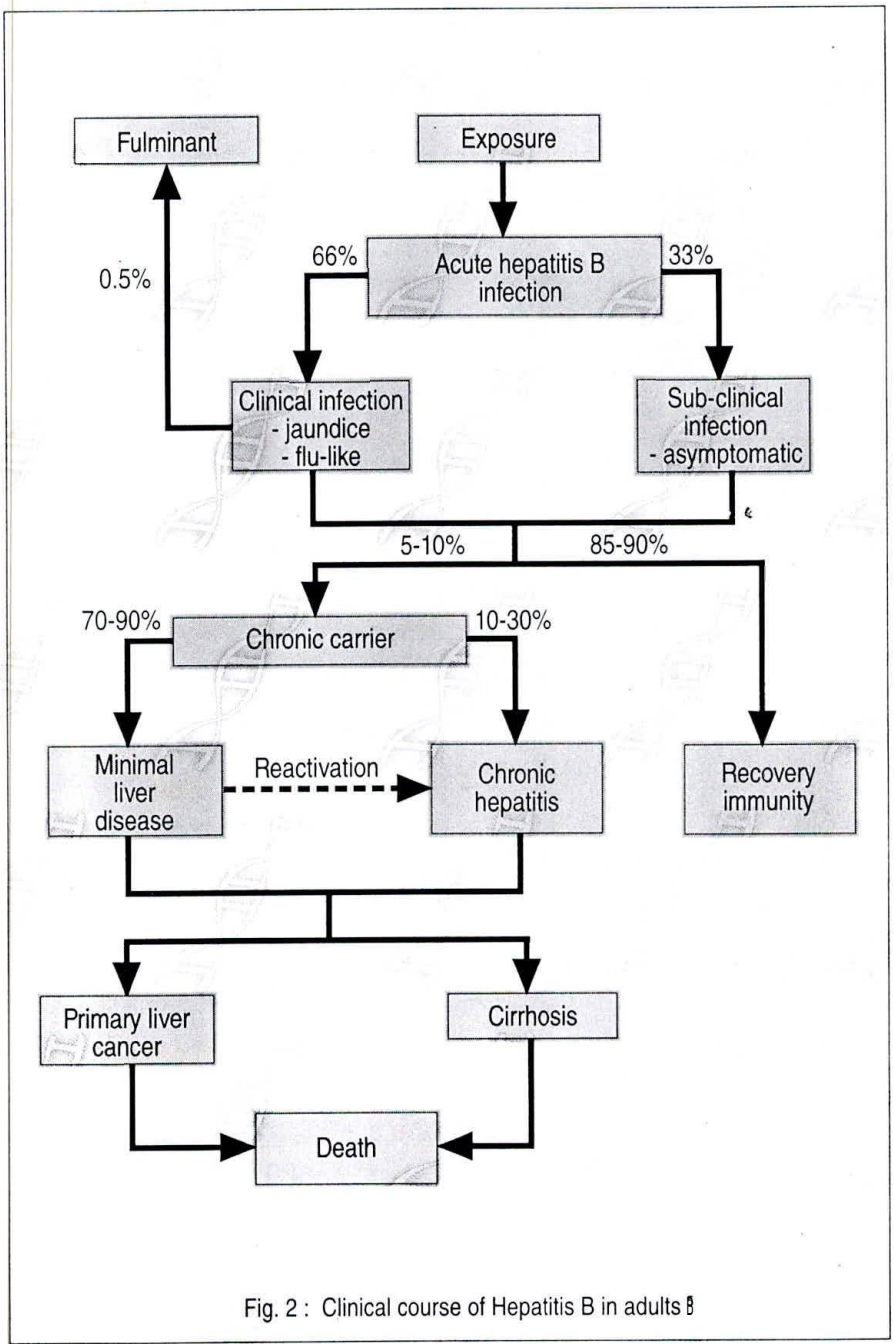


Fig. 2 : Clinical course of Hepatitis B in adults [8]

1.6

Startling statistics of HBV infection

- As many as 90% of children infected with HBV become chronic carriers compared to about 5% of adults infected with HBV.[4]
- Only about 1% of chronic carriers clear their infection each year.
- Carriers are more likely to have had an asymptomatic rather than a symptomatic form of hepatitis B.
- Males have a higher chronic carrier rate than females.
- There is a 40% lifetime risk of development of hepatocellular carcinoma and cirrhosis of the liver in patients who are chronic HBV carriers.
- Carriers have a 230 times greater risk of developing hepatocellular carcinoma than the general population.[6]
- 80% of all liver cancers are due to hepatitis B, which is second only to tobacco as a worldwide carcinogen.

1.7

Transmission of HBV

- Man is the only reservoir of HBV infection.
- HBV is highly infectious - infact it is estimated to be 100 times more infectious than the AIDS virus (HIV).[7]
- The virus is secreted in virtually all secretions and excretions of the body in chronic HBV carriers.
- The three major recognised routes of HBV transmission include the following :
  - Parenteral or percutaneous-usually by infected blood or blood products, contaminated syringes or needles, contaminated surgical instruments, tattooing, ear or nose piercing, shared razors & tooth brushes, acupuncture etc.
  - Perinatal - from infected mother to the newborn (vertical transmission). This also usually occurs at the time of birth rather than during pregnancy.
  - Sexual - especially homosexuals. Heterosexuals with multiple partners are also prone to contracting the disease.

1.8

High risk groups

The following subjects constitute high risk groups of acquiring hepatitis B infection:

- Healthcare personnel : Physicians & surgeons, dentists, nurses, staff in hemodialysis & hematology units, laboratory personnel handling blood & other clinical specimens, blood bank workers, emergency & first aid workers.
- Patients requring repeated blood transfusions e.g. hemodialysis & oncology patients, patients with thalessemia & hemophilia.
- Sexually promiscuous persons, homosexuals & prostitutes.
- Intravenous drug users.
- Household contacts of any of the above groups & of patients with acute or chronic hepatitis B.
- All young children & neonates especially those born to HBsAg positive mothers.
- Police, Fire Brigade & Armed Forces personnel.

2

ABOUT THE PATHOGEN

2.1

Hepatitis B virus

- Hepatitis B virus is a DNA virus whose only host is man.
- The infectious part of the virus is its nucleus, which is surrounded by a complex structure (the nucleocapsid) containing several proteins.

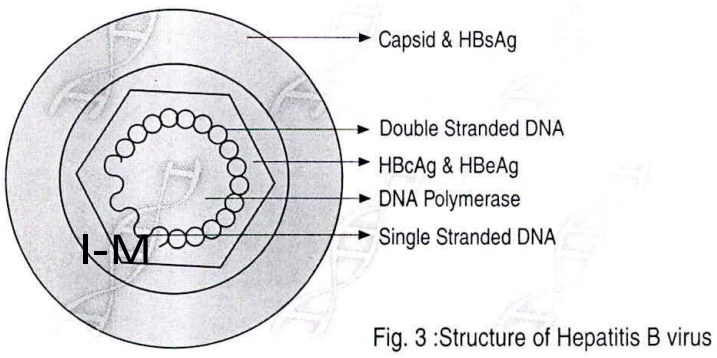


Fig. 3 :Structure of Hepatitis B virus

2.2

Antigenic components of HBV

- The HBV has three antigens, namely, a surface antigen derived from the nucleocapsid (HBsAg) and two antigens from the viral core (HBcAg and HBeAg).
- Vast quantities of HBsAg are produced within the liver cell infected with HBV. Only a small proportion becomes incorporated into the daughter viruses and the rest reaches the blood, where it forms characteristic filaments & spheres.
- HBeAg is a subunit of HBcAg and unlike its parent, has the virtue of being detectable in plasma. Its positivity is considered as a sign of active viral replication & high infectivity.
- All the 3 antigens raise antibodies which are called anti-HBs, anti-HBe and anti-HBc respectively.

2.3

Serological markers of acute HBV infection

In HBV infected people who subsequently clear the virus from their system (Fig. 4), titres of HBsAg & HBeAg rise to a maximum & then fall, followed by a rise in the three antibodies, first anti-HBc, then anti-HBe and finally anti-HBs which confers immunity.

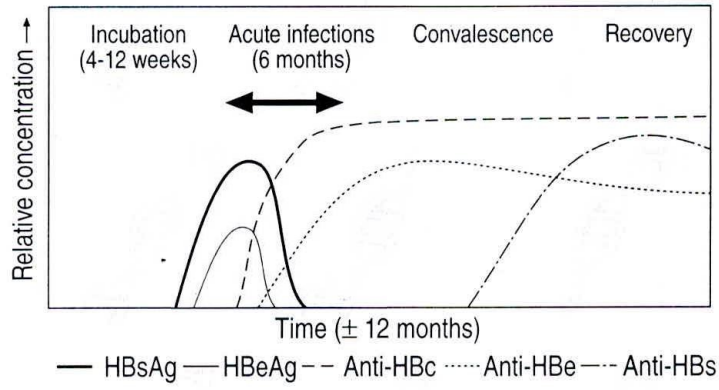


Fig. 4 : Serological markers of acute hepatits B infection leading to immunity

Immunity to HBV is indicated by adequate levels of anti-HBs (>10 mIU/mL) while failure to clear HBsAg and develop anti-HBs is a clear sign that the individual has become a chronic carrier.

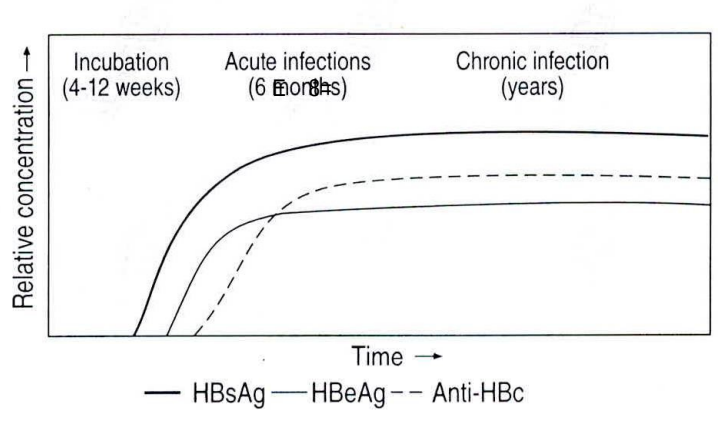


Fig. 5 : Serological markers of acute hepatits B infection leading to chronic carrier state

2.4

Commonly encountered serological patterns of HBV infection

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Actute HBV infection, high infectivity
+	–	IgG	+	–	Chronic HBV infection, high infectivity
+	–	IgG	–	+	Late-acute or chronic HBV infection, low infectivity
+	+	+	+/–	+/–	1. HBsAg of one subtype and heterotypic anti-HBs (common) 2. Process of seroconversion from HBsAg to anti-HBs (rare)
–	–	IgM	+/–	+/–	1. Acute HBV infection 2. Anti-HBc window
–	–	IgG	–	+/–	1. Low-level HBsAG carrier 2. Remote past infection
–	+	IgG	–	+/–	Recovery from HBV infection
–	+	–	–	–	1. Immunization with HBsAg (after vaccination) 2. Remote past infection (?) 3. False-positive

Table 1 : Commonly Encountered Serologic Patterns of Hepatitis B Infection

3

ABOUT THE SOLUTION

3.1

Search for a solution

- There is no assured & successful treatment of Hepatitis B infection. Antiviral drugs and interferon are not effective in more than 40% of cases with chronic HBV infection.
- Mass vaccination is probably the most effective & most practical means of reducing the burden of HBV infection in the community.

3.2

Historical perspectives of HBV prophylaxis

a. The pre - 1982 era

- Until 1982, prevention of Hepatitis B was based on "passive" immunoprophylaxis either with standard immunoglobulin (IG) containing modest levels of anti-HBs or specific Hepatitis B immunoglobulin (HBIG), containing high titre anti-HBs.[8]
- The efficacy of standard IG has never been established and remains questionable; even the efficacy of HBIG has been challenged and its contribution appears to be in reducing the frequency of clinical illness, not in preventing infection.[8]

b. The post - 1982 era : Plasma derived vaccines

- The first vaccine for active immunisation, introduced in 1982, was prepared from purified, non-infectious 22-nm spherical forms of HBsAg derived from the plasma of healthy HBsAg carriers.[8]
- Such plasma derived vaccines were found to be very effective but had the following limitations :
  - Since the vaccine is derived from the plasma of chronic carriers, the limited numbers of potential blood donors to provide the said plasma could lead to scarcity of the vaccine.
  - Widespread fear that the vaccine may contain some other infectious agents like AIDS virus or some other unknown pathogens, despite using sophisticated purification and inactivation techniques.
  - Production of batches of variable potency since the vaccine is derived from pooled blood from different chronic carriers.

c. The post - 1987 era : Recombinant vaccines

- In 1987, the plasma derived vaccine was supplanted by a genetically engineered vaccine derived from recombinant yeast.[8]
- Such vaccines overcome the drawbacks of the plasma-derived vaccines :
  - Since no blood is used in the preparation of this vaccine, there is practically no risk of transmission of blood-borne diseases.
  - Since each batch is produced from the yeast source, consistency from one batch to another batch is ensured.
  - There are no supply problems with the yeast cells required for the production of the vaccine.

3.3

More about recombinant DNA vaccines

- The basic principles of the production of recombinant DNA vaccines involve the following steps :
  - Firstly, the viral DNA segment containing the gene coding for the surface antigen (HBsAg) is identified and isolated.
  - This isolated HBsAg gene is then fused to a yeast expression control sequence and then built into a plasmid E. coli.
  - The final plasmid is introduced into the yeast DNA thus enabling the transformed yeast cell to produce HBsAg - this HBsAg produced is indistinguishable from natural HBsAg particles.
  - The large quantities of HBsAg are then recovered and purified. This is then processed further to produce the Hepatitis B Vaccines.
- Bacteria which are commonly used hosts in recombinant DNA technology are unsuccessful hosts for HBsAg. On the other hand, yeast cells have been found to be suitable hosts for HBsAg expression.
- Yeast cells used commercially for HBsAg production are either Saccharomyces cerevesiae or Hansenula polymorpha.

4

ABOUT HB Vac

4.1

HB Vac : Production[9]

HB Vac is a highly purified recombinant DNA Hepatitis B Vaccine developed by Korea Green Cross Corporation, KGCC.

Steps used in the production of HB Vac are briefly summarised as follows :

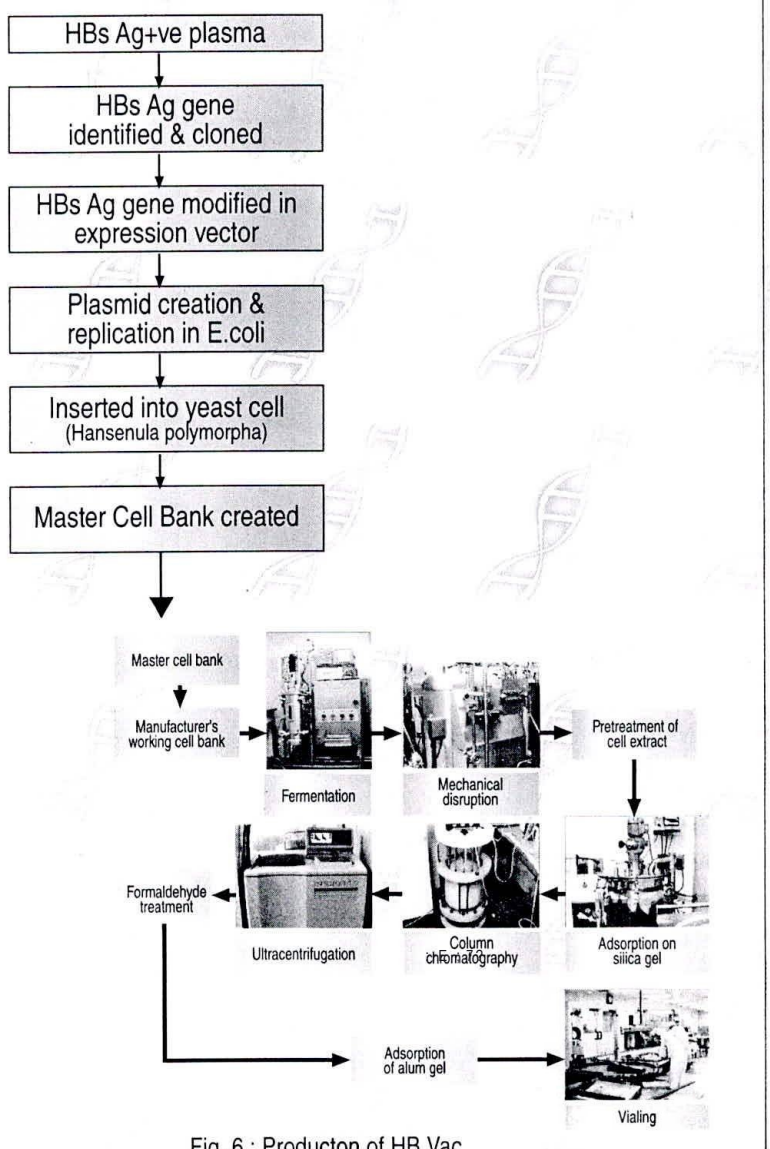


Fig. 6 : Producton of HB Vac

4.2

HB Vac : The host yeast cell[9]

- The host yeast cell used in the final step for HBsAg expression in HB Vac is Hansenula polymorpha as compared to the conventional Saccharomyces cerevesiae.
- The advantages of using H polymorpha as the host cell include the following :
  - higher production
  - higher stability
  - lesser hyperglycosylation & hence better immunogenicity
  - high activity
- The comparisons between the two different host yeast cell are briefly tabulated below :

	KGCC expression system	Saccharomyces origin
Host strain	Hansenula polymorpha	Saccharomyces cerevisiae
Safety of strain	Generally recognised as safe	Generally recognised as safe
Promoter	FMD	PGK,Alpha-factor etc.
Control of promoter	Strong and easy	Somewhat difficult
Endotoxin	No	No
Integration mode	Integrated into chromosomal DNA	Not integrated
Stability of plasmid	High mitiotic stability (800 generation)	Low (Below 100 generation)
Glycosylation mode	No over glycosylation	Over glycosylation (High mannose chain)
Productivity	High (500mgHBsAg/L)	Low (100mg HBsAg/L)
Media cost	Cheap and Low	Higher than that of Hansenula
Process control	Easy to handle and control	Somewhat difficult
Scale up	Easy	Somewhat difficult
Investment	Low	High

Table 2 : Characteristics of KGCC Expression system

3

Stability@

- HB Vac is highly stable.
- It has to be stored at +2 to +8°C and the vaccine does not have to be frozen.

5

CLINICAL RESULTS With HB Vac

5.1

An efficacious vaccine

- The efficacy of HB Vac has been demonstrated in several clinical trials conducted in Europe and South-East Asian countries including India.
- The results with HB Vac have been found to be comparable or better than those with plasma derived vaccines or other yeast derived recombinant DNA vaccines presently available.

5.2

Indices to judge efficacy

The efficacy of Hepatits B vaccine is judged on the following indices :

- **Immunogenic efficacy or immunogenicity of the vaccine :**

  It is the titre of the anti-HBs antibodies produced in the individual after vaccination and is expressed as Geometric Mean Titre (GMT) in units of mIU/mL.

- **Seroconversion :**

  It is defined as the percentage of individuals who mount an anti-HBs antibody titre of $\geq$ 1 mIU/mL after vaccination.

- **Seroprotection :**

  It is defined as the percentage of individuals who mount an anti-HBs antibody titre of $\geq$ 10 mIU/mL after vaccination.

- **Protective efficacy :**

  It refers to the prevention of both acute symptomatic illness and carriage of HBsAg in the blood after vaccination.

5.3

International experience in healthy adults[9]

(a) South Korean Study :

A 20 mcg dose of HB Vac was administered intramuscularly at 0, 1 and 6 months in the deltoid region in 118 seronegative healthy Korean adults. The anti-HBs titres were determined one month after administration of the third dose of vaccine by radioimmunoassay.

Results :

	Seroconversion Rate (%)	GMT (mIU/ml)
Male	93.9 (31/33)	91.6 ± 3.9
Female	98.3 (59/60)	200.6 ± 2.6
Total	96.8 (90/93)	153.1 ± 1.8

- Of the 93 subjects who completed the study, the seroconversion rate was 96.8% (90 out of 93) with seroprotective rate of 95.7% (89 out of 93).
- Average geometric mean titres (GMT) of the anti-HBs response was 153.1 mIU/mL in seroconverters.
- Females showed a higher anti-HBs response than males.
- An age dependent effect was also observed in the anti-HBs response with the younger adults having a higher immunogenic response.

(b) U K Study :

20 healthy male & female volunteers were administered a single 20 mcg infection of H B Vac at 0, 1 and 6 months. Immunogenicity was assessed by estimating the anti-HBs titres 1 month after the last dose of vaccination.

Results :

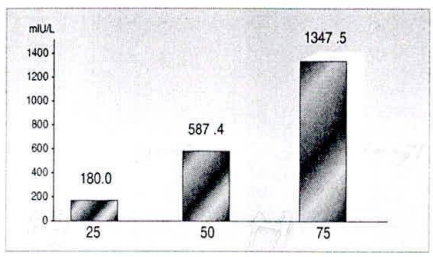
- 100% (all 20) of the volunteers had seroprotective anti-HBS levels at 1 month after the completion of vaccination.
- The Geometric Mean Titres of anti-HBS were more than 100 mIU/mL in 95% of the subjects (19 out of 20).

5.4

Indian experience in healthy adults[10]

27 healthy adults received HB Vac at 0, 1, 2 months and anti-HBs was estimated 1 month after the last dose.

Results :



✶ 100% of the volunteers had anti-HBs titres above the seroprotective levels. In fact, the mean GMT levels in the study was 503.5 mIU/mL (range 46.2 - 3204.3 mIU/mL).

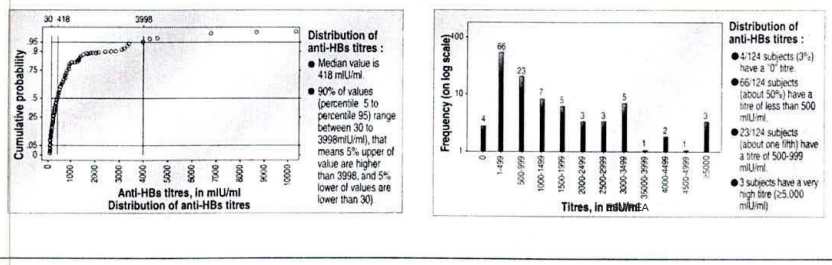
5.5

International experience in infants & children[9]

(a) Vietnamese study :

124 healthy infants were administered 3 injections of 10 mcg of HB Vac at 0, 1 and 2 months with the anti-HBs estimation 1 month after the last dose.

Results :



✶ The seroconversion rate was 97% with a Geometric Mean Titre of anti-HBs 446.5 mIU/mL.

(b) Turkish study :

In this study, the immunogenic effects of half dose HB Vac (5 mcg) given at 0, 1, 4 and 7 months were compared to that of full dose HB Vac (10 mcg) given conventionally at 0, 1, and 6 months in 22 children (age 2 - 14 years).

The immunogenic response was judged by estimating the anti-HBs titres at 7 months & 8 months in all children.

Results :

✷ *Seroconversion rates after HB Vac vaccination (Anti-HBs mIU/mL)*

	Full dose group						Half dose group							
Gender (n)	After the 1st dose		After the 2nd dose		After the 3rd dose		After the 1st dose		After the 2nd dose		After the 3rd dose		After the 4th dose	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Girls (5)	2	40	4	80	5	100	1	20	4	80	5	100	5	100
Boys (6)	5	83.3	6	100	6	100	2	33.3	6	100	6	100	6	100
Total(11)	7	60.3	10	90.9	11	100	3	27.2	10	90.9	11	100	11	100

✷ At 7 months, there was a 100% seroconversion in both groups and anti-HBs levels were greater than 10 mIU/mL in all children.

✷ However, children receiving a low dose 4 shot schedule had higher Geometric Mean Titres of anti-HBs than those given the full dose vaccine conventionally.

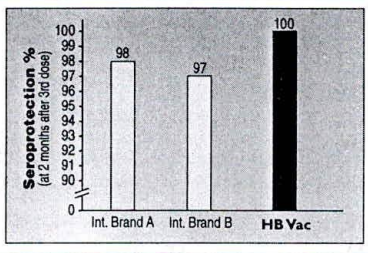
5.6

Comparative trials of three different Hepatits B vaccines in children[9]

(a) University School of Medicine Pediatry and Microbiology Clinics, Turkey.

A total of 398 preschool anti-HBC negative children (195 boys and 203 girls) were divided into three groups. Three doses of 10 mcg each of Intenational Brand A, International Brand B and HB Vac were administered at 0, 1 and 6 months to the first, second and third groups respectively.

Results :

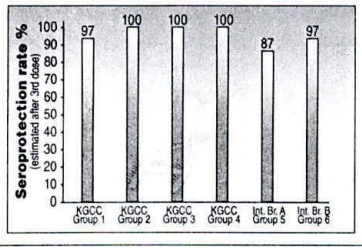


✶ Two months after the third dose, the anti-HBs levels were determined in each child and seroprotection rates of International Brand A, International Brand B and HB Vac were 98%, 97% and 100% respectively.

(b) Cerrahpeps Medical Faculty, Istanbul, Turkey

A total of 204 term newborn (5-25 days of age) were randomly distributed into six groups, Group 1 HB Vac (KGCC) 10 mcg at 0, 1, 2, 12 months (n:36); Group 2 HB Vac (KGCC) 20 mcg at 0,1,6 months (n:29); Group 3 HB Vac (KGCC) 20ug at 0,1,2,12 months (n:31); Group 4 HB Vac (KGCC) 10 mcg at 0,1,6 months (n:32); Group 5 International Brand A 20 mcg at 0,1,2,12 months (n:32) and Group 6 International Brand B 10 mcg at 0,1,6 months (n:44). Serum samples were drawn for determination of anti-HBs titers, one month after each vaccination.

Results :



✶ The seroprotection rates observed with KGCC vaccines i.e. HB Vac were superior to that seen with other international brands.

5.7

Safety[9]

- While having excellent efficacy on one hand, HB Vac also is very well tolerated in adults as well as in children and neonates.
- The common adverse effects reported include :
  - Local - Pain, erythema and local tenderness
  - Systemic - Myalgia, fatigue, dizziness & arthralgia

  Rarer reported side effects include fever, headache, anorexia, skin rash, nausea & vomitting, diarrhoea & extreme crying in children.
- The adverse reactions reported are usually transient in nature and mild in severity. In none of the patients, the administration of the vaccine had to be discontinued on account of adverse events.[6,8]

6

HB Vac : INDICATIONS & ADMINISTRATION PROCEDURES

6.1

HB Vac : Composition

Each 1 ml of HB Vac contains :

Purified HBsAg	20 mcg
Aluminium hydroxide gel	0.5 mg
Thiomersal	0.01 w/v %
PBS	q.s

6.2

HB Vac : Formulations

HB Vac is marketed as :

- Monodose vial of 0.5 ml (10 mcg of HBsAg)
- Monodose vial of 1.0 ml (20 mcg of HBsAg)
- Multidose vial of 10.0 ml (200 mcg of HBsAg)

6.3

Aims of Vaccination

The aim of vaccination is to reduce both the overall incidence of acute hepatitis B infection and also the chronic complications associated with it such as chronic active hepatitis and cirrhosis.

6.4

Indications

HB Vac is presently indicated for individuals in high-risk groups who are at an increased risk to acquire hepatitis B infection. *(see page no. 10, Section 1.8)*

The Indian Academy of Paediatrics strongly recommends that hepatitis B vaccination be made a part of Essential Programme of Immunisation and that all children should be vaccinated for this highly lethal disease.

6.5

Dosage schedule

The primary vaccination consists of three doses of vaccine administered intramuscularly.

1st dose : At elected date
2nd dose : 1 month later
3rd dose : 6 months from the first dose

Group	Formulation	Initial Dosage	1 Month	6 Months
Neonates	10 mcg/0.5 ml	0.5 ml	0.5 ml	0.5 ml
<10 yrs	10 mcg/0.5 ml	0.5 ml	0.5 ml	0.5 ml
>10 yrs	20 mcg/1.0 ml	1.0 ml	1.0 ml	1.0 ml

6.6

Duration of protection

- The primary course of vaccination provides protection for several years.
- A booster dose would generally be required every 5 years after the primary course of vaccination.

6.7

Route of administration

HB Vac is usually administered intramuscularly in the deltoid muscles. However, in children & neonates, because of the small size of the deltoid muscles, the anterolateral muscles of the thigh are preferred. The vaccinne should not be administered in the gluteal muscles or given subcutaneously or intradermally because of low immunogenicity. It should not be administered intravenously.

6.8

Special patient groups

- The Indian Academy of Paediatrics recommends that all neonates be administered Hepatitis B Vaccine and that the primary vaccination can start at birth or immediately thereafter.
- In immunocompromised patients e.g. patients with chronic renal failure or in patients on hemodialysis or in patients on immunosuppressive therapy, a

double-dose (40 mcg) of the vaccine is recommended. Such patients may either be given primary vaccination as per the coventional schedule i.e. 0, 1 and 6 months or a 4-dose schedule be given i.e. 0, 1, 2 and 6 months so as to develop adequate antibody response.

- The safety of HB Vac in pregnancy is not fully established. It should be used in high risk situations only if the benefits outweigh the risks.

6.9

Contra-indications

- HB Vac is contra-indicated in patients with hypersensitivity to any component of the vaccine. It should also be avoided in patients with severe febrile infections.

6.10

Precautions & Warnings

- Because of the long incubation period of hepatitis B, it is possible for unrecognised infection to be present at the time of vaccination. HB Vac may not prevent hepatitis B in such cases.
- HB Vac does not prevent infection caused by other viruses such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.
- If being co-administered with hepatitis B immunoglobulin (HBIG) or with any of the other childhood vaccines, HB Vac should not be mixed with any of the above in the same syringe & should be administered at different sites or at the same site at least 3 cms. apart.

6.11

Presentation

As a single dose vial of vaccine : 20 mcg / 1ml vial • 10 mcg / 0.5ml vial

As a multi-dose vial of vaccine : 200 mcg/ / 10 ml vial

STORE AT 2°C-8°C. DO NOT FREEZE.

7

QUESTIONS & ANSWERS

Q.1 How can Hepatitis B be prevented ?

Ans. Hepatitis B can be prevented by either of the following :

- Passive immunisation by Hepatitis B immunoglobulin (HBIG)
- Active immunisation by Hepatitis B vaccines : Plasma derived or Genetically engineered

Passive immunisation is useful for post-exposure prophylaxis (to be administered within 48 hours of exposure), but the duration of protection offered is very short-lived, about 3 months. Only active immunisation provides efficient long-term protection against Hepatitis B.

Q.2 Will a HBsAg +ve individual also benefit from HB Vac ?

Ans No. Individuals positive for HBsAg are chronic carriers and no benefits will accrue in administering HB Vac to such persons.

Q.3 What about vaccinating an individual who is anti-HBs +ve ?

Ans. An individual with anti-HBsAg is protected against Hepatitis B since there are already protective antibodies against HBsAg circulating in the blood. Such individuals again do not routinely require need HB Vac.

Q.4 Do Hepatitis B immunoglobulins (HBIG) interfere with the response of HB Vac if they are co-administered e.g. in patients who have been recently exposed to HBsAg +ve blood ?

Ans. Hepatitis B immunoglobulins (HBIG) do not interfere with the immune response to HB Vac. The only precaution needed in such a setting is that the two should not be mixed in one syringe or administered at the same site. If a same site is chosen, then the two should be administered at a minimum distance of 3 cms. apart.

Q.5 Do patients receiving HB Vac routinely require anti-HBS titre estimation post vaccination ?

Ans. HB Vac is a highly efficacious vaccine providing seroprotection in more than 97-99% of patients. Hence, routine anti-HBs titre estimation is not advocated in every patient receiving HB Vac. However, if done, it would definitely help in identifying patients who have either not responded or responded weakly to the vaccine.

Q.6 What should be done in such patients who either do not respond or respond weakly to HB Vac ?

Ans. The number of such patients is likely to be very small, as confirmed from several trials. Even such patients are likely to respond to either additional doses of HB Vac or to higher doses of the vaccine.

Q. 7 Can HB Vac be given concomitantly with other paediatric vaccines ?

Ans. There are no reported contra-indications of concomitant administration of HB Vac with any of the essential paediatric vaccines namely BCG, OPV & DPT. The only precaution needed in such a situation is that HB Vac should not be mixed with the other vaccines in the same syringe or administered at the same site. Live measles vaccine can interfere with the immune response to HB Vac but this is not likely to be a clinical problem since measles vaccine is usually administered after 9 months of age and by this time, the infant would have already completed the 3 dose primary vaccination with HB Vac if it was started at birth or shortly thereafter.

Q.8 Is HB Vac contra-indicated in pregnant and lactating mothers ?

Ans. Vaccination during pregrency is generally not recommended and the decision to administer HB Vac in pregnant mothers is based on the relative benefit to risk ratio. As per the limited published data, there is no evidence of teratogenicity or of an increased incidence of miscarriage in women vaccinated during pregnancy. There is absolutely no reason why the vaccine cannot be given during lactation.

Q.9 Can HB Vac be given to immunocompromised patients or individuals on steroids or immunosuppressive therapy ?

Ans. HB Vac can be safely administered to such individuals. It is only the live vaccines that are contra-indicated in such patients. However, the response to the conventional dose and administration schedule may be sub-optimal in such patients and they may require a higher dose or additional dose of HB Vac so as to attain a satisfactory immune response.

Q.10 What are the factors associated with failure to HB Vac ?

Ans. Vaccine failure is often not due to the vaccine, but due to faulty storage, wrong site or technique of administration, advanced age or obesity. Responsiveness is also poor in immunocompromised persons such as those on hemodialysis or on immunosuppresive medication like steroids etc.

8

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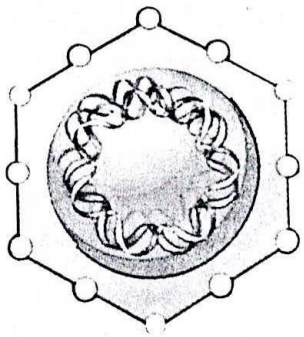
Notes

HEPATITIS B

YOUR QUESTIONS ANSWERED

(Publication of Mumbai Branch of IAP)



Proceedings of the Dialogue Session on Hepatitis B held on 5th October, 1997 at Mumbai during the Annual Conference of Mumbai Branch of IAP

Editors :

Dr.Nitin Shah
Dr.Sandeep Bavdekar

Supported by an educational grant from:

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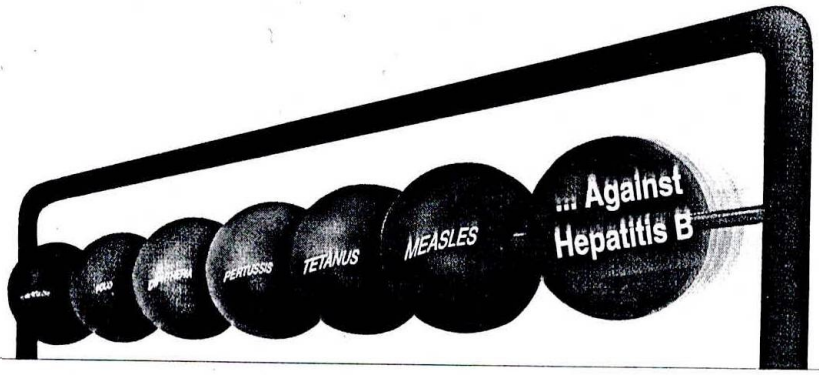

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For more information about Hepatitis B and its prevention, please write to Hepatitis B Awareness Centre, P. B. No. 2, Bangalore 560 049

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1. What is the magnitude of problem of hepatitis B world over ?

Hepatitis B is one of the commonest viral infections afflicting the mankind. It is hyperendemic in many countries of Asia, Africa and Oceania, with the prevalence of current and past infection ranging from 30 to 100%. Worldwide there are over 370 million carriers of surface antigen of hepatitis B virus (HBsAg). More than 10% of the population in some areas may suffer from chronic liver disease due to hepatitis B.

2. How do you classify the severity of problem of Hepatitis B ?

The prevalence of Hepatitis B is classified on the basis of carrier rate of surface antigen of Hepatitis B (HBsAg) in the population. Countries with carrier rate between 0.2 and 2% are classified as low prevalence countries while those with carrier rate between 2% and 7% are designated as countries with intermediate prevalence rate. High prevalence rate countries are those that have carrier rate frequency in excess of 7%.

3. What is the status of prevalence in different countries around the world ?

Australia, North America and countries in Northern Europe have low prevalence rates. Countries of West and South Asia, South America, Eastern Europe and those in the Mediterranean belt have intermediate prevalence. China, countries of tropical Africa and Pacific region and the South-East Asian countries have carrier rates ranging from 7% to 20%. Hence, they are included in the group of countries with high prevalence rates.

4. Which zone does India belong to ?

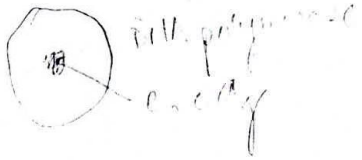
India belongs to the group of countries with intermediate prevalence rates. The average carrier rate in India is estimated to be 3.8% to 4.2%

5. What is the status of mixed infections in India ?

Some patients have mixed infections of HBV, HAV and HCV. Of particular importance is the combination of HBV and HCV. This combination is seen more commonly in young patients and carries high propensity for chronicity. In India, 20-30% of patients with chronic liver disease have mixed infections.

6. What type of virus is Hepatitis B virus (HBV) ?

HBV is a DNA virus belonging to the family Hepadnaviridae. The virion of hepatitis B (Dane particle) consists of surface and core. The core contains DNA polymerase, core antigen and e antigen. The DNA structure of the virus is double-stranded and circular. The double stranded DNA genome of HBV has been cloned and sequenced.



7. What are HBV mutants ?

Following HBV mutants are known to occur :

Mutant form	Mutation	Biological significance
Pre-core	Single or multiple mutations in the pre-C region, at codon 28 or 29; preventing synthesis of HBe	Commonest mutation. Association with severe disease and fulminant hepatitis
Core	Clustering mutations in core gene often associated with pre-core mutations	Progressive liver disease
Envelope vaccine escape mutant	Does not synthesize HBsAg, HBV DNA positive	Responsible for vaccine failure, sometimes associated with chronic liver disease
X-gene	Mutations in X-gene	Not known
Pre-S gene	Mutation in Pre-S region	Not known

Incidence of mutants in India varies from 5-14% of total HBV infections.

8. How do mutants matter ?

i) Some mutants can escape recognition by routine HBV serology.

ii) HBV serology being negative, these persons may be accepted as blood donors and hence transmission of infection can occur.

iii) Vaccination may not be able to offer protection against some of the mutants.

iv) Some mutants do not have HBeAg and hence do not induce formation of anti-HBe antibodies. The virus replication continues inspite of HBeAg being negative leading to a false sense of security.

9. What are the reservoirs of HBV ?

In nature HBV infects only humans, and infected humans are the only known reservoir of virus for new human infections. Although some higher primates other than humans may be infected, there is no evidence that they are important source of human infections.

10. What are the known modes of transmission of HBV infection ?

Vertical transmission : From pregnant mother to her fetus and baby during the perinatal period.

Parenteral transmission : Transmission through blood and blood products is the major contributor for parenteral transmission. Needle-stick injuries, unsterile needles, tattooing, ear-piercing and acupuncture can also transmit infection.

Sexual transmission : It is a major mode of transmission in developed countries. It is mainly seen among male homo-sexual individuals and those with promiscuous heterosexual behaviour. Transmission can also occur during artificial insemination.

Horizontal transmission : Virus transmission is known to occur unrelated to sexual, vertical and parenteral modes transmission. This transmission is probably due to close contact. In fifty percent of cases no definite history of contact can be elicited.

Fifty percent of the carrier pool is contributed by vertical transmission; while other modes of transmission (especially horizontal transmission) account for the rest.

11. Which categories of individuals are most susceptible to HBV infection ?

The following individuals are at high-risk to suffer from HBV infection :

- Infants born to HBsAg-positive mothers
- Homosexual men
- Heterosexuals individuals with multiple sex partners or with sexual transmitted diseases
- Parenteral drug users who share needles
- Patients on hemo-dialysis therapy
- Health care individuals coming in contact with blood and secretions
- Patients receiving blood or blood products, especially on multiple occasions
- Household contacts of HBsAg positive individuals
- Sexual partners of persons with acute HBV infection/carriers
- Inmates of institution for developmentally disabled children
- Prison inmates and staff

12. When does vertical transmission of HBV occur ?

Vertical transmission is because of contact between secretions of mother and the baby. This most commonly occurs in late perinatal period or at the time of delivery. It is known to occur via breastfeeding and handling by mother in the postnatal period. The latter can be prevented by timely vaccination in the neonatal period.

13. What is the efficacy of vertical transmission and what does it depend on ?

The overall efficacy of vertical transmission is 30-40%. This increases to 70-90% if mother is also HBeAg positive, but drops to less than 30% if she has anti-HBe antibodies. In India, about 10% of carrier mothers are also HBeAg positive.

14. What happens to newborns infected through vertical transmission ?

Newborns infected through vertical transmission usually do not develop acute symptoms but have a high risk of developing chronic carrier state. Approximately 90% of newborns infected at birth become chronic carriers and over 25% of these will die of cirrhosis or hepatocellular carcinoma in later life. Thus perinatally acquired infection has serious consequences for the infant.

15. What about HBV transmission following needle-stick injury ?

Accidental needle-stick injury carries a comparatively high risk of transmission due to high amounts of virions in the blood. Even 0.00001 ml of blood is infectious. The efficacy of transmission is 3-20 %.

16. What should one do after needle-stick injury to avoid infection with HBV ?

i) Wash hands thoroughly with copious amounts of soap and water.

ii) Administer HBIG which will protect against HBV. Simultaneously start vaccination against HBV.

17. What should you do following accidental administration of HBsAg positive blood ?

- Stop transfusion
- Administer HBIG
- Commence vaccination against HBV simultaneously
- Check for HBsAg positivity of recipient after 3 months

18. How does HBV infection transmitted through blood products differ from that acquired by other means ?

HBV infection gets easily transmitted through blood. The efficacy of transmission could be as high as 98%. The hepatitis manifests after a shorter incubation period.

19. Can mosquitoes transmit HBV ?

HBV persists in mosquitoes but can not replicate. HBsAg has been detected in mosquitoes but transmission of infection through mosquitoes is unknown.

20. What is the risk of iatrogenic transmission of HBV ?

The risk of iatrogenic transmission depends on the health personnel and the recipient. Health personnel like surgeons and dentists are more likely to transmit infection accidentally. Also, the chances of transmission are higher during dental procedures, dressing of open wounds, hemo-dialysis and surgical and invasive procedures.

Infected doctors may be posted in low-risk services such as medical or administrative services.

21. Is horizontal transmission known to occur with HBV ?

Yes. Familial clustering of hepatitis B is known. Children attending day care centres can also possibly transmit HBV infection to each other. Whenever close and long-term contact exists, HBV may become widely disseminated through horizontal transmission. Twenty-five percent of HBV infections are known to follow familial clustering. Almost fifty percent of carrier pool is estimated to be due to horizontal transmission.

22. What are the risk factors for sexual transmission of HBV ?

The risk of sexual transmission of HBV infection increases with homosexuality and promiscuity. Anal intercourse is associated with increased chance of transmission due to higher risk of trauma, injury and bleeding. Presence of other sexually transmitted diseases also raises the possibility of transmission due to the presence of mucosal ulcers and bleeding.

23. Is HBV more infectious than HIV ?

Yes. HBV is thousand times more potent than HIV in efficacy of transmission.

24. What is the natural course of Hepatitis B infection in children and adults ?

Natural infection with hepatitis B virus has different course in children as compared to adults. Earlier the age at which it occurs, milder is the clinical course and higher is the chance of becoming a chronic carrier. In fact, newborns infected perinatally rarely develop clinical disease but their chances of becoming carriera are as high as 90% if mother is HBeAg positive and 22-30% if she is HBeAg negative. Many of these carriers will develop chronic liver disease and some would go on to develop carcinoma of liver in their second to fourth decade of life.

Adults infected with HBV suffer from acute hepatitis and 10% of them become chronic carrier. Of the carriers some would develop chronic liver disease and Ca liver after a decade or two. If the adult with acute HBV hepatitis has marginally raised liver enzymes then the chances of becoming chronic carrier are high as compared to the one with markedly raised enzymes. Fulminant hepatitis with HBV occurs in 1-2% of cases.

25. Is the course of acute hepatitis following HBV different from acute hepatitis due to other viruses ?

Acute hepatitis following HBV infection in children usually has a milder and prolonged course. But in an individual case, definitive diagnosis of HBV infection cannot be solely made on clinical grounds. Children who tend to have milder hepatitis following HBV infection are more likely to develop chronicity later on.

26. Are there any extra-hepatic manifestations of HBV infection ?

The extra-hepatic manifestations of HBV infection include :

- Arthralgia
- Arthritis
- Urticaria
- Lymphadenopathy
- Angioedema
- Rashes
- Papular-acrodermatitis
- Polyarteritis
- Aplastic anemia
- Glomerulonephritis

27. What is *Gianotti-Crosti* syndrome ?

Papular acrodermatitis associated with Hepatitis B infection is called *Gianotti-Crosti* syndrome.

28. What forms of chronic liver disease are known with HBV ?

The chronic liver diseases known to be associated with HBV include chronic hepatitis, cirrhosis of liver and hepatocellular carcinoma.

29. How early or how late can carcinoma of liver develop following HBV infection ?

Hepatocellular carcinoma can develop as early as three years of age in an infant infected with HBV through vertical transmission. Usually it develops in second or third decade.

30. How does routine serology help in HBV infection ?

Estimation of hepatic transaminases in the serum :

SGOT and SGPT helps in diagnosis of acute hepatitis though not in differentiating amongst various viruses causing hepatitis. These levels are raised manifold during acute hepatitis. However, in severe fulminant hepatitis the levels of these enzymes could be paradoxically low or may drop suddenly.

Persistence of elevations in their levels could also be a pointer to presence of chronic liver disease.

If the elevations in levels is minimal during presentation as acute hepatitis, it carries higher chances of development of chronic liver disease later on.

31. What serological markers can one do in HBV infection ?

The following antigens and antibodies can serve as serological markers of HBV infection :

HBsAg	Serum, secretions, tissue fluids
HBeAg	Serum
(HBcAg	Liver-detected by staining)
Anti-HBs antibody	Serum
Anti-HBc antibody	Serum
Anti-HBe	Serum

32. What is the interpretation of these markers ?

Marker	Interpretation
HBsAg	Appears within weeks to months after exposure. Persistence for more than 6 months is indicative of chronic carrier state.
HBeAg	It appears along with or shortly after the appearance of HBsAg. In acute self-limited cases it disappears shortly after the peak elevation of transaminases. Its disappearance precedes that of HBsAg.Its presence signifies ongoing viral replication & high degree of infectivity.
HBcAg	Its presence suggests viral replication.
Anti-HBs	Protective antibody appears in serum as HBsAg declines following an acute infection. It persists indefinitely following acute infection & for atleast 10 years following effective immunization.
Anti-HBc	Initially following acute infection, IgM anti-HBc appears in serum and then IgG Anti-HBs makes its appearance. IgM Anti-HBc is useful in the diagnosis of HBV infection during the window period. IgG anti-HBc suggests the diagnosis of past or chronic infection.
Anti-HBe	It correlates with period of reduced infectivity.

Interpretation of results

Pattern	HBsAg	HBeAg	Anti-HBs	Anti-HBc IgM	Anti HBc IgG	Interpretation
I	+	-	-	-	-	Active infection
II	+	+	-	-	-	Active infection, highly infectious
III	+	+	-	+	-	Active infection, highly infectious
IV	+	-	-	+	-	Active infection
V	-	+	-	+	-	Active infection by surface mutant virus
VI	-	+	-	-	-	Active infection with surface mutant virus
VII	-	+	-	+	+	Highly infectious
VIII	-	-	-	+	-	Probably active infection
IX	-	-	+	-	+	Past infection but immunity developed
X	+	-	+	-	+	Chronic carrier with disturbed immune response
XIa	+	-	-	-	+	Chronic carrier,infectious
XIb	+	-	-	+	+	Chronic carrier but infective
XII	+	+	+	-	+	Chronic carrier with high infectivity
XIII	-	-	+	-	-	Vaccine induced protection
XIV	+	-	+	-	-	Variant HBV infection
XV	-	-	-	-	+	Infection by HBV mutant
XVI	-	-	+	+	+	Recently infected, immunity developed, not infectious
XVII	-	-	-	-	-	Warrants vaccination

33. What is healthy carrier state ?

A small percentage of chronic carriers of HBsAg are asymptomatic and remain healthy. This is termed as healthy carrier state.

34. What is the magnitude of the problem of different clinical manifestations of HBV in India ?

Acute Hepatitis : Hepatitis B is responsible for 60-70% of acute hepatitis in adults and 20-25% of that in children.

Chronic liver disease : Fifty percent of cases of chronic liver disease are due to Hepatitis B.

Chronic Hepatitis : Sixty to seventy percent of cases of chronic hepatitis are due to hepatitis B.

Fulminant hepatitis : 20-30% of cases are due to HBV.

Carcinoma of liver : 80% of pediatric cases of hepatocellular carcinoma are due to HBV and many more cases have been shown to have HBV-DNA in malignant cells.

35. When and why do you do liver biopsy in HBV infection ?

Liver biopsy may be undertaken for following conditions or reasons :

i) To determine the chronicity of HBV infection and the type of liver affection.

ii) For histopathological diagnosis of chronic active hepatitis or cirrhosis of liver.

iii) For prognostication of chronic liver disease.

iv) For diagnosis of carcinoma of liver.

v) Prior to and following interferon therapy, to judge the response.

36. When does one do HBV DNA studies ?

a) To determine presence of HBV when other markers are negative, especially when HBV mutants are suspected.

b) To determine infectivity as presence HBV DNA is indicative of replicating virus and high degree of infectivity.

c) Quantitative HBV-DNA determination is a prerequisite before & after interferon therapy to judge the response to therapy.

d) HBV-DNA marker studies could be carried out on liver tissues especially in cases of carcinoma, to determine etiology of liver disease or carcinoma.

37. What is the cost of doing these studies ?

The cost of doing HBsAg is approximately Rs.150-200/- per test. The cost of doing other HBV markers is Rs.400-500/- for each of them. The cost of doing HBV-DNA is in the range of Rs.4000-5000/- per test. All these costs are commercial costs.

38. What are universal precautions ?

Universal precautions are predicated on the assumption that the blood and certain body fluids (amniotic fluid, pericardial fluid, peritoneal fluid, pleural fluid, cerebrospinal fluid, semen, vaginal secretions, and any body fluid visibly contaminated with blood) of all patients are potentially infected.

The universal precautions include :

i) Wearing of gloves when exposure to blood or a designated body fluid is anticipated, for contact with mucous membranes or non-intact skin, venipuncture and all invasive procedures, and for handling items soiled with blood or body fluids.

ii) Use of other barrier precautions (masks, gowns, protective eye-ware) when splashes are expected to be generated.

iii) Immediate washing of hands after contact with blood or one of the specified body fluids, and immediately after removal of gloves.

iv) Appropriate disposal of sharp needles and instruments into puncture - resistant containers, without recapping or other manipulations of the needle.

Although implementation is expensive, these are designed to protect health care workers against undiagnosed infected patients and hence all patients are targeted. Implementation of universal precautions has significantly reduced the health workers' contact with blood and body fluids.

39. What types of Hepatitis B vaccines are available ?

Two types of vaccines against Hepatitis B are available. These are plasma-derived vaccine and the DNA-recombinant vaccine. The plasma derived vaccine consists of purified inactivated HBsAg particles obtained from the plasma of chronic carriers. In the DNA-recombinant vaccine the antigen particles are obtained from the yeast Saccharomyces cervisiae through recombinant DNA technology.

Single pediatric dose vial of both the vaccines contains 10 mcg of antigen and that for adult use contains 20 mcg. Multi-dose vials are available containing 20 mcg/ml.

40. Which Hepatitis B vaccine is recommended ?

Both the vaccines are shown to be equally efficacious and safe.

41. What is the efficacy of Hepatitis B vaccine ?

Protective serum titres of anti-HBs (more than 10 mIU/ml) develop in 95 to 98 percent of healthy infants and children who receive a series of three intramuscular doses. In carefully conducted field trials, efficacy has been estimated to be upto 95 percent. Vaccine has been shown to induce long-term protection for 10 or more years due to immunologic memory. It is anticipated that those immunized as infants should be protected as adolescents and young adults with a booster 10 years after the primary doses.

42. What is the dose and schedule of routine vaccination ?

Dosage for plasma derived and DNA recombinant vaccines are same :

Age < 10 yrs. : 10 mcg.
> 10 yrs. : 20 mcg.

Schedule :

Usually 3 doses are advised at 0, 1 and 6 months. It is preferable to start vaccination as early as possible. This may be preferably done within 12 hours of birth especially as routine antenatal screening for HBsAg is not practised in our country.

43. What if the child comes late for subsequent doses ?

If there is a gap of upto six months between the first and second dose or a gap of upto one year between second and third dose, there is no need to restart vaccination. Complete the remaining doses as per the original schedule. It is important to realize that such delays are not desirable, as the person remains unprotected till the schedule is completed.

44. What are the reasons for vaccine failure ?

Improper storage of vaccine and failure to maintain cold chain are the most important causes of vaccine failure. Immunocompromised individuals (those on chemotherapy etc) may also fail to respond. Surface mutants of HBV may be able to cause infection even in vaccinated children. In addition, there are individuals who do not respond to the vaccine for no apparent reason. However, half of these people who do not develop anti-HBs antibodies after a three-dose series will do so after additional dose(s).

45. What schedule is recommended for immunizing a neonate born to an HBsAg positive mother ?

In infants born to HBsAg positive mothers, the first dose of HBV should be given at birth (within 12 hours). This should be given along with Hepatitis B immunoglobuline (HBIG) in the dose of 0.5 ml. Both vaccine and HBIG can be given at the same time but they should be administered intramuscularly at separate sites. The second dose of vaccine should be given at the age of 1 month and the third dose at 6 months of age. One can also use accelerated schedule of 4 doses given at 0, 1, 2 and 12 months.

46. What are the side-effects of Hepatitis B vaccination ?

Side-effects of hepatitis B vaccine are very few. They consist primarily of local reactions or low-grade fever. Serious reactions like anaphylaxis are very rare but can occur as with any other vaccine.

47. What schedule is used for immunocompromised children ?

In immunocompromised hosts one should use double the dose recommended for that age. They may also require additional doses in case they do not show seroconversion following 3 doses. In situations where early seroconversion is required, one may use accelerated schedule of doses at 0, 1, 2 and 12 months. Despite this, it has been shown that not more than 30% of children with leukemia undergoing chemotherapy show seroconversion. In such cases, it may be better to use regular passive prophylaxis with HBIG.

48. What is the role of intradermal route of administration for Hepatitis B vaccination ?

Intradermal administration of Hepatitis B vaccine reduces the cost tremendously as the dose consists of 0.1 ml. But it has not been found to result in protective antibody titres in all recipients. Hence, testing for antibody response becomes mandatory. Antibody titres may not persist for long, as well. Thus, this route has not been routinely advocated.

In case the patient does not demonstrate seroconversion after 3 doses by intradermal route, the fourth one should be a full dose given intramuscularly.

49. Comment on high-risk versus universal immunization approaches for prevention of HBV infection ?

Considering the high cost of vaccination, initially, high-risk approach was followed, wherein individuals at added risk for acquiring infection (such as intravenous drug abusers, patients on chronic hemodialysis therapy, individuals requiring blood and blood products, spouse of an infected or carrier person, infants born to HBsAg positive mothers, laboratory and health care personnel likely to come in contact with blood and body fluids, sex workers etc) were targeted. However, these failed to have any impact on the size of carrier pool in the population.

Universal immunization targets every newborn, child and adult, thereby eliminating all modes of transmission. It also raises the possibility of ultimate eradication of this dreaded virus, as humans are its only reservoirs. Universal immunization may be expensive in the short term and reduction in carrier pool may take decades to manifest. However, effects on carrier pool are already evident in countries that took to universal immunization earlier. It is also possible that cost of vaccine may come down drastically with obvious increase in demand.

IAP recommends that if affordable universal immunization of all children should be followed.

50. Are there any countries where vaccination against Hepatitis B is included as universal immunization ?

USA and most of the European countries have advised universal immunization against Hepatitis B.

51. What advances have occurred with regards the Hepatitis B vaccine ?

i) Improvement in antigenicity by including the pre-S component.
ii) Combining Hepatitis B antigen with other antigens like DPT, DTaP, killed polio vaccine, Hepatitis A vaccine, Hib vaccine etc. For example :

a) Hepatitis A, Hepatitis B : (Twinrix)
b) DTaP, killed polio vaccine and Hepatitis B : (Pentavalent vaccine)
c) DTaP, killed polio vaccine, Hepatitis A, Hepatitis B, Hib : (Septavalent vaccine)

52. What is the role of HBV vaccine containing Pre-S component ?

This vaccine has better immunogenicity especially as it confers protection against an HBV surface mutant as well.

53. Can plasma derived HBV vaccine be given to newborns in 5 mcg. dose ?

No standard textbook or literature recommends 5 mcg. dose of plasma derived vaccine for newborn babies.

54. Till what age can the HBV vaccination be given ?

Vaccination against HBV can be started at any age. Earlier one starts, the better it is.

55. What is the role of HBIG ?

HBIG offers immediate protection against HBV :

i) Post-exposure prophylaxis with HBIG is recommended for newborn babies born to HBsAg positive mothers.

ii) Post-exposure prophylaxis with HBIG is also recommended for health-personnel who suffer from accidental needle-stick injury and for patients who receive HBsAg positive blood inadvertently.

iii) With effective and safe vaccines available indications for preexposure prophylaxis with HBIG are dwindling. In past, it was given to patients on chronic dialysis therapy. Now, preexposure passive prophylaxis with HBIG is reserved for individuals failing to respond to vaccine (eg. immunocompromised children), or in children with disorders that preclude a response (e.g. agammaglobulinemia), when they are likely to be exposed to the risk of acquiring HBV infection.

56. Do you recommend routine antenatal screening for HBsAg status ?

Routine antenatal screening for detecting carrier state in pregnant women is ideally required but has not been found to be feasible in our country. This process is cost-prohibitive and impractical in India as more than half the deliveries occur outside the formal health-care delivery systems.

57. What is the role of interferons ?

Recombinant inteferon-alpha is used for therapy of chronic active hepatitis B. It has been shown to suppress HBV replication in many studies. Recently conducted placebo-controlled trials have established that interferron-alpha has significant although limited clinically useful effects. Prior to starting interferon therapy, it is advisable to carry out HBV-DNA studies as well as liver biopsy.

58. What is the dose, efficacy, cost and complications of interferon therapy in treatment of HBV infection ?

The dose of alpha-interferon in HBV infection is 3 miu per sq.m. daily or 6 miu per sq. m. given on alternate day given subcutaneously for 4-6 months. The efficacy of such treatment in eliminating HBsAg is 7.8% (as compared to 1.8% chance of it occuring spontaneously) and that of eliminating HBeAg is 33% (as compared to 12% chance of spontaneous recovery). Both these results are statistically significant. Before starting interferon one should do liver biopsy, estimate baseline enzyme levels and determine HBV-DNA load. Response is said to have been obtained when the enzymes become normal, liver biopsy shows improvement and HBV-DNA load decreases or disappears. Response may take 6 months to occur. These tests, hence should be repeated at 3 months and at 6 months of therapy. In those who respond the tests are repeated 6 months to 1 year later to see whether patient has relapsed. In those who do not respond or who have relapsed one can use combination of alpha-interferon and thymosin-alpha. Each bulb of alpha-interferon contains 3 miu in ready to use solution form. Each bulb costs Rs.700-900/-. The side effects of interferon therapy include early symptoms like flu-like syndrome, myalgia, headache, nausea, etc. Late effects include fatigue, myalgia; anxiety, depression, weight loss, diarrhoea, alopecia, irritability and bone marrow suppression.

59. What is the role of indigenous medicine in HBV infection ?

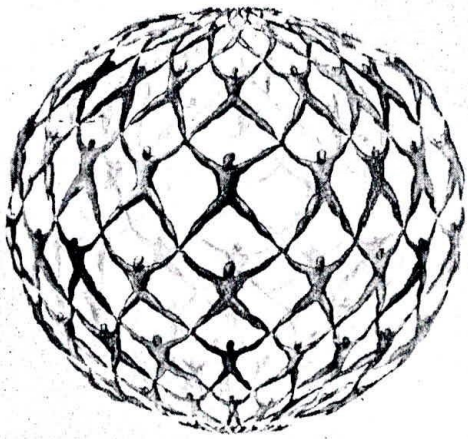
Indigenous medicines like Phylanthus species including Phylanthus amaranthus and niruri have been studied in many trials in India and abroad. Dr. Blumberg has also conducted some controlled trials using these agents. The studies show that these agents decrease the attachment of the virus to hepatocytes. However, there is no significant clinical benefit with regards to acute course or chronicity.

INDIAN ACADEMY OF PEDIATRICS

Immunisation Time Table

Birth	*BCG* *Oral Polio Vaccine - 1st dose* *Hepatitis B Vaccine - 1st dose*
6 Weeks	*DPT - 1st Dose* *Oral Polio Vaccine - 2nd dose* *Hepatitis B Vaccine - 2nd dose*
10 Weeks	*DPT - 2nd dose* *Oral Polio Vaccine - 3rd dose*
14 Weeks	*DPT - 3rd dose* *Oral Polio Vaccine - 4th dose*
6-9 Months	*Oral Polio Vaccine - 5th dose* *Hepatitis B Vaccine - 3rd dose*
9 Months	*Measles Vaccine*
15-18 Months	*MMR (Measles, Mumps, Rubella)* *DPT - 1st booster dose* *Oral Polio Vaccine - 6th dose*
5 Years	*DPT - 2nd booster dose* *Oral Polio Vaccine - 7th dose*
10 Years	*TT (Tetanus) - 3rd booster dose* *Hepatitis B Vaccine booster dose*
15-16 Years	*TT (Tetanus) - 4th booster dose*

A World of Experience in Hepatitis B Protection



Till date, 80 million individuals worldwide in all age groups have been protected against hepatitis B with Engerix B.

A clear testimony of worldwide trust and confidence in hepatitis B protection.

Engerix™ B

recombinant hepatitis B vaccine

Protecting Millions Worldwide

SUMMARY OF PRESCRIBING INFORMATION

Description: Each 1 ml adult dose contains 20 mcg of hepatitis B surface antigen protein and each 0.5 ml paediatric dose contains 10 mcg of hepatitis B surface antigen protein. **Indication:** Active immunization against hepatitis B virus infection. **Dosage and Administration:** For intramuscular use only. To be shaken well before use. *For healthy subjects:* A dose of 20 mcg of antigen protein recommended for adults and children 10 years of age and older. A dose of 10 mcg antigen protein in 0.5 ml suspension is recommended for neonates, infants and children below 10 years of age. Three doses should be given. 1st dose at elected date, 2nd dose - 1 month later and 3 rd dose - 6 months from the date of the first dose. For more rapid immunization the 3rd dose can be given two months after initial dose with a booster at 12 months. *For immuno compromised subjects.* 1 dose of the vaccine containing 40 mcg of the antigen (2 x 20 mcg per ml of vaccine) to be administered intramuscularly at intervals. 1st dose at elected date, 2nd dose - 1 month later and 3rd dose - 2 months from the date of the first dose and 4th dose - 6 months from the first dose. Re vaccination should be considered when anti HBs titres fall below 10 IU/L. It must not be given intravenously. **Contraindications:** Hypersensitive to any components of the vaccine and severe febrile infections. **Precautions:** Vaccination is not recommended for pregnant women. Adrenaline 1 : 1000 should be available for rare anaphylactic reaction. **Adverse Reactions:** Mild transient soreness, erythema and induration at injection site. Occasionally low grade fever, malaise, fatigue, myalgia, arthritis, headache, nausea and dizziness. **Recommended storage and shipment conditions:** The vaccine should be shipped under refrigeration and stored at +2 C to +8 C. DO NOT FREEZE. **Expiry Date:** The shelf life of 'Engerix' B is three years from the date of manufacture when stored at +2 C to +8 C. The expiry date is shown on the labelling. **Presentation:** Packs of one mono adult dose vial, one mono paediatric dose vial and one multidose vial for vaccinating 10 adults and children above 10 years of age or 20 infants and children below 10 years of age.

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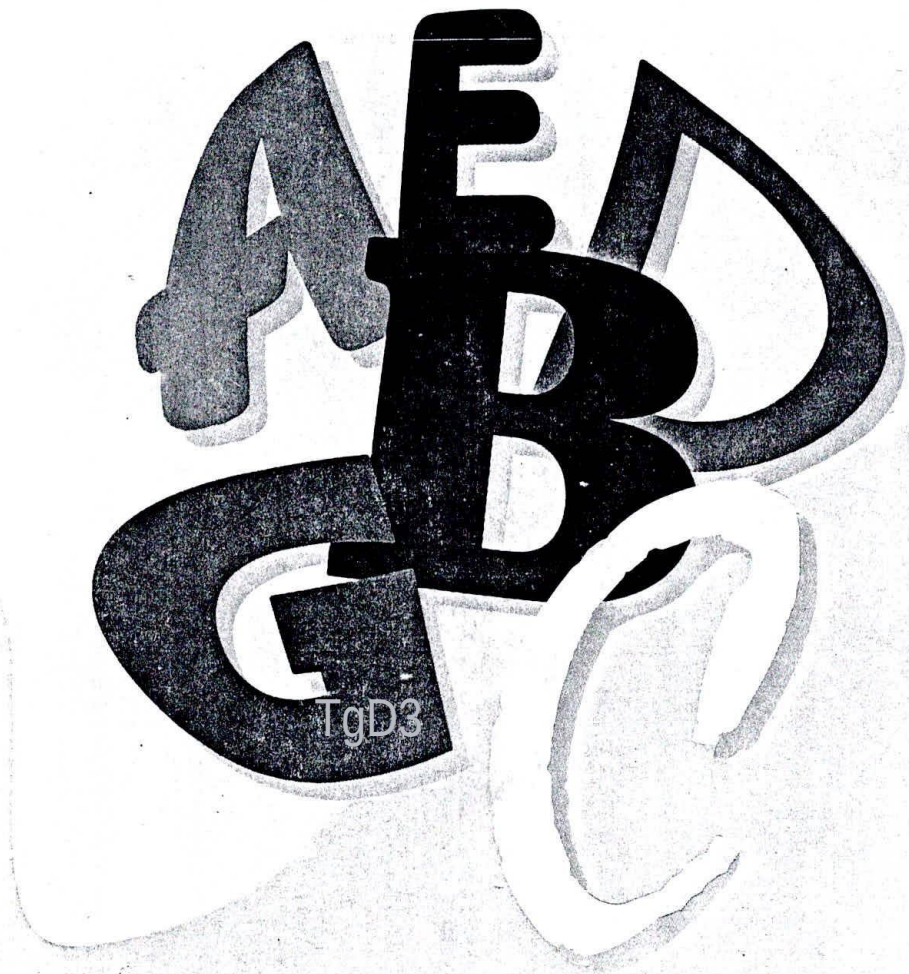
Hepatitis

AN OVERVIEW



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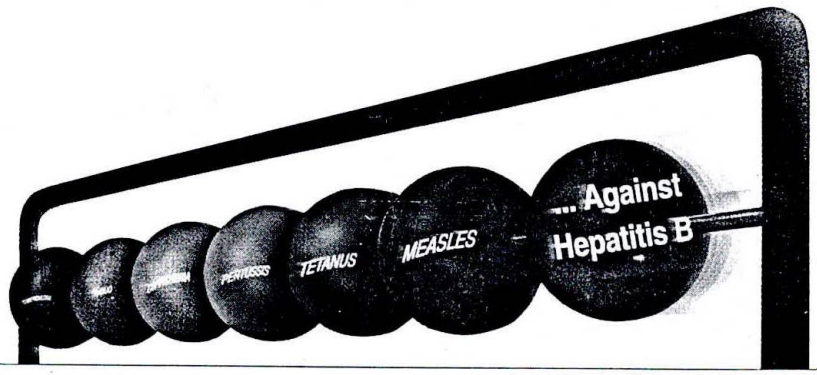

Available as MULTIDOSE VIAL for vaccinating 20 infants and children below 10 years of age

Also available as Paediatric Monodose

Marginal difference in seroconversion rates has been observed when /'Engerix'-B is administered alone or co-administered with HBIg in infants born to HBsAg/HBeAg positive mothers *

SUMMARY OF PRESCRIBING INFORMATION

Description: Each 0.5 ml dose contains 10 mcg of hepatitis B surface antigen protein. **Indications:** Active immunization against hepatitis B virus infection. **Dosage:** To be shaken well before use. A dose of 10 mcg of antigen protein of 0.5 ml suspension is recommended for neonates, infants and children below 10 years of age. For routine immunization, 3 doses of the vaccine should be given; 1st dose preferably at birth, 2nd dose at 6 weeks and 3rd dose at 6-9 months from the date of the first dose. Alternatively, 3 doses of 'Engerix'-B can be co-administered with other vaccines at 6, 10 weeks and 6 to 9 months of age in case, the 1st dose of the vaccine could not be administered at birth. For infants born to HBsAg or HBeAg mothers alongwith the first dose of vaccine at birth, HBIg can be given simultaneously at a separate injection site. **Method of Administration:** 'Engerix'-B should be injected intramuscularly in the deltoid region in older children or in the anterolateral thigh in neonates, infants and young children. It must not be given intravenously. **Contraindications:** Hypersensitivity to any components of the vaccine, severe febrile infections. **Interaction with other medicaments and other forms of interaction:** 'Engerix'-B has been administered at the same time as vaccines of the Expanded Programme on Immunization (DPT, BCG, Measles and OPV). DPT, BCG and Measles should always be administered at a different injection site. **Precautions:** Adrenaline 1 : 1000 should be available for rare anaphylactic reaction. **Adverse Reaction:** Mild transient soreness, erythema and induration at injection site. Occasionally low grade fever, malaise, fatigue, myalgia, arthritis, headache, nausea and dizziness. **Recommended storage and shipment conditions:** The vaccine should be shipped under refrigeration and stored at +2°C to +8°C. DO NOT FREEZE. **Expiry Date:** The shelf life of 'Engerix'-B is three years from the date of manufacture when stored at +2°C to +8°C. The expiry date is shown on the labelling. **Presentation:** Packs of one mono dose and multidose vial, for vaccinating 20 infants and children below 10 years of age.

For more information about Hepatitis B and its prevention, please write to Hepatitis B Awareness Centre, P. B. No. 2, Bangalore 560 049

* Poovorawan T et al. Long Term Efficacy of Hepatitis B vaccine in Infants Born to Hepatitis B e Antigen Positive Mothers. Pediatr Infect Dis J. 1992;11(10):816-821.

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EXB : A1 : 97 Paed

Hepatitis

AN OVERVIEW

Epidemics of jaundice have been reported since the 5th century BC, with major epidemics documented in Europe during the 17th and 18th centuries[1]. Many agents cause liver disease resulting in jaundice. They include viruses of yellow fever, coxsackie virus, CMV, infectious mononucleosis, HSV, rubella virus. Jaundice can also occur as complications of leptospirosis, syphilis, tuberculosis, toxoplasmosis and amoebiasis. However, the term viral hepatitis usually refers to the disease caused by a group of hepatotrophic viruses named A, B, C, D, E and G.

Though awareness of the types of viral hepatitis have increased by leaps and bounds, measures to prevent its occurrence have not kept pace. In most tropical areas, acute viral hepatitis is relatively uncommon among local people, because infection is acquired early in life when it is usually subclinical. Outbreaks have occasionally been reported when food or water becomes contaminated with human feces and sporadic cases are common among visitors. Chronic sequel are apparently limited to infection with the parenterally transmitted viruses B, C and D[2]. Viral hepatitis still remains a major public health problem in India, causing considerable morbidity and mortality[3].

Enterically transmitted hepatitis

Hepatitis A

Hepatitis A virus (HAV) is a RNA hepatotrophic virus belonging to the picornaviridae family. HAV causes an acute necroinflammatory disease of the liver[4]. Although disease occurs worldwide incidence figures are unreliable because most cases are mild and underreported[1].

It causes an acute self limiting infection of the liver. Epidemiologically, areas of hepatitis A virus endemicity have been described as high, intermediate and low[5]. In high endemicity areas infection in childhood below the age of 5 years is common. Epidemiological rates indicate that almost 100% of Indians have been exposed to HAV by the second decade and are protected from further reinfection[3]. In low endemicity areas the percentage of seropositive persons is low in childhood, increases during adolescence and early adulthood and reaches a high level by late adulthood. With increasing socio economic development, the epidemiology is changing in both underdeveloped and developing countries[5]. Although HAV infection is usually self limiting fulminant hepatitis and death can occur in a small proportion of patients usually in the older age groups[5]. It is also a significant cause of morbidity[6]. The disease occurs sporadically or in epidemic form and has an incubation period of 15 - 50 days. It is usually spread by the fecal oral route[7,8]. Person to person transmission commonly occurs between family members and also among children[9].

The frequency of HAV infections has declined dramatically in many industrialised countries and these changes have been attributed to improved standards of public health. Reduction of food and water contamination with the subsequent interruption of fecal oral spread of virus together with improvement of personal hygiene have brought similar changes in the developing countries[10]. These nonspecific measures have increased the number of susceptible adults and creates the potential for large scale epidemics like the one in Shanghai. Active immunisation is therefore the best method of protection against the disease. Two inactivated hepatitis A vaccines are available in many countries worldwide, marketed by SmithKline Beecham and Merck Sharp Dohme.

Hepatitis E

Hepatitis E (HEV) is a RNA virus probably a member of the calci virus group which are normally associated with severe diarrhoea[7]. Epidemics of hepatitis occur frequently in the Indian subcontinent and are mostly due to the enterically transmitted hepatitis E virus[11]. Transmission of this virus is by the feco oral route. It is intimately related to contaminated water supply and overcrowding[12]. It was first recognised during an epidemic of hepatitis which occurred in the Kashmir valley in 1978[13].

Hepatitis E is the commonest cause of acute sporadic hepatitis in India. There is a high attack rate in adults in the 15-30 year age group with a lower attack rate in children. Hepatitis E occurs more commonly and with greater severity in pregnant women. Mortality is high in the last trimester of pregnancy[13].

Clinical features of hepatitis E resemble those of hepatitis A. It has a self limited course. Chronic liver disease does not occur. ELISA and Fluorescent antibody blocking assay are used for detection of IgM antibodies to HEV. Diagnostic tests such as PCR and immunoelectron microscopy are mostly used for research.

Prevention is of paramount importance and this can be achieved by clean water, better sanitation, and better hygiene. Vaccine for HEV is not available as yet. In a recent study, nonhuman primates were protected against hepatitis E after immunisation with a recombinant protein representing part of the HEV capsid[14].

Parenterally transmitted hepatitis

Hepatitis B

Hepatitis B virus (HBV) belongs to the hepadna virus family. Hepatitis B is the world's most common and serious infectious diseases. The virus may cause complications like acute fulminant hepatitis, cirrhosis and hepatocellular cancer[15]. There are an estimated 300-350 million chronic carriers worldwide many of whom will die of chronic liver disease - cirrhosis or hepatocellular carcinoma. These carriers are the main reservoirs of HBV infection. An estimated one million people worldwide die of hepatitis B each year[16].

HBV infection is a major public health problem and is responsible for considerable morbidity and mortality in India[3,17]. Hepatitis B prevalence in India has been reported to be about 2 - 7%[18].

Transmission is by four major routes:

Parenteral (blood transfusions, contaminated needles and syringes, unsterile instruments; ear piercing, tattooing and acupuncture are also known.)

Sexual

Vertical/perinatal from an infected mother to her baby at or around the time of birth.

Horizontal (shared razors, toothbrushes, child to child)

Worldwide, most hepatitis B transmission is horizontal, in household and social settings. Transmission in household and social playground settings is thought to occur because of the high viral titre found in plasma of those infected, particularly children. The small infectious dose and the presumed microscopic amount of blood or saliva, entering through breaches of skin or mucosa, during close contact may transmit the virus[16].

The clinical picture of Hepatitis B virus infection ranges from acute hepatitis to chronic liver disease with minimal acute manifestations. The course may be icteric or non-icteric. These cases may appear silent because the disease is largely subclinical. They may be unaware that they are infected with HBV and may unknowingly transmit the infection to others.

The clinical picture of hepatitis B is very similar to that caused by other hepatitis viruses. Exposure to HBV usually results in a self limiting acute infection that may go undetected. Differentiation from hepatitis caused by other viruses is

by detection of serological markers. The immune response to the HBV antigens is responsible both for viral clearance and severity of liver disease. Spontaneous clearance of the virus is achieved in 90% of adults infected with the virus. 5-10% of those infected develop a chronic infection. Successful recovery depends on the immune response mounted by the patient. In children who have acquired HBV infection in early childhood, the immune response is poor and progression to a chronic state is the rule, with minimal acute manifestations. In contrast patients with fulminant hepatitis B have a very strong immune response and rarely progress to chronic liver disease[3].

Presence of HBsAg in the serum of patients for more than six months is termed as chronic carrier state. Approximately 10% of patients contracting hepatitis B as adults and 90% of those infected as neonates will not clear HBsAg from the serum within six months. Males are six times more likely to become carriers than females[7]. Carriers are only detected during routine screening procedures such as those for blood donors. About 95% of these are asymptomatic and have near normal liver biopsies and about 1.6% proceed to chronic hepatitis (symptomatic). Patients from both groups may progress to cirrhosis and hepatocellular carcinoma.

Sensitive, specific and rapid techniques for the detection of HBV antigens and antibodies are rapidly available, tough the accuracy depends on the method used[3]. RIA and ELISA are very sensitive. Diagnosis of acute hepatitis B is based on the presence of HBsAg and IgM anti-HBc in the serum. Anti-HBs is generally found after clearance of HBsAg and indicates immunity to hepatitis B. HBsAg indicates highly infective blood and that an individual either has acute hepatitis or is a highly infectious, chronic carrier. The appearance of anti-HBe is a strong evidence that the patient will recover completely . These markers help in determining the stage of an infection and the potential to transmit hepatitis B. The detection of anitgen and antibody levels is also used to identify those at risk for hepatitis B related liver damage specially hepatocellular cancer. The risk of development of PHC in HBV carriers is about 200 times greater than in the general population.

There is no therapy for acute viral hepatitis and therefore emphasis is placed on prevention through immunisation[19]. Management is

symptomatic. Treatment is aimed at controlling complications. Successful antiviral therapy can reduce or stop inflammatory necrosis in a percentage of patients who are chronically infected. The commonly used drugs are alpha interferons, nucleoside analogues - lamivudine & famciclovir and corticosteroids[7].

The control of HBV infection can be achieved by non specific measures and immunisation. HBV can be prevented by improving hygienic conditions in laboratories, operating theatres, blood banks and dialysis units, carefully screening blood donors in blood banks, sterilisation of instruments, use of disposable syringes and needles and providing active immunisation[3].

The IAP and INASL have recommended immunisation of all new borns irrespective of whether their mothers are infected with hepatitis B virus or not. The World Health Organisation (WHO) has endorsed the inclusion of hepatitis B vaccine in routine childhood immunisation programmes.

Hepatitis D

Hepatitis D virus (HDV) infection is caused by an unusual RNA virus previously called delta agent. This is coated with HBsAg and requires HBV to replicate hepatitis[20]. Hepatitis D infection can occur simultaneously with HB (co-infection) or when a carrier of HBV becomes infected with HDV (superinfection). Infected blood transfusion, sexual or household contact and intravenous drug abuse is the most common mode of transmission. It can affect all risk groups of hepatitis B infection .

Coinfection is generally indistinguishable from acute hepatitis and is self limited. Superinfection on the other hand may be a silent infection or manifest as fulminant hepatitis. Diagnosis is based on serological tests[2]. Diagnosis is based on the presence of IgM anti-delta antibodies in serum. Presence of IgM anti-delta antibodies after six weeks predicts chronicity[7].

Vaccination against hepatitis B makes the recipient immune to HDV infection. Nonspecific measures to prevent HBV infection should also be implemented to prevent HDV infection[21]. Treatment with alpha interferons reduces severity in only a minority of patients.

Hepatitis C

Hepatitis C virus is an RNA virus related to the flavivirus and pestiviruses.

Hepatitis C is now recognized as the major cause of non-epidemic non-A, non-B hepatitis in most countries[2]. 80-90% of all post-transfusion hepatitis are caused by HCV. The major routes of transmission are through blood transfusion, unsterile medical instruments, tattooing, drug abuse. Sexual transmission plays a secondary role. Most of the cases may be asymptomatic and only 25% of the sufferers are jaundiced[7]. Upto 80% of infections result in chronic hepatitis and at least 20% of them develop cirrhosis. Many of these cases develop hepatocellular carcinoma[21]. Serological tests for HCV detect antibodies to viral antigens. Serum IgM anti-HCV correlates with active viral infection[7].

Prevention is by screening blood donors, reduction in the use of shared needles and syringes. Screening blood donors has reduced incidence of post-transfusion hepatitis.

There is as yet no specific treatment or vaccine for this infection. Development of a vaccine is still in its infancy.

Hepatitis G

Hepatitis G virus (HGV) represents a group of recently discovered viruses belonging to non-A-E viruses[22]. Risk factors are similar to those for HCV. They include past transfusion, non-A, non-E hepatitis, intravenous drug abuse, haemophiliacs receiving blood products and multiple transfusions[7]. Vertical transmission has been reported during birth[22]. Acute hepatitis is usually mild, with only modest or no rise in transaminase. However it has been known to be associated with fulminant hepatitis.

Prevention would be as for other parenterally transmitted viruses. There is no known vaccine or treatment available.

We have no effective drug for the treatment of hepatitis. Therefore prevention and immunisation where possible should be the mandate. Strict measures need to be taken to improve blood banks, proper screening of donors, strict asepsis during procedures and improve general hygiene & sanitation. Awareness of the dangers of hepatitis, blood bank guidelines, cleanliness as a way of life, definite therapy and education to medical community on the need for strict aseptic precautions even during a simple procedure should form the A to E of hepatitis[3].

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Compiled by : Dr. Radhika Bobba - Medical Adviser
SmithKline Beecham Pharmaceuticals (India) Limited
P. B. No.2, Bangalore - 560 049.

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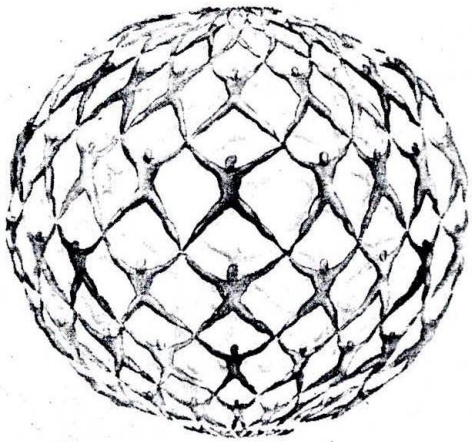

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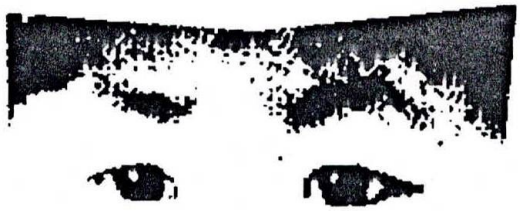
HEPATITIS B



THE TAIWAN EXPERIENCE

Report of a talk by

Dr. S. D. Lee

Professor and Chairman, Department of Medicine,
Veterans General Hospital, Taiwan

Dr. S. K. Mittal

Professor and Head, Department of Pediatrics,
Maulana Azad Medical College, New Delhi

New Delhi
15 September 1997

Dr. Shou-Dong Lee

For nearly 2 decades Dr. S. D. Lee has been involved in the movement to control, and ultimately to eradicate, hepatitis B virus infection in Taiwan, the country that had the highest HBV carrier rate in the world. His pioneering studies on hepatitis B vaccination provided the impetus for the Taiwanese government's mass vaccination programme launched in 1984, one of the most remarkable success stories in the field of public health.

Born in China and educated in Hong Kong, Taiwan and USA, Dr. Lee joined the Veterans General Hospital, Taipei, in 1978 as attending physician and progressed to become Chief, Division of Gastroenterology, Department of Medicine, in 1989, and Chairman, Department of Medicine, in May 1996, a position he currently holds.

During his distinguished career, he has published over 400 papers and won several awards and honours for his research contributions, also won the Outstanding Research Award of the year given by the National Science Council, Republic of China for 4 years.

Dr. Lee is a referee and editorial board member of a number of leading international medical journals.

Hepatitis B: Dimensions of a Public Health Problem

Primary liver cancer is common in Africa and parts of Asia including mainland China and Taiwan, where the annual incidence ranges from 10-15%. Until the discovery of 'Australia antigen' by Blumberg in 1965, the high incidence of liver cancer in the Chinese people was blamed, variously, on poor nutrition, parasitic infection, and alpha-toxin.

Blumberg's discovery made it possible to test people for hepatitis B virus, using hepatitis B surface antigen (HBsAg) as marker. The first prevalence survey among healthy subjects in Taiwan 1970 showed a HBsAg- positivity rate of 15%, the highest reported figure in the world (US 2%, India 2-7%). In patients with liver cancer, the positivity rate was even higher, at 80%, suggesting a causative link.

Ten years later(1980), a survey carried out in Taiwan revealed that over 90% of the general population before 40 years of age had been infected by HBV and 15-20% were chronic carriers.

We studied hepatitis B markers in patients with chronic liver disease, namely, chronic active hepatitis, liver cirrhosis, and liver cancer. In contrast to the 15% positivity in healthy subjects, the patients with liver disease were found to have a carrier rate of 80%.

According to WHO reports, every year about 2 million people worldwide die of hepatitis B-related liver disease: liver cancer, cirrhosis, chronic hepatitis, acute hepatitis or fulminant hepatic failure.

Subsequently, many horizontal and longitudinal studies assessed the prevalence rates of HBsAg, anti-HBs and anti-core antibodies among different age groups in Taiwan, and concluded that the hepatitis B virus was related to acute hepatitis and to deaths due to fulminant hepatitis, with some infected people going on to develop a chronic carrier state, chronic persistent hepatitis, liver cirrhosis and liver cancer.

In a famous study published by Beasley and co-workers in the Lancet in 1981, a group of 22,707 men, all government employees in Taiwan receiving regular health checks, were followed up for 3 years, from 1978 to 1980. Over 3,000 were diagnosed as HBsAg carriers, of whom 49 developed hepatoma. Among the nearly 20,000 non-carriers, only one person developed liver cancer. Thus HBsAg carriers in Taiwan were shown to have a 273-times increased risk of liver cancer compared to non-carriers.

According to WHO reports, every year about 2 million people worldwide die of hepatitis B-related liver disease: liver cancer, cirrhosis, chronic hepatitis, acute hepatitis or fulminant hepatic failure. Over 75% of these deaths occur among the Chinese, causing some people to refer to hepatitis B and liver cancer as a Chinese disease.

Hepatitis B: Control Strategies

As the enormity of the hepatitis B problem unfolded in Taiwan, the health authorities began to search for a control strategy. In the absence of a medicine to treat and cure the infection, prevention was seen as the only solution, parallel to the small pox situation a few years ago, when an effective vaccine helped to wipe out the disease from the globe. For instituting prevention, it was first necessary to find out the major route of transmission, whether maternal-infant, blood transfusion, shaving, ear piercing, haemodialysis, tattoo, tooth extraction, wound, or sexual intercourse.

Studies showed that over 90% of babies born to mothers who were HBsAg and e-antigen positive were infected by their mothers.

Early evidence, showing mother-to-infant transmission, appeared in a paper published in 1975. The authors reported following up 158 HBsAg-positive mothers and their infants at various hospitals in Taiwan. At 6 months of age, 40% of the infants were positive for HBsAg. Among the 20 controls, HBsAg-negative mothers, not a single baby showed positivity. The results proved conclusively that hepatitis B is transmitted from mother to baby.

At the time the paper appeared, the associated HBV antigens - e antigen, core antigen and delta antigen - were unknown. The e antigen is a marker of infectivity. Our studies showed that over 90% of babies born to mothers who were HBsAg and e-antigen positive were infected by their mothers. The infectivity rate went up to 100% when the mothers were positive for HBV-DNA, DNA being a derivative of the virus. On the other hand, the infection rate was only 10% in babies of mothers who were HBsAg-positive but e-antigen negative. The annual incidence of infection in Taiwanese adults was found to be 2.7%. It began to be realised that early infection, at the neonatal stage, leads to chronicity in 90% while adults contracting the infection rarely develop chronic hepatitis. Therefore, for a vaccination programme to be successful, it would have to be delivered early, at the newborn stage.

Beasley described the vertical transmission of infection in Taiwan as: (1) HBsAg-positive mothers transmit the infection to 50% of the babies, rendering them carriers. (2) Female babies grow up and transmit the infection to their babies, passing HBV from one generation to the next, the reason for the high incidence rates among the Chinese, regardless of whether they live in mainland China, Taiwan, UK or the USA. (3) Male children of carrier mothers would tend to develop liver disease, of whom 14% would die.

In Taiwan, several instances of family clustering have been demonstrated, with at least 3 generations of mothers testing positive for HBsAg.

In 1982, prior to the vaccine programme, the population of Taiwan was 18 million, the number of new cases of viral hepatitis was 20,000, deaths due to cirrhosis were 3,200 (sixth leading cause of death) and deaths due to hepatocellular carcinoma were 3,700 (leading malignancy among males).

We estimated the medical costs of treating these patients at US$ 60 million per year. By contrast, a mass vaccination programme would be cheap. We presented the cost-benefit data to the government, urging the officials to begin a vaccination programme to prevent people from becoming carriers, developing liver disease, and burdening the national exchequer.

The government considered 2 options for blocking prenatal transmission of hepatitis B infection, (1) passive immunisation, and (2) active immunisation. Passive immunisation with hepatitis B immunoglobulin (HBIG) had several disadvantages. Not only was it expensive, but the protection it conferred was short-lasting. In contrast, active vaccination had the potential for preventing the infection for a significantly longer period.

Hepatitis B: Mass Vaccination Programme. A Success Story

In 1980, only plasma-derived hepatitis B vaccines were available. These were prepared by a French and American company from the serum of carriers, after inactivating HBsAg. As the PDV vaccines were fairly new, the media protested against using the Chinese as guinea pigs, alleging that the plasma derived vaccine caused diseases ranging from AIDS to cancer. Pilot studies were carried out to convince the Taiwanese government and the people about the benefits of hepatitis B vaccination.

As the PDV vaccines were fairly new, the media protested against using the Chinese as guinea pigs, alleging that the plasma derived vaccine caused diseases ranging from AIDS to cancer.

We first calculated the economics of the viral hepatitis problem in Taiwan, based on the annual birth rate of 300,000. We pointed out that every year, at a vertical transmission rate of 6%, there would be 20,000 new cases HBV. If vaccination were postponed for one month, 1,500-1,750 new cases would result; if vaccination were postponed by one day, 50-58 new carriers would be born and grow up to develop chronic hepatitis, liver cirrhosis or liver cancer. The government accepted vaccination as a cost-effective solution, especially after the health minister himself was

diagnosed as HBsAg-positive. To disprove the myths about the vaccine, I and my children, who were then in the kindergarten, became the first to receive the hepatitis B vaccine in Taiwan.

Our group at the Veterans General Hospital in Taiwan conducted 3 vaccine trials, beginning from 1981. These were preceded by a serological marker screening of 10,000 pregnant women. 16% were found to be HBsAg-positive, of whom 41% were HBeAg-positive.

The government decided that the HB vaccine alone is enough for the prevention of HBV infection in neonates born to HBeAg-negative mothers, provided it is given as early as possible after birth.

The first vaccine trial was conducted in neonates born to HBeAg-positive carrier mothers. It was designed to identify the most economic and efficient way for immunoprophylaxis of HBV infection in high-risk neonates. Neonates were randomly assigned to receive the vaccine alone or in combination with HBIG. Infants whose parents refused vaccination formed the controls. Group one received the vaccine alone, group 2 got the vaccine plus HBIG at birth, and group 3 got the vaccine plus HBIG at zero and one month. At 6 months of age, the HBV carrier rate was 24% in neonates who received the vaccine only, 11% in group 2 neonates who received the vaccine plus one dose of HBIG at birth, and only 5% in group 3 neonates who received the vaccine plus 2 doses of HBIG. Compared with 90% neonates who became HBV carriers in the control group, the efficacy of HBV vaccination in preventing HBV infection among high-risk infants was 74% in group 1, 88% in group 2, and only 94% in group 3.

From these results, the government accepted HBV vaccination plus one dose of HBIG at birth as the method of choice for preventing perinatal transmission of HBV in high-risk neonates.

The second vaccine trial was conducted in neonates born to HBeAg-negative mothers, to determine the most effective method of preventing perinatal and postnatal infection in babies at a relatively lower risk. Neonates born to HBsAg positive but HBeAg-negative mothers were randomly divided into 2 groups, to receive the vaccine alone or the vaccine plus one dose of HBIG at birth. Neonates whose parents refused vaccination served as controls. 100% of neonates given the vaccine alone developed anti-HBs positivity at 6 months of age, while 96% of neonates who received the vaccine plus HBIG were anti-HBs positive at 6 months. Therefore, the government decided that the HB vaccine alone is enough for the prevention of HBV infection in neonates born to HBeAg-negative mothers, provided it is given as early as possible after birth.

The third vaccine trial evaluated the immunogenicity of smaller doses of the HB vaccine, in an attempt to reduce the costs of vaccination. The smaller doses (1 and 2 micrograms) produced significantly lower antibodies than the standard dose (5 micrograms). Therefore, in Taiwan, the standard dose was adopted for the HB vaccination programme.

To allay anxieties about the side effects of the vaccine in neonates, we compared the HB vaccine with the DPT and measles vaccines. Fever occurred in only 2.8% of neonates vaccinated against HBV, compared to 38.4% and 28% respectively in neonates given the DPT and measles vaccines. Other side effects such as diarrhoea and redness were also significantly lower in the HB vaccinated group.

The government launched a nation-wide vaccination programme in 1984 to control hepatitis B in Taiwan. For the first 2 years the programme covered only neonates born to mothers who were HBsAg carriers, but it was extended to all neonates in 1986. Those who missed the scheduled vaccination were encouraged to receive the vaccine on a fee-for-service basis.

Four years into the programme, the government carried out an evaluation, to compare the results of mass vaccination with those of the pilot study. Sera from children born to 786 carrier mothers, positive for HBeAg, were tested. The HBsAg positivity rate was found to be 11%, and the protective efficacy 85%, exactly the same as in the pilot study.

Around 1992 the recombinant HBV vaccine became available. Due to its improved safety profile, people in Taiwan brought pressure on the government to replace the plasma-derived vaccine with the genetically-engineered product.

After several years, we carried out a study of long-term immunogenicity and efficacy, among 7-9 year-old children of HBeAG-positive mothers, who were vaccinated at birth. The 199 children were living with their highly contagious mothers and were therefore at high risk of developing HBV. High antibody titres were detected in 92% of the children; only 5% had lost their protective antibodies by the age of 7 years. Among children of non-carrier mothers, who received the standard dose of the vaccine as neonates, 10% had lost their antibodies by the age of 9 years

The study of long-term vaccine efficacy gave rise to a new worry. Would children who lost their antibodies become infected with HBV? A group of children with low antibody levels were followed in an effort to find the answer, and their titres were regularly monitored. In some cases the virus entered the body but instead of producing disease acted as a natural booster, enhancing the titre levels. None of the children became HBsAg positive despite disappearance of protective antibodies.

Around 1992 the recombinant HBV vaccine became available. Due to its improved safety profile, people in Taiwan brought pressure on the government to replace the plasma-derived vaccine with the genetically-engineered product. The efficacy of the new vaccine was compared with the traditional vaccine as booster in primary school children who had received the original plasma-derived vaccine. Children in both groups were found to have similar antibody levels. They were followed up to the age of 14 years. About 80% of children, regardless of whether they received the recombinant vaccine (Engerix-B) or the plasma-derived vaccine, still had antibodies in their serum, and none became positive for HBsAg. We concluded that there was no case for a second booster, and WHO currently does not recommend booster vaccination for children under 15 years.

Ten years after the launch of the nation-wide vaccination programme in Taiwan, the HBsAg carrier rates in children have dropped from 10% to less than 1%.

Results showed a significant decline in the annual incidence of hepatocellular carcinoma in children 6-14 years of age.

Ten years after the launch of the nation-wide vaccination programme in Taiwan, the HBsAg carrier rates in children have dropped from 10% to less than 1%. However, it remained unclear whether the goal of reducing HBV-induced mortality, particularly that from hepatocellular carcinoma, had been achieved. As hepatocellular carcinoma peaks in the sixth decade of life, any decrease in the incidence as a result of vaccination would be seen after 40 years or more. A group of researchers in Taiwan, led by Dr. M. W. Chang, set up a study to assess the trend in children as an early indicator of the effectiveness of vaccination in reducing the rate of hepatocellular carcinoma. Data on liver cancer in children were collected from Taiwan's Cancer Registry. When analysed, the results showed a significant decline in the annual incidence of hepatocellular carcinoma in children 6-14 years of age from 0.71 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994. The corresponding rates of mortality also declined.

The Taiwan Childhood Hepatoma Study Group has strongly recommended that hepatitis B vaccination be integrated into the worldwide Expanded Programme on Immunisation to interrupt perinatal and early horizontal transmission of HBV and the subsequent development of chronic liver disease.

DISCUSSIONS

Dr. S. K. Mittal

Chairman's Remarks

We compliment Professor Lee and others for their untiring work and ultimate achievement of control of hepatitis B in Taiwan. Before inviting questions from the audience, I would like to outline the hepatitis B scenario in India.

As is well known, hepatitis B is a childhood infection but an adult disease. Only 15% of the total hepatitis B infections in India occur in children below 6 years of age but these children constitute 90% of the chronic carriers in the country. Estimates of the number of carriers in India vary from 35 million and 43 million.

Prof. Lee has stated that in Taiwan about 6% of the pregnancies are at risk of transmitting hepatitis B to their babies. Corresponding data from India are still very scanty, and about half-a- dozen studies indicate that the transmission rate may be a little over 1% (range 0.9%-1.7%). But even at this level, a large number of pregnant women are at risk of transmitting the infection perinatally. The chronic carrier rates among pregnant women have been reported at 3.5% to 4.7%, of whom about 17%, on an average, are HBeAG positive, except for a couple of studies where HBeAg positivity has been reported in the range of 40%. About 250,000-300,000 carriers are added every year by perinatal transmission of HBV in this country, contributing 30%-50% to the overall number of carriers.

It is believed that about 40,000 to 50,000 new cases of hepatocellular carcinoma and an equal number of deaths due to chronic liver disease are occurring in the country. Roughly 60% of the cases may be due to hepatitis B, with hepatitis C and other causes responsible for the rest. At the worst estimate, about 100,000 deaths are caused by chronic liver disease and hepatocellular carcinoma related to hepatitis B, constituting about 1 out of 170 deaths in this country.

With these remarks I invite questions to Prof. Lee.

Q. Which vaccine is currently used in the Taiwan immunisation programme?

A. We are using Energix-B made by SmithKline Beecham for vaccinating our neonates, as it is believed to be safer than the plasma-derived vaccine. As a matter of fact, due to the difficulty in obtaining carrier serum, the factory in Taiwan making plasma-derived vaccine has closed down.

Q. You mentioned a vaccine failure rate of 5% in HBeAg positive mothers. Could this be due to interference by malarial infection?

A. The 5% failure rate you refer to may have been due to intrauterine - not perinatal — infection.. In any case, a vaccination failure rate of 5% is acceptable. Only a few imported cases of malaria have occurred in Taiwan. So I have no experience with malaria patients who have received the hepatitis B vaccination.

Q. Could you explain why 24% children in your first pilot study became HBsAg-positive after vaccination with the plasma derived vaccine ?

A. This occurred in children who received the vaccine alone. As you know, the first dose produces antibodies in only 40%, going up to 95% after the second dose. Hence, in the first month, 60% of babies would be susceptible to HBV infection despite immunisation, needing additional protection with HBIG.

Q. Are mutants in the vaccine a cause of concern?

A. There have been a few reports of viral mutants in the serum of babies who received the hepatitis B vaccine and went on to develop HBV infection. On checking the mothers' serum, similar mutants were found, indicating that the vaccine was not the source. In Taiwan we have been using the vaccine for 17 years and mutants have never been a problem.

Q. The dosage of the plasma-derived vaccine is 5 micrograms while the doses recommended for the recombinant vaccines are 10 micrograms in children and 20 micrograms in adults. Why the difference?

A. Dosages are evolved from clinical trials conducted by the manufacturers. The plasma-derived vaccine is given in 4 doses (0, 1,2 and 12 months) and Engerix-B in 3 doses (0,1 and 6 months) to attain maximum antibody levels. Each vaccine is formulated differently, and the antigenic composition varies.

Q. Is the recombinant vaccine immunogenic in adults over the age of 40 years?

A. After the second dose of the recombinant vaccine, all adult recipients would develop antibodies. Currently, we are using a combined hepatitis A and B vaccine which produces satisfactory antibody levels after a booster dose at 6 months.

Vaccine failure is often not due to the vaccine, but to faulty storage, wrong site of injection (buttock instead of deltoid), advanced age or obesity. Responsiveness is also poor in immunocompromised persons such as those on haemodialysis or in homosexuals.

Q. From your data it would appear that neonatal vaccination would confer protection till the age of 15 years. When girls reach the child-bearing age, would they not be susceptible to infection? How do you protect women in the reproduction age against the infection?

A. At a recent meeting in Thailand, experts showed that antibodies persisted till the age of 20 years against the HBV. Hence I do not believe a booster is necessary after the age of 15.

Q. In India, healthy school children in the 10-14 year group are getting vaccinated. Do you think this is rational, knowing that the infection rate is low and carrier rate is even lower?

A. I strongly recommend you give the vaccine to the children for hepatitis B, because when children get the infection they very easily become carriers. In older children, you may have to consider the cost-effectiveness.

Q. When do you vaccinate the neonates?

A. We vaccinate within 3 days of birth.

Q. Can the recombinant vaccine be given intra-dermally?

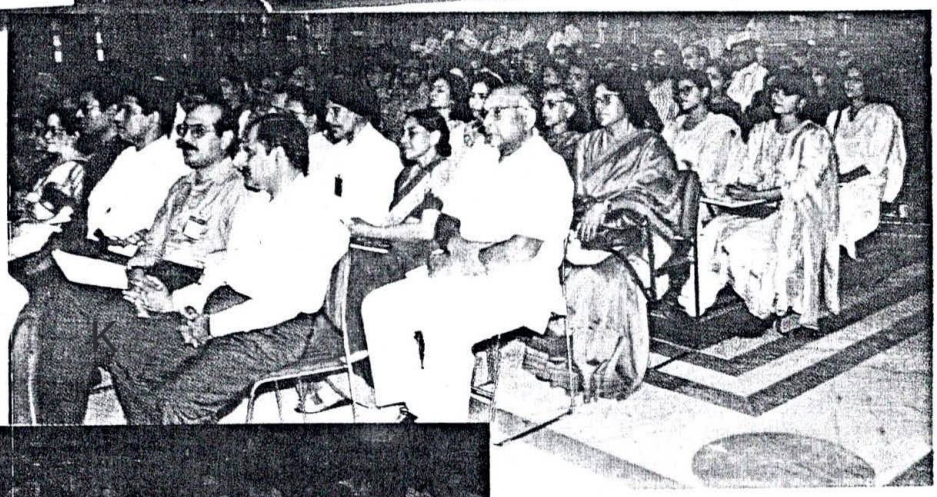
A. We use only the intramuscular route.

Dr. Mittal. The studies from India on intradermal hepatitis B vaccine administration, using reduced doses, have shown poor antibody response. Moreover, the intradermal route, which requires technical expertise, is not recommended for mass vaccination.

To summarise the discussions this evening, we have seen that hepatitis B is one disease in which we do not top the world in terms of numbers unlike, say, tuberculosis or leprosy. India contributes about 17% of the total HBV carriers in the world. But this is no reason to rejoice, we must act to decrease the problem in our country. If we decide to go for mass vaccination, then it must start at birth, because of the difficulty in tracing babies once the mothers leave hospital. Pediatricians and obstetricians have a special responsibility in this regard.

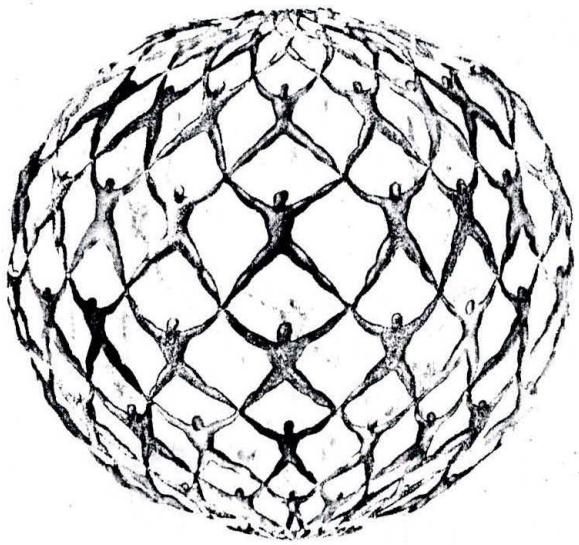
Dr. Lee & Dr. S. K. Mittal

A view of the audience



Prepared and Published by Communicore, Mumbai.
On behalf of
SmithKline Beecham Pharmaceuticals (India) Limited, Devanahalli Road, Off Old Madras Road, Bangalore - 560 049.

A World of Experience in Hepatitis B Protection



Till date, 80 million individuals worldwide in all age groups have been protected against hepatitis B with Engerix B.

A clear testimony of worldwide trust and confidence in hepatitis B protection.

Engerix™ B

recombinant hepatitis B vaccine

Protecting Millions Worldwide

SUMMARY OF PRESCRIBING INFORMATION

Description: Each 1 ml adult dose contains 20 mcg of hepatitis B surface antigen protein and each 0.5 ml paediatric dose contains 10 mcg of hepatitis B surface antigen protein. **Indication:** Active immunization against hepatitis B virus infection. **Dosage and Administration:** For intramuscular use only. To be shaken well before use. *For healthy subjects:* A dose of 20 mcg of antigen protein recommended for adults and children 10 years of age and older. A dose of 10 mcg antigen protein in 0.5 ml suspension is recommended for neonates, infants and children below 10 years of age. Three doses should be given. 1st dose at elected date, 2nd dose - 1 month later and 3 rd dose - 6 months from the date of the first dose. For more rapid immunization the 3rd dose can be given two months after initial dose with a booster at 12 months. *For immuno-compromised subjects:* 1 dose of the vaccine containing 40 mcg of the antigen (2 x 20 mcg per ml of vaccine) to be administered intramuscularly at intervals. 1st dose at elected date. 2nd dose - 1 month later and 3rd dose - 2 months from the date of the first dose and 4th dose - 6 months from the first dose. Re-vaccination should be considered when anti HBs titres fall below 10 IU/L. It must not be given intravenously. **Contraindications:** Hypersensitive to any components of the vaccine and severe febrile infections. **Precautions:** Vaccination is not recommended for pregnant women. Adrenaline 1 : 1000 should be available for rare anaphylactic reaction. **Adverse Reactions:** Mild transient soreness, erythema and induration at injection site. Occasionally low grade fever, malaise, fatigue, myalgia, arthritis, headache, nausea and dizziness. **Recommended storage and shipment conditions:** The vaccine should be shipped under refrigeration and stored at +2 C to +8 C. DO NOT FREEZE. **Expiry Date:** The shelf life of 'Engerix'-B is three years from the date of manufacture when stored at +2 C to +8 C. The expiry date is shown on the labelling. **Presentation:** Packs of one mono adult dose vial, one mono paediatric dose vial and one multidose vial for vaccinating 10 adults and children above 10 years of age or 20 infants and children below 10 years of age.

SB

SmithKline Beecham

Leading the way in vaccines

VACC:B2:98

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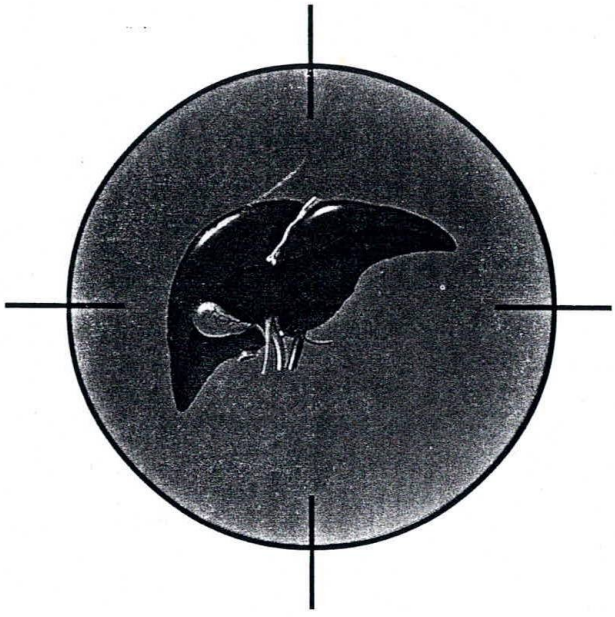
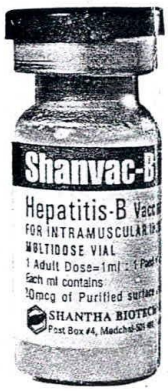


Solution



Our sincere thanks to

University of Missouri-Columbia, U.S.A
Centre for Cellular & Molecular Biology, Hyderabad
Osmania University, Hyderabad
Indian Institute of Chemical Technology
King Edward VII Memorial Hospital, Bombay
Nizam's Institute of Medical Sciences, Hyderabad
Department of Biotechnology (Govt. of India)
Department of Science & Technology (Govt. of India)
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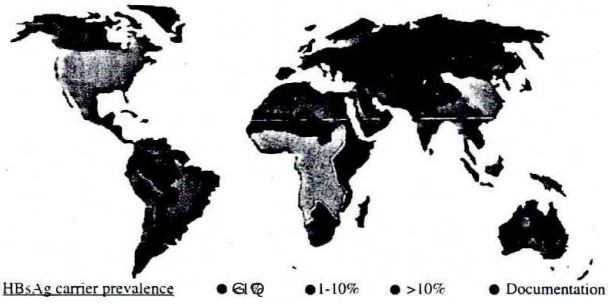
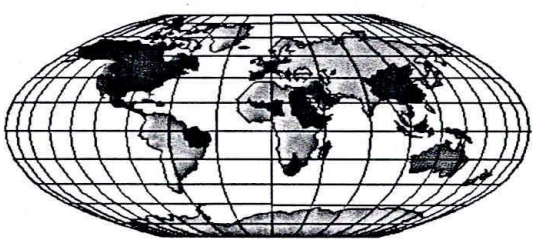
Drugs Controller General of India (Govt. of India)
National Institute of Nutrition
Technology Development Board (Govt. of India)
Central Drugs Laboratory (Govt. of India)
Oman International Bank. S.A.O.G
ICICI (Technology Group)
Indian Overseas Bank

Tackling the alarming spread of Hepatitis B



HBsAg carrier prevalence ● <2% ● 1-10% ● >10% ● Documentation inadequate



Countries in which a universal Hepatitis-B vaccine policy is in place or being planned (1996)

● National policy ● Planning

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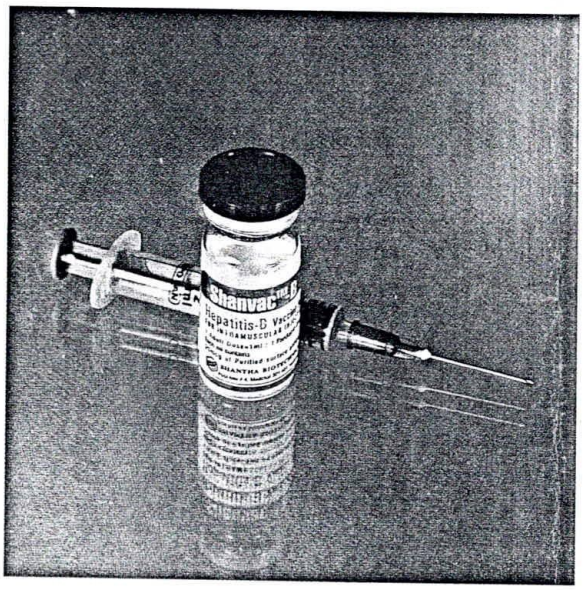
SHANVAC-B the timely development



The Indian Academy of Paediatrics has also taken up the challenge of eradicating this disease by directing all its members to immunise as many children as possible.

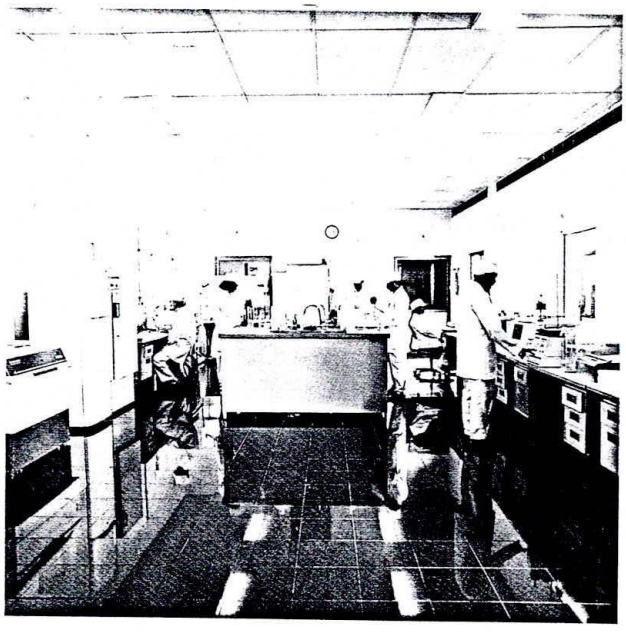
But there has been an obvious lacuna. We have needed a more accessible and cost effective vaccine than the imported one hitherto available.

Enter SHANVAC-B...India's first genetically engineered r-DNA Hepatitis B vaccine.

To be administered in three doses, SHANVAC-B is now widely available to everyone. It is efficacious as well as cost-effective!

SHANVAC-B, India's first genetically engineered r-DNA vaccine enters the scene

Successfully subjected to tests....



SHANVAC-B has been successfully tested for its :
Physico-chemical characteristics, Toxicity, Safety and Efficacy.

SHANVAC-
Biotechnics

Millions of
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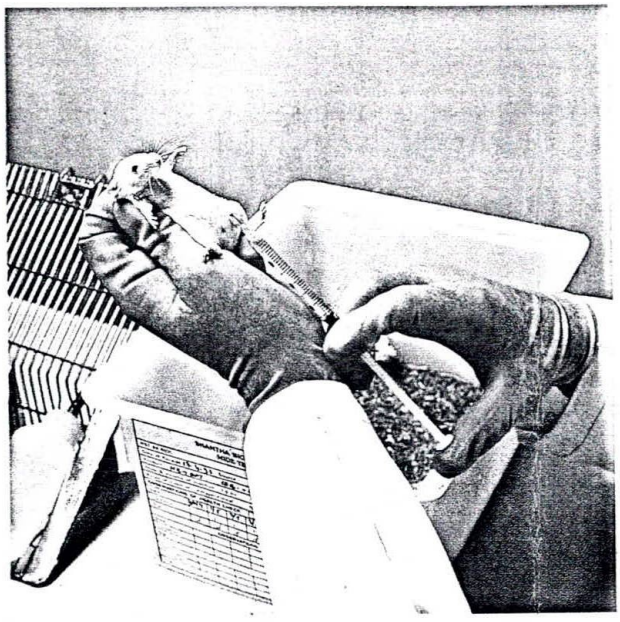
....at prestigious institutions....



RESULTS

1. *No toxic signs or tissue reaction at the site of injection.*
2. *No pre-terminal deaths.*
3. *No significant treatment effect on the body weight of male and female animals subjected to these tests. A significant lower net body weight gain (not dose related) in females at the high dose.*
4. *No treatment or dose-related effects on the food intake, except for incidental decrease in food intake of males and combined sex of the treatment groups.*
5. *No treatment or dose-related changes in the haematological and clinical chemistry parameters, excepting for some incidental changes.*
6. *No treatment or dose-related effects on the terminal body weights, organ weights and their ratios. There were no gross and/or microscopic changes in the visceral organs attributable to the treatment.*

The study indicates that SHANVAC-B administered intramuscularly at the tested dosages is not toxic to Swiss albino mice and Wistar rats under the experimental conditions employed.

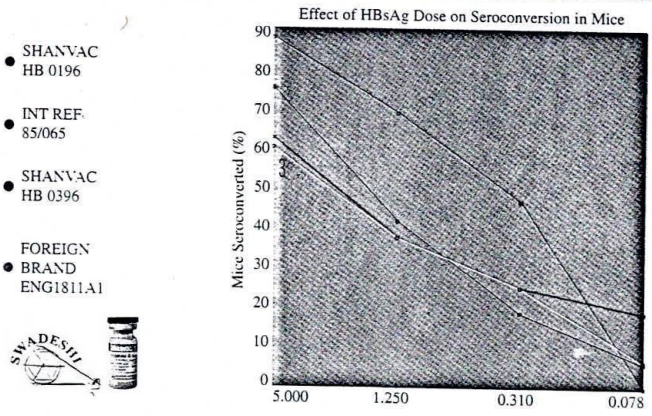
SHANVAC-B clears Toxicity study at Rallis Research Centre and Efficacy test at IICT

SEROCONVERSION

HBsAg DOSE (mcg)	SEROCONVERSION(%) SHANVAC HB 0196	INT REF. 85/065	SHANVAC HB 0396	FOREIGN BRAND ENG1811A1
5.000	62.5	87.5	75.00	60.00
1.250	37.5	68.7	41.66	37.50
0.310	25.0	46.6	18.75	25.00
0.078	18.7	0.0	6.25	6.66

GEOMETRIC MEAN TITER

HBsAg DOSE (mcg)	GEOMETRIC MEAN TITER(mIU / ml) SHANVAC HB 0196	INT REF. 85/065	SHANVAC HB 0396	FOREIGN BRAND ENG1811A1
5.000	101.5	206.4	138.3	70.9
1.250	99.7	77.5	83.9	68.7
0.310	68.7	24.6	67.7	11.3
0.078	30.5	0.0	50.8	21.8



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RESU

VACCINE

SHANVAC
INT. REF
SHANVAC
Foreign brand

ED_{50} IS TH
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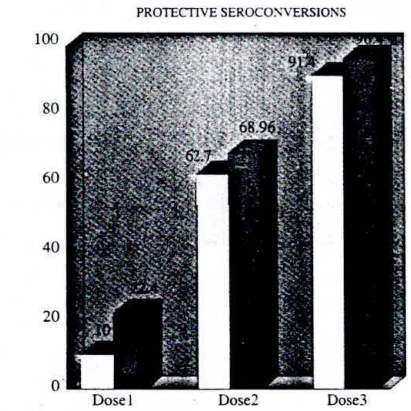
LOG

SHANVAC-B fares better

NIZAM'S INSTITUTE OF MEDICAL SCIENCES, HYDERABAD

*A Comparative Single Blind Randomised Controlled Trial was conducted at the **Nizam's Institute of Medical Sciences (NIMS)** to study clinical safety and efficacy of SHANVAC-B, manufactured by Shantha Biotechnics Pvt. Limited, vis-a-vis the available r-DNA foreign brand. Superior results were observed with SHANVAC-B.*

Please refer Graph 1 & 2

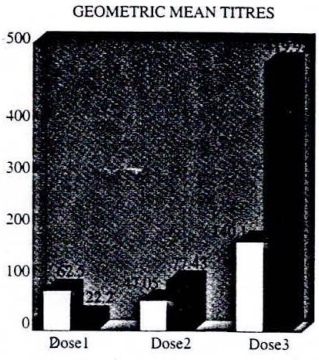


GRAPH 1

% Seroprotected by foreign brand ● % Seroprotected by Shanvac - B

the well known international brand

— *Geometric mean titres obtained after the third dose was significantly higher the other vaccine (140.10 mIU/ml).*



GRAPH 2

GMT (mIU/ml) best known international brand. ● GMT (mIU/ml) SHANVAC-B

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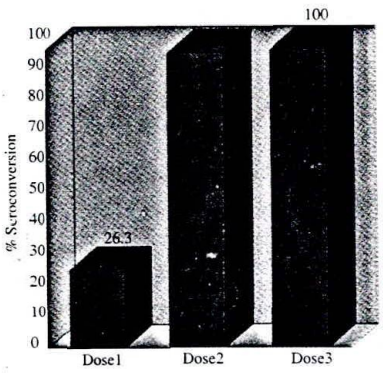
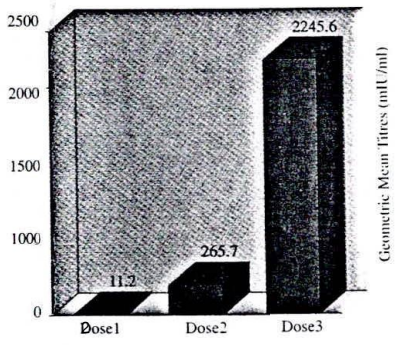
NIMS

...proving safety & efficacy





Range of Antibody Titres 30 days after dose 3

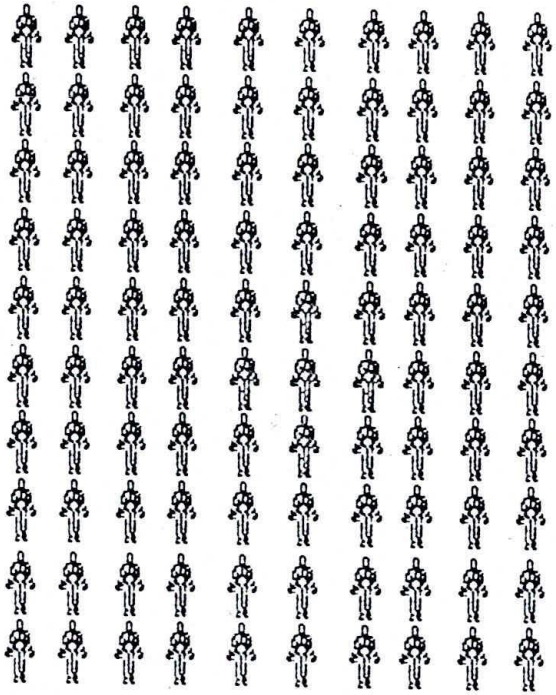
ANTIBODY TITRE (mIU/ml)	*NO.OF VOLUNTEERS*	*PERCENTAGE*
10-100	*0*	*0*
100-1000	*14*	*18.9*
>1000	*60*	*81.1*

KEM HOSPITAL, BOMBAY

CONCLUSIONS

This indigenous recombinant Hepatitis B Vaccine, SHANVAC - B, was administered successfully to healthy subjects. Seroconversion was near-universal (98.8%) after dose 2, and 100% after dose 3. All titres after dose 3 were in the protective range i.e. >10 mlU/ml, with GMT being 2246 mlU/ml. Except for one subject who developed an urticarial rash after dose 2, no significant adverse effects were noted.

"The vaccine is thus safe, efficacious and well tolerated," – Department of Gastroenterology, KEM Hospital, Bombay.



5% of population carries the Hepatitis-B virus

A STEP IN TIME

All along, the Hepatitis B virus had a free run.

Striking terror among an unsuspecting populace and claiming its victims in silence.....

But, not any longer.

SHANVAC-B, the powerful weapon to effectively checkmate this deadly disease is now within your reach.

Prescribe now !

Shanvac-B

r-DNA Hepatitis B vaccine

SHANVAC - B the ideal solution to a silent killer

SHANTA BIOTECHNICS PVT. LTD.

Corporate Office : Plot No : 1355 C, Road No. 45, Jubilee Hills, Hyderabad. Tel : 040 - 213010, 238843. Fax : 040 - 248476.
Plant : Post Box No. 4, Medchal - 501 401, Hyderabad, A.P., INDIA. Ph : 8418-22922, 22693, 22694 Fax : 8418-22656.

From: ADMIN@leo.ilban.ernet.in
To: @ilban.ernet.in, sochara@blr.vsnl.net.in
Date: Wed, 3 Feb 1999 13:35:53
Subject: For your information: No response yet from Education Dept
Reply-to: admin@leo.ilban.ernet.in
Priority: normal
Organization: ESG , BANGALORE

Mr. U. Tripathi
Commissioner
Directorate of Public Instruction
Nrupathunga Road
Bangalore 560 001

14 January 1999

Reg.: Ongoing Vaccination Campaign against Hepatitis B, seek corrective action.

Dear Mr. Tripathi,

As you are aware, Environment Support Group is a non-profit research
and advocacy NGO working on various issues of public concern. (Encl.
A brief on our activities)

We wish to bring to your attention that there is a mass vaccination campaign against Hepatitis B, which is being promoted by certain commercial organisations. Often times these campaigns have been conducted in collaboration with well meaning social service organisations, but without adequate information dissemination on the
disease or its control, or conforming with the rigour involved in providing such vaccinations. Over a period of time, it has also been
observed that the agencies involved have exploited the ignorance of the public and created a panic situation, thereby causing a widespread feeling that everyone has to be vaccinated against the disease.

School children and their parents have been the worst victims of this
campaign. Within our limited capacity we have tried to bring it to the notice of various schools and the public that such panic reaction
and epidemic control programme is not warranted for this particular

reboard 7/2/99. JN 5/2

disease in the Indian context. However, when the campaign continued
to grow in strength we considered it essential to come out with a Public Statement on the issue, the same being achieved by a Press Conference held yesterday and reported widely in the papers today.

Various medical experts have been consulted for this initiative and some leading experts have indeed spared time to participate in the Press Conference. Further, the initiative has been supported by the
Drug Action Forum, Community Health Cell, doctors of St. John's Medical College Hospital, Sanmathi and the Environment Support Group.

Considering that school children are the prime victims of this campaign, we request you to please consider our appeal to ban such campaigns immediately. Our rationale for demanding the same is explicated in the enclosed Press Release and Fact Sheet on the Disease and the Vaccine. This could best be achieved if your office
can come out with a Memorandum to all Schools and Colleges, to be guarded against the ongoing vaccination campaign, and as well be well
informed about the disease and the vaccine.

Along with our associate organisations and the medical experts we have consulted, we will be most willing to support you in such action.

Thank you for your earliest response and positive action on this matter of enormous public consequence.

With best wishes for the New Year,

Yours sincerely,

Leo F. Saldanha
Coordinator
Environment Support Group

Environment Support Group(R)
36, Reservoir Road
Basavanagudi
Bangalore 560 004
INDIA
Telefax: 91-80-6614855
Tel: 91-80-6657995/6722563
Fax (PP): 91-80-2274699
Email: admin@leo.ilban.ernet.in
esg@bgl.vsnl.net.in
Website: http://www.altindia.net/esg/index.htm

155

Kumar

03/02/99

8:20pm

To. Dr CHF/RN/IRP/DrVBI ARS/R+ND for info JN

D15-16A.

ADMIN@leo.ilban.ern, 01:33 PM 2/3/99, Campaign against misuse of H

From: ADMIN@leo.ilban.ernet.in
To: @ilban.ernet.in, il-health@unv.ernet.in
Date: Wed, 3 Feb 1999 13:33:06
Subject: Campaign against misuse of Hepatitis-B vaccination succesful!
Reply-to: admin@leo.ilban.ernet.in
CC: il-environment@unv.ernet.in
Priority: normal
Organization: ESG , BANGALORE

Dear Friends,

Recently, various medical professionals and NGOs of Bangalore initiated a campaign against the misinformation and misuse of the Hepatitis B Vaccination Programme engaged by various commerical organisations including MNCs.

The organisations involved in the campaign included Drug Action Forum, Environment Support Group, Community Health Cell, St. John's Medical College Hospital, and Sanmathi. Dr. Shrdi Prasad Tekur, Dr. Prakash Rao (DAF-K) and Dr. Sebastian (CHC) very actively
involved.

A Press Conference was held and the Press Release that documents the
issues involved, and concerns raised is enclosed below. The media reported the Conference very widely.

The Government which had not taken any action on the ongoing abuse for several months, was presurised by the Campaign to come out with clear steps. In a most significant development, Karnataka Health Minister Dr. Mahadevappa ordered an high level enquiry into the entire matter, with the involvement of the Health Secretary, Director
Drug Control Authority, and several other senior officers. The commission of enquiry has been ordered to submit a report within a month's time.

In light of such abuse, the Health Minister has also called for a National Policy on Immunisation.

Based on this initiative, it is hoped that groups across the country
can press for immediate action against such misuse in their regions,
and press for similar enquiries from their Health Minister. Also

JN 5/2 CM 5/2/99

it
might aid to pressurise Health Ministers of every State to write to the Cental Health Minister/Prime Minister for a National Immunisation
Policy, that is not susceptible to the pressures of various business
interests.

It might also be of interest to list members, that subsequent to the
enquiry ordered, Smithkline Beecham, the MNC manufacturing the vaccine against Hep B and who held the patent till last year, flew a
doctor from Zurich, who has been addressing the Press on the need for
NRI's to go for Hepatitis Vaccinations!! This report is also enclosed.

Best regards

Leo F. Saldanha
Coordinator
Environment Support Group

{ESG is a research, training and advocacy initiative working on various issues of concern relating to environmental justice, public health, planning, citizen engagement, etc.)

Press Release

Ongoing Vaccination Campaign against Hepatitis - B Unjustified Causing Needless Alarm

13 January 1998

There is a major ongoing campaign initiated by some commercial agencies towards Hepatitis-B vaccination
through vaccination camps, by providing injections of such vaccines as Engerix-B, Shanvac-B and Hepavac. These are being conducted along
with very wide publicity by non-professional agencies exploiting the
ignorance of well-meaning social organisations. The claims made by

these agencies certainly do not present an accurate picture of the incidence of this disease, nor the imperative for such a massive vaccination programme.

As such campaigns are continuing without any intervention whatsoever
from the relevant Health agencies, and there have been reported instances of excessive indulgence in making money by exploiting the ignorance of the public, the undersigned wish to make the following statement in the wide public interest. We take strong objection to such developments and aim to awaken the relevant Health authorities,
Local and State Governments, and public interest agencies and public-
spirited individuals to join us in evolving a relevant and rational policy of immunisation.

Hepatatis-B is only one form of Jaundice, and not the most widely communicable or of immediate public health importance. For instance,
there are various other types of viruses that cause jaundice, spread
through water and foodstuffs, which affect the public more, e.g., Hepatitis A, C, D, E and G. Other diseases of the liver also cause jaundice for instance when there is obstruction to bile flow. Hepatitis-B is transmitted in a manner very similar to AIDS transmission, i.e., through blood and blood products, injections, sexual activity, and from an infected mother to her child.

Hence, the needless alarm created by the mass vaccination drive and associated information disseminated by the various agencies involved
is wholly unjustified in its proportion and not relevant at all from
the public health point of view. The ignorance of the people is being
exploited, spreading fear and a wrong impression about the disease as
well as the effectiveness of the vaccine.

Unfortunately, people have been led to believe that the vaccine guarantees protection against all forms of "jaundice" and "cancer" of
the liver. Dissemination of such misguided opinion gravely limits possibilities of effective community intervention for even more serious diseases prevalent in our society. For instance, TB, Malaria, Typhoid, Measles, Polio and other such diseases that take

a
heavier toll are being ignored to the detriment of the public health.

The introduction of these vaccines is highly questionable considering
that there is no evidence based on community studies to justify the same on a mass scale in Indian conditions. Studies quoted in justification of the present campaign are extrapolations of very limited research based on hospital data, largely supported by drug companies with vested interests. Further, any documented evidence in our context has not proved the extraordinary claims that are being
made about the effectiveness of the vaccine. On the contrary, small
local studies negate the claims to efficacy of the vaccine.

The Department of Health has been shockingly silent on the essential
facts relating to the disease, quality of the vaccine, the cost of the product and the manner in which the vaccines are being promoted.
This silence has been significantly exploited to the detriment of the
public. In fact, people feel swindled by the varying costs of the different vaccines at different camps. Most dangerously, there is no
legal and medical responsibility being taken in case the vaccines react adversely or if the vaccination is ineffective, as should be the case.

Such gross mis-information which are half-truths, unwarranted, unscientific and unethical and which unnecessarily scare the general
public into vaccination for all, is highly condemnable, and should be
stopped immediately.

Considering the gravity of the situation, we demand the following action with immediate effect:

1. Stop the mass vaccination that is being introduced in schools, at
public camps and to non-risk groups.
2. The drug control authorities and relevant government agencies should immediately step in to take corrective action against the prevailing vaccination campaign and involve in a mass information

dissemination exercise presenting the facts of the disease in arriving at a rational disease control approach.
3. The vaccination programme should only be conducted under proper medical supervision and not at all for profit, as is presently the case.
4. The Government must take the responsibility of constituting a committee of experts to prepare Guidelines for the prevention of the
disease and introduce vaccination only where needed.
5. The Government should step in to subsidise the cost of the vaccine
so that high risk groups such as health care workers, high-risk adults including sex workers, street children, pourakarmikas, fire-force and police personnel, house-hold contacts of Hepatitis B patients, those given to cultural rituals such as tatooing, etc., are
protected from contracting this disease or spreading it to others.

In short, this statement is being made in the public interest to prevent confusion in the public mind over the disease and the exaggerated need for vaccination. This is also a strong entreaty to
the Government to end its ambivalent attitude to the ongoing campaigns, and prevent exploitation of the public by the vested interests. Finally, this is an initiative to inform the public to be guarded against the ongoing campaign and approach the relevant authorities and other sources for accurate information on the disease
and its control.

Statement issued in the public interest by:

Dr. Shirdi Prasad Tekur, Consulting Child Health Specialist and Community Health Expert.

Dr. C. Prakash Rao, Family Physician and Secretary, Drug Action Forum-
Karnataka (A voluntary agency concerned about the social and scientific aspects of rational drug use).
Tel: 3379016

In consultation with:

Community Health Cell, 367, Srinivasa Nilaya, Jakkasandra, 1st Main,
1st Block Koramangala, Bangalore 560 034 Tel: 5531518

Dr. Harshad Devarbhavi, and Dr. Philip, Gastroenterologists, St. John's Medical College Hospital, Bangalore.

Supporting organisations:

Leo F. Saldanha, Coordinator, Environment Support Group, 36, Reservoir Road, Basavanagudi, Bangalore 560 004 (ESG is a non-profit
research and advocacy agency working on various issues of public concern)

Dharma Somashekar, President, Sanmathi, 1188, 3rd Cross, 26th Main, 1st Phase, J. P. Nagar, Bangalore 560 078. (Sanmathi is a group of mothers working towards creating safe and healthy neighbourhoods in Bangalore)

Fact Sheet about Hepatitis-B and the Vaccine

About the disease:

Hepatitis B (HB) is caused by a virus and is only one form of Jaundice, others being A, C, D, E and G. HB is several times more infectious than AIDS, and very much like AIDS only prevention works as there is no cure.

HB transmission is strikingly similar to the transmission of AIDS, i.e. through blood and blood products, injections, sexual activity and from an infected mother to her child. Transmission of HB infection through mosquito bites is unknown.

Some estimates put the quantum of disease carriers in India at about
4 crores (40 million), though this evidence is not based on large-scale community studies. 90% of those infected will recover, whilst
10% may remain as highly infectious carriers. Only 1% of these develops Fulminant Hepatitis. Chances of an infection at birth are high and directly related to the number of injections received (as quoted from WHO report No WHO/EPI/GEN/88.5). The chances diminish such that at 12 months age, it is the same as in adults. The incidence of HB virus is highest in blood donors, frequent Intravenous users, health care workers, sexually promiscuous adults,
and children born to infected mothers.

HB is one of the top 10 causes of liver cancer (ibid.). 80% of liver
cancers are attributable to HB infection. However, liver cancers

form only 1.4% of all cancers.

World Health Organisation recommends that "in countries with chronic carrier rates of hepatitis B of over 2%, HB immunisation should be introduced as an integral part of existing childhood immunisation programmes as quickly as resources permit. Efforts to use this vaccine in ways which do not strengthen existing programmes should not be encouraged."

Though the cost of childhood immunisation in India against HB is only Rs. 500 crores, the Government has not yet included this vaccination in its immunisation programmes. On the contrary, the Government's ambivalent attitude in addressing the problem has given rise, unfortunately, to misuse of the public ignorance creating a scare amongst them and promoting unnecessary vaccination camps.

About the vaccine:

The Hepatitis B vaccine is among the best ever developed against any disease. It is seen is as the first and effective major cancer vaccine. The current price is the only major deterrent towards launching a mass immunisation programme.

The vaccine is stable and effective only if kept at temperature ranging between 20 to 80 Centrigrade. It should not be frozen or exposed to higher ambient temperature ranges.

The vaccine is most effective when first given within 48 hours of birth, and the scheduled repeat dosages are completed depending on the type of vaccine given. If the repeat dosages are not complete, then the immunity of the individual to the disease reduces significantly.

The effectivity of the vaccination above 1 year of age is the same as for adults. Thereby, from a public health point of view childhood immunisation is extremely important and the adults who need this vaccination on a priority basis are only from high-risk groups. Such high-risk adults are medical personnel, rescue workers (police, fire-force, military), pourakarmikas (municipal waste collectors),

street
children, sex workers and people with multiple sex partners, patients
on haemodialysis or those receiving blood and blood products, frequent intravenous (IV) users, house-hold contacts and sex partners
of HB patients and international travelers.

Vaccination must necessarily be given under medical supervision. Proper records of vaccination must be maintained for future reference.

Very little is known about the long-term effects of the vaccine. In
India very little evidence is available about the efficacy and any other effects of the vaccination programme as no community surveys have been conducted on a significantly large scale.

Issued in the public interest by:

Drug Action Forum Tel: 3379016
Community Health Cell, 367, Srinivasa Nilaya, Jakkasandra, 1st Main,
1st Block Koramangala, Bangalore 560 034 Tel: 5531518
Environment Support Group, 36, Reservoir Road, Basavanagudi, Bangalore 560 004. Tel: 6614855
Sanmathi, 1188, 3rd Cross, 26th Main, 1st Phase, J. P. Nagar, Bangalore 560 078.

'NRIs Visting Country need to be immunised'

The Hindu, Bangalore. 03 February 1999

Bangalore, Feb 2. Non Resident Indians visiting the country after long years need to be immunised against diseases as has been the case
with foreign tourists visiting India, according to Dr.Robert Steffen,
Head, Division of Communicable Diseases and Director of Travellers' Health Institute, University of Zurich, Switzerland. The NRI's coming home on a holiday should take shots against tetanus, polio, diptheria, hepatitis A and B and typhoid and prophylactics against malaria, he said.

The NRIs should also follow the advice often given to foreign

tourists coming to India. "Never drink water unless it is mineral water in bottles". Even drinking whisky with ice cubes could result
in serious infections from viruses used in the water for the ice, the
Swiss medical expert said.

Dr. Steffen, who is visiting India to give a series of lectures on the Hepatitis A vaccine, told The Hindu that the vaccine had few side
effects. Some pain in the inoculated spot, soreness and a few days of fever were likely in some persons. The vaccine for children has been introduced in India by SmithKline Beecham Pharmaceuticals, and 30 million doses have been used worldwide with no serious side effects.

The hepatitis A virus was identified in the Eighties and an inactivated virus was developed into vaccine some years ago. The vaccine has been found to be safe and effective with no case of hepatitis infection reported in those vaccinated and there was long term immunity. Dr. Steffen said. The vaccine was introduced in Europe in 1992.

When children contracted hepatitis A, they usually recovered faster and the fatality rate in children was around 0.1 per cent. The infection was more serious later in life with fatality of around 2 per cent or higher. THe infectiion was more serious later in life with fatality of around 2 per cent or higher. The infection did not
usually recurr. Vaccinating children was found to be the most effective way to control the spread of the virus. Vaccinatino also reduced the number of "carriers" who could infect others.

A fullblown hepatits infection could destroy most of the liver and there was till now no medication in Western medicine which acted on the liver, Dr. Steffen said. Persons from the more affluent sections
of society were more in danger from hepatitis. THose from poor families often had the virus in a milder form as young children and then developed immunity.

In regard to travel medicine, he said that with more people travelling around the world now immunisation was necessary. Work on
developing a malaria vaccine had been going on for some years with some Swiss and US pharmaceutical companies engaged in research. The

results so far had been unsatisfactory. Dr. Steffen said "No vaccine
against malaria was likely to be developed in the next few years".

For typhoid (called enteric fever by our doctors) two types of injectible vaccines and one oral vaccine were available. A mixed vaccine for hepatitis A and B was a distinct possibility in the next
few years, Dr. Steffen said. HE is giving talks on the hepatitis A vaccine to audience of doctors in Calcutta, Mumbai, Hyderabad, Delhi
and Kochi.

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Press Release

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As such campaigns are continuing without any intervention whatsoever from the relevant Health agencies, and there have been reported instances of excessive indulgence in making money by exploiting the ignorance of the public, the undersigned wish to make the following statement in the wide public interest. We take strong objection to such developments and aim to awaken the relevant Health authorities, Local and State Governments, and public interest agencies and public-spirited individuals to join us in evolving a relevant and rational policy of immunisation.

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Hence, the needless alarm created by the mass vaccination drive and associated information disseminated by the various agencies involved is wholly unjustified in its proportion and not relevant at all from the public health point of view. *The ignorance of the people is being exploited, spreading fear and a wrong impression about the disease as well as the effectiveness of the vaccine.*

Unfortunately, people have been led to believe that the vaccine guarantees protection against all forms of "jaundice" and "cancer" of the liver. Dissemination of such misguided opinion gravely limits possibilities of effective community intervention for even more serious diseases prevalent in our society. For instance, TB, Malaria, Typhoid, Measles, Polio and other such diseases that take a heavier toll are being ignored to the detriment of the public health.

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World Health Organisation recommends that "in countries with chronic carrier rates of hepatitis B of over 2%, HB immunisation should be introduced as an integral part of existing childhood immunisation programmes as quickly as resources permit. Efforts to use this vaccine in ways which do not strengthen existing programmes should not be encouraged."

Though the cost of childhood immunisation in India against HB is only Rs. 500 crores, the Government has not yet included this vaccination in its immunisation programmes. On the contrary, the Government's ambivalent attitude in addressing the problem has given rise, unfortunately, to misuse of the public ignorance creating a scare amongst them and promoting unnecessary vaccination camps.

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The effectivity of the vaccination above 1 year of age is the same as for adults. Thereby, from a public health point of view childhood immunisation is extremely important and the adults who need this vaccination on a priority basis are only from high-risk groups. Such high-risk adults are medical personnel, rescue workers (police, fire-force, military), pourakarmikas (municipal waste collectors), street children, sex workers and people with multiple sex partners, patients on haemodialysis or those receiving blood and blood products, frequent intravenous (IV) users, house-hold contacts and sex partners of HB patients and international travelers.

Vaccination must necessarily be given under medical supervision. Proper records of vaccination must be maintained for future reference.

Very little is known about the long-term effects of the vaccine. In India very little evidence is available about the efficacy and any other effects of the vaccination programme as no community surveys have been conducted on a significantly large scale.

Issued in the public interest by:

Drug Action Forum Tel: 3379016
Community Health Cell, 367, Srinivasa Nilaya, Jakkasandra, 1st Main, 1st Block Koramangala, Bangalore 560 034 Tel: 5531518 .
Environment Support Group, 36, Reservoir Road, Basavanagudi, Bangalore 560 004. Tel: 6614855
Sanmathi, 1188, 3rd Cross, 26th Main, 1st Phase, J. P. Nagar, Bangalore 560 078.

VIRAL HEPATITIS

HISTORY.

Viral Hepatitis is major public health problem in India It is amongst the first ten leading Causes of morbidity and mortality in the Country for quite some time till recently the data regarding viral hepatitis were obtained only from outbreak investigation and from certain Special Studies Carried on, Cowen died not give Complete picture. in order to have effective Surveillance picture System a Seminar was held at NICD Delhi in Jan. 1984. to prepare national action plan two more workshop at national level held in May to prepare two manuals, one on lab. procedure of viral hepatitis and another on epidemiological Surveillance procedure For Selected epidemic prone diseases including viral hepatitis. with the assistance of WHO, The National Viral hepatitis Surveillance programme was launched in September 1984. NICD on behalf of DGHS was designated as Co-ordinating Centre for the activities of ten Regional Surveillance Centres under the programme. The first annual meeting-cum-workshop on viral hepatitis Surveillance was held in July 1985 at NICD. To review activities Carried out after the first meeting a Second meeting was held at NICD in Sept. 1986

FACTORS

AWARENESS
VACCINE COMPANIES
IMMUNIZATION.
PANIC REACTION.
COST.

INCIDENCE & PREVALENCE

Nearly 40 million (4 crore) Hepatitis B Carrier are present in India (5%) and it is estimated that nearly 200,000 people die of HBV die every year in India.

Infection pool is maintained by younger age population when the infection at adults as later infection hardly ever lead to Carrier Status.

Out of 350 million Carrier world wide nearly 40 million are Indians and 30% of them Succumb to Complication.

India has a dubious distinction of being next to China in pool of Carriers (40 million) (43 million)

Infected pregnent mother Can transmit the virus to the new born of whom 90% will die of liver Cancer at the age of 40.

One in two Cases of Chronic liver disease and 8 out of 10 Cases of pr. liver Cancer is due to infection perticularly by this virus.

Hepatitis A and E are the most Common Cause of Epidemics in India

Hepatitis B, C, D Strains are more malignant comparatively

Impact

Mortality due to various hepatitis virus
A - 0.1%, B - 1-3%, C - 1-20%, D - 20% E - 20% in pregnancy.

Carrier/Chronicity Status
A - None, B - 5% (Neonate 90%), C - 6-60%, D - acute - 2%. Chronic - 70-90%. E + None.

The risk of chronic infection is believed to be highest in infants (70-90%) for infants who acquire the infection during the perinatal period., lower (20-50%) for children younger than 5 years, and lowest (5-10%) of older children

Infants who become chronically infected have an estimated 95% life time risk of cirrhosis or HCC. In Compare to adults who acquire the Chronic the Chronic HBV infection have an estimated 15% life time risk.

The HbSAg carrier rate being about 10-15% in adults in Children upto to age of 5 years it is reported to be 5%.

Symptoms of acute hepatitis occour in only 5-10% of neonates.

Contrary to popular belief that jaundice due to Hepatitis B virus is a dangerous illness, a large majority i.e., 95% of Such adult pt recover Spontaneously in matter of Few week.

RISK FACTORS

1. Inoculation with blood of HBV Carrier
2. Re use of infected needles and Sharp instruments without Sterilization
3. In about 30-40% of cases with acute viral hepatitis however no risk factors could be Identified.
4) Child to child
5) Mother to child } Main modes of infection
6. Carrier rates are higher in pt with leprosy, leukemia, Haemophilia. Steroid drug users.

RESPONSE.

No of reputed City School authorities have been mis led by unscrupulous drug multinationals into Carrying out mass immunization.

[Routine vaccination at School children is useless as risk of infection at birth are highest and reduces with age after the age of Six risk of infection is not Significantly different from that in adults and it is Seen that 95% of adult infection recover Spontaneously) (in few

Includs first genetically engineered vaccine against Hepatitis. B. is evelopes by Hyderabad based

Response.

Shantha Bio technriques. was launched by union minister for State for health Ms. Renuka Choudhary and promised all the help and encouragement to any future effort in Such a direction.

Experts are dismayed at the nexus between public Schools and vaccine manufacturer at "unscientif mass vaccination" by forcing each Students to Shell out about Rs 1000/- for three doses of immunisation.

Indian Academy Paediatricians (IAP) had taken up a project with assistance with NGOs for providing medical Coverage to Street Children living on footpaths, railway Station

IAP has demanded a ban on move to immunize School Children against Hepatitis B by vaccine Companies and also demand that govt Should formulate proper guideline for its use. like that of RNTCP.

Some Schools have made Hepatitis vaccination Mandatory

ECONOMIC IMPACT

1. A Course of 3 mcg doses for children Currently Costs about Rs 600/- if we recommend it for universal immunisation of all neonates (4.5 million babies born annually) the total Cost of vaccine alone would be rupees 240 crore.

2. To Bring down the Cost appropriate Strategy would be To float a Global tender. eg. koreans are offering the price for about less than a dollar per dose. which would bring down the Cost ~~less~~ less than 40 crores annually

b) Wait and watch Strategy. According to one Singapore Study reduced dosage of 2.5 microgram and even .6 microgram was effective as against Standard dosage of 5 microgram. Thus we can bring down the Cost of the vaccine required to immunise all our neonates to about 100 million (10 crore) which is very much with in the resources of govt.

3. The disease occours in prime of youth and Cost Society heavily in the form of loss of man power and expenditure on medical Care. It has been estimated that nearly 30% of hepatitis B Carriers ultimately die entirely due to it Complications.

4. It is Estimated that Rupee Spent on Vaccination against Childhood Infection will save ~~Rupees~~ Rs10 in medical Cost. (Thus Saving 2,250 crores)

ECONOMIC IMPACT.

The world Health Organisation (WHO) has already offered to assist in purchase of vaccine at price of Us. $ .55 per dose this translates to under Rs 60/- for 3 doses.

Expanding the Coverage of vaccine by including it in National programme of Immunisation would mean an additional requirement about 800 crores every year or 1/4 of budget allocation made to H.F.W. dept.

(I & P)

The risk is 90% if a child is ifected at birth
80% " " " " " 1-6 months
60% " " " " " 7-12 ~~years~~ months
35% " " " " = 1-4 years
10% " Infection occours at adult age.

The Indigenous yeast derived recombinant DNA vaccine. Christined Shanvac-B. will lower the vaccine's Cost. in India by almost one third. The adult dose will Cost 190 against Rs 485 for imported vaccine Vial. A paediatric dose will Cost Rs 140 instead of Rs 290. Financed by Technology Development Board under the dept of Science and technology. The technology Develoment board ~~under~~ the Dep' had granted 3 crore to phase I of project wemen Cost Rs 15 crore.

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D15-16A

Main Identity

From: "Dr Dabade" <drdabade@sancharnet.in>
To: "healthy skepticism." <drugactionindia@healthyskepticism.org>
Sent: Friday, January 02, 2004 10:12 AM
Attach: HB-killer.jpg; Hepatitis B vaccination in India.doc
Subject: [drugactionindia] Health Minister

THESES 5 PGS. do you require? I think I have given this pg out earlier.

57, Tejaswinagar,
Dharwad 580002,
0836-2461554,
drdabade@sancharnet.in

DRUG ACTION FORUM-KARNATAKA

yes last print

for DAFK Lib - Hepatitis B file

1 January 2004

To,

Smt Sushma Swaraj,
Union Minister for Health & Family Welfare,
Ministry of Health & Family Welfare,
Government of India,
Maulana Azad Road,
New Delhi 110 011

Respected Sushma Swaraj,

Drug Action Forum-Karnataka is a committed group of citizens voluntarily involved in bringing awareness among consumer regarding Rational Drugs Promotion and Policy.

We learn from the media reports that Government of India is planning to implement hepat B vaccination as a part of its Universal Vaccination Programme in a phased manner in all distric of India. We express our grave concern on this issue because of the following reasons:-

1. ***Lack of resources:-*** To vaccinate all newborn with hepatitis B vaccine and to implement which would cost Rupees 1250 million annually for the hepatitis-B vaccine alone, at the rate of Rupees 50 per new born for the 25 million annual births in India. If this is compared with the budget in the year 2000-2001 of Rupees 1250 million allotted by the Government of India for its National Tuberculosis Programme and Rupees 1050 million for Malaria control. Tuberculosis & Malaria are obviously major killers in India.

It is necessary to address these questions in a developing country like India, where financial resources is always a constraint. Secondly, in any case, modern health care management should consider cost efficacy and effectiveness of any healthcare intervention paid through public money.

2. ***Absence of epidemiological basis:-*** The quoted study, by medical bodies has been that of S.P.Thyagaran et al, which puts the carrier state in India at 4.7%. This is not acceptable, as it suffers from errors as per Phadke Anant & Kale Ashok. Actually the epidemiological HBsAg carrier rate works out to be 1.42%. Based on low carrier rate alone, it is clear that the Universal Strategy is invalid in India.

Therefore we would like to suggest:-

1. That Government of India take up the Selective Vaccination Strategy, in which the pregnant

women be screened for HBsAg and vaccinate such newborn only if mother is positive. It has been observed that the cost efficacy of this Selective Vaccination Strategy, (around Rupees 5227), is much greater, than Universal Vaccination Strategy, (around Rupees 9260) for protection from HBeAg (hepatitis B e antigen). Secondly, to cover all the pregnant women and their newborn in a year, the total annual cost of the programme for Universal and Selective vaccination for a cohort of 10,000 would be Rupees 5,00,000 and Rupees 1,15,000 respectively.

A detailed write up on the issue titled "Hepatitis B vaccination in India – a controversy" has been enclosed for your kind reference and perusal.

2. That the Government should regulate the promotional material of the vaccine manufacturers, which has been misleading the common man. We enclose one such advertisement from a vaccine manufacturer and we believe that there are several such. Only effective regulation on the part of the Government can stop this.

We hope that you will look into this matter urgently as it is an important public health issue an you need more information we would be happy to provide you the same.

Yours sincerely,

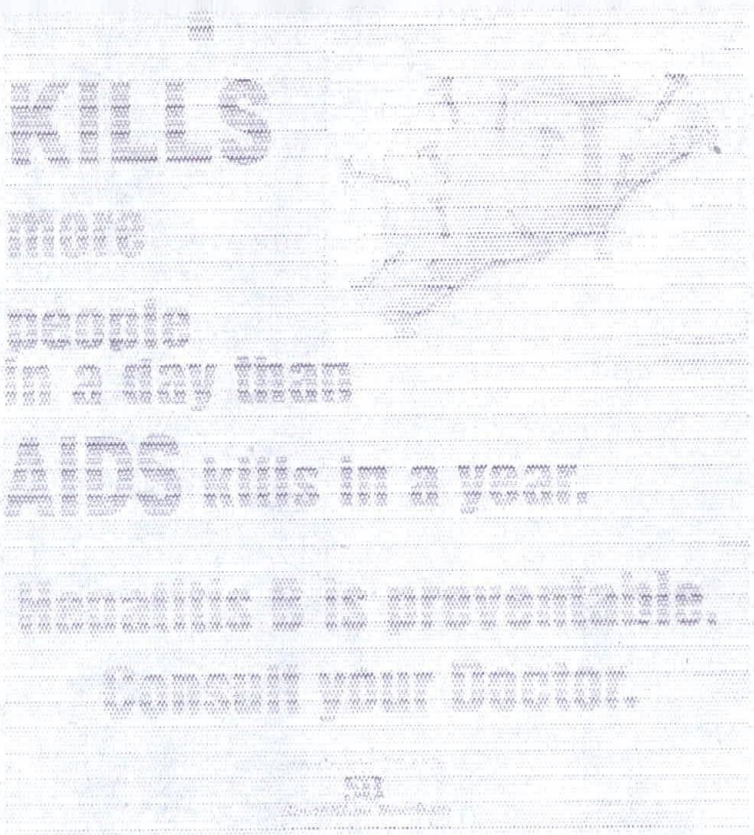
(Dr Gopal Dabade)

Attachments;

1) Hepatitis B vaccination in India a controversy.

2) Misleading advertisement by drug company SKF, about hepatitis B vaccine.

1/5/04



Hepatitis B vaccination in India- a controversy

As per the guidelines of the medical bodies in India, the government of India has decided to go ahead with universal immunisation for hepatitis-B. But, in the Indian context the cost is prohibitive, the 'universal' programme as is planned in India, would leave out the most vulnerable section amongst the infants and there are cost effective alternatives to this universal immunisation so as to reduce the HBeAg pool.

It is necessary to address these questions in a developing country like India, where financial resources is always a constraint. Secondly, in any case, modern health care management should consider cost efficacy and effectiveness of any healthcare intervention paid through public money.

Introduction;

Government of India on 7th June 2002, embarked upon the ambitious plan for introduction of hepatitis-B vaccine under its National Immunization Programme (NIP), titled Expanded Immunization Programme (EPI), initially in 15 cities and in 32 districts, which earlier included only for BCG, Measles, Diphtheria, Pertussis, Tetanus and Polio. Government plans to expand the hepatitis-B programme, in phases, during the Tenth Five Year Plan Period.[1] Though the present pilot project is funded by GAVI (Global Alliances for Vaccination & Immunisation) but from next year, the government of India, would have to put up with these expenses.

The medical academic bodies in India like the Indian Academy of Paediatrics (IAP) and the Indian National Association for the Study of Liver Diseases (INSAL), have been advocating the same to the government. [2] The controversy about introducing hepatitis-B vaccine has been taken up by a non-government organisations, [3] in India, CEHAT (Centre for Enquiry into Health and Allied Themes) (http://www.cehat.org/), which is a active critic, in the field of public health. The major concerns of it has been on the issue of lack of resources for introducing the vaccine and the absence of epidemiological basis of hepatitis-B and also in addition has come out with better alternatives for the same.

Today vaccination policies seem to have shifted towards public-private 'partnerships' and away from equity. The Director General of the WHO has come out strongly in favour of public-private ventures to treat infectious diseases. Health has become an economic asset and is no longer primarily seen as a basic human right. In vaccination programmes the focus now appears to be creating markets for new vaccines. Achieving equity in access to a limited number of essential vaccines, the objective of the EPI does not seem to be the primary objective any more. The notion of market failure and the lack of new vaccines are attractive ideas for the pharmaceutical industry as it can play a leading role in 'supporting' the development of new vaccines. [4]

Lack of resources,

The Indian Academy of Paediatrics (IAP), an organisation representing the paediatricians of the country has recommended that all the new born infants should be vaccinated with hepatitis B vaccine and to implement which would cost Rupees 1250 million (around 26 million US$) annually for the hepatitis-B vaccine alone, at the rate of Rupees 50 (around 1.04 US$) per new born for the 25 million annual births in India. Compare this with the budget in the year 2000-2001 of Rupees 1250 million (around 26 million US$) allotted by the Government of India for its National Tuberculosis Programme. And Rupees 1050 million (around 22 million US$) for Malaria control. Tuberculosis & Malaria obviously being major killers in India.

According to World Health Organization (WHO); "India has more TB cases than any other country in the world. Every year, 2 million people in India develop TB and nearly 500,000 die from it – more than 1,000 every day. The disease has become a major barrier to social and economic development. More than 300,000 children are forced to leave school each year because of their parents' tuberculosis, and more than 100,000 women with tuberculosis are rejected by their families due to social stigma." [5]

It is necessary to address these questions in a developing country like India, where financial resources is always a constraint. Secondly, in any case, modern health care management should consider cost efficacy and effectiveness of any healthcare intervention that is paid through public money.

Also given the fact that for the maximum efficacy of hepatitis-B vaccine, to prevent the 'mother to child' (which is the most dangerous mode of transmission in India), this vaccine would have to be given during the first twelve to twenty-four hours of birth as per the recommendation of WHO, the American Academy of Paediatrics and other major agencies. This would be impossible, because 77% of deliveries, in India take place at home.

Absence of epidemiological basis;

Recommendations by WHO are that, Universal and Selective Vaccination for countries with a carrier rate of and below 2%, respectively, should be carried out. In India, there has been controversy over the prevalence of the disease. The quoted study, by medical bodies has been that of S.P.Thyagaran et al, which puts the carrier state in India at 4.7%. This is not acceptable, as it suffers from three errors as per Phadke Anant & Kale Ashok;

1. HBsAg (hepatitis-B surface antigen) positive rate has been confused with carrier rate- the studies used are all one time, cross-sectional studies of prevalence of HBsAg positive in mostly blood donors. This positive rate is quite different indicator than the carrier rate. Carrier stage in hepatitis-B virus infection is persistence of infection for six months or more.
2. Thyagarajan et al have included three studies on professional blood donors and one from the dental personnel. The basic limitation of blood bank data is that, some of the blood donors are professional blood donors (blood donation is often income generation, for the donor), all though they are recorded as voluntary blood donors. The prevalence of hepatitis-B is quite high in professional blood donors. Also many of the blood donors do so repeatedly. So it is wrong to include such high-risk groups in estimating prevalence in general population.
3. An elementary error had been committed in calculating the average from various studies. The average of 4.7% has been calculated by simple taking average of the averages of individual studies, irrespective of number of the cases in the studies.

Phadke Anant & Kale Ashok have used the same data used by Thyagarajan et al, and have rightly excluded the studies on professional blood donors and dental personnel, and calculated the average of the HBsAg positive rate in different centres. In this process, excluded studies, which did not mention the number of persons tested. The average of the positive rate in the remaining studies was found to be 2.64%, which broadly agrees with the data available from other studies. For example, in the same book in which Thyagarajan et al's paper has been published, a study of HBsAg positive rate in pregnant women coming to the antenatal clinics was found to be 2.8%.

Phadke Anant & Kale Ashok further clarify that the rate of 2.64% based on the data used by Thyagarajan et al is not the point-prevalence. To find out the proportion of the HBsAg positive, being actually infected with the hepatitis-B virus, apply the corrective factor of Positive Predictive Value (PPV). Assuming the sensitivity and specificity of the HBsAg test to be 100 and 99 percent respectively, the PPV of this screening test is 67.1% at the prevalence rate of 2%, as mentioned in the chart given below. Assuming for a moment that the prevalence of HBsAg positive in India is around 2% then the true prevalence of HBsAg positive would thus be;

L-@<K@A-

---------- =1.77%, 17.7 million in a population of 1000 million.

100

Studies, which have followed up initial HBsAg positive patients for six months, have found that about 75 to 80% of these continue to be positive and hence are carriers.

Extrapolating from these findings to the above estimation of HBsAg point-prevalence of 1.47% in India, HBsAg carrier rate works out to be;

1.77%*0.80=1.42%. [6]

Based on low carrier rate alone, it is clear that the Universal Strategy is invalid in India.

Alternatives;

The critics are of the opinion that Selective Vaccination Strategy is an alternative, where in screening of all pregnant women for HBsAg and then give the first dose of the vaccine within 24 hours of birth, to the newborns of only hepatitis-B positive mothers. This strategy can be further be made Highly Selective Vaccination (HSV) strategy which would involve the following:-

1. In first year, screening all pregnant women for HBsAg positive and then from second year onwards, to conduct this screening every year for the primigravida only.
2. Administer the first dose of vaccine immediately after birth, to all the new born of the HBsAg positive mothers in the first year and also to subsequent newborns of these HBsAg positive mothers.
3. From second year onwards vaccinate also the newborn of every additional group of HBsAg positive primiparous women.

It has been observed that the cost efficacy of this Selective Vaccination Strategy, (around Rupees 5227, which is around 109 US$), is much greater, than Universal Vaccination Strategy, (around Rupees 9260, which is around 193 US$) per infant protected from HBeAg (hepatitis B e antigen). Secondly, to cover all the pregnant women and their newborn in a year, the total annual cost of the programme for Universal and Selective vaccination for a cohort of 10,000 would be Rupees 5,00,000 (around 10425 US$) and Rupees 1,15,000 (around 2398 US$) respectively.

This cost can be further reduced considerably, if we screen only the primagravida pregnant women from the second year onwards, and continue to vaccinate infants subsequently borne to the cohort of the HBsAg positive mothers detected earlier.

Apart from the cost-efficacy advantage described of this Highly Selective Vaccination Strategy, it would automatically provide data for monitoring the prevalence of HBsAg positive rate amongst childbearing women. Secondly this strategy is logistically much more practical than the Universal Vaccination Strategy, as it gives 6-7 months to screen the pregnant women for HBsAg during antenatal check-ups. Secondly only about 3% of the newborns will have to be vaccinated within 24 hours of birth. The mothers of these babies would have been detected well in advance and it would be much easier to track down and vaccinate within twenty-five hours, five (around 3%) of the 150 births that would occur in one year in a 5000 population. [7]

Chart A

Positive Predictive Values (PPV) of a screening test with a sensitivity of 100% & specificity of 99% with a varying degree of prevalence subsets of population of 10,000 each.

Prevalence	Infected Persons	Sensitivity 100%		Non-infected persons	Specificity 99%		PPV (c/c+g) x 100
		True (+) -tives	False (-) -tives		True (-) -tives	False (+) -tives	
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
1%	100	100	0	9900	9801	99	50%
2%	200	200	0	9800	9702	98	67.1%
3%	300	300	0	9700	9603	97	75%
4%	400	400	0	9600	9504	96	80%
5%	500	500	0	9500	9405	95	84%
6%	600	600	0	9400	9306	94	86.5%
7%	700	700	0	9300	9207	93	88.2%
8%	800	800	0	9200	9108	92	89.7%
9%	900	900	0	9100	9009	91	91%
10%	1000	1000	0	9000	8910	90	91.7%
25%	2500	2500	0	7500	7425	75	97%

The other additional alternative is Intradermal Vaccination of hepatitis-B, as this would reduce the vaccine cost to one-fifth, since the dose of vaccine in intradermal route is one fifth, that of intramuscular route. Though there are no studies that have followed up the vaccine for 3 to 5 years, but there is evidence that this could give adequate protection, though further studies are required to confirm these results. Majority of the published studies show that intradermal route, when given in adequate dose, is as effective as intramuscular route and that acceptability is not a problem, if it is much cheaper then it is more likely to be widely used. [8]

Summary;

Of the adults who are infected with the virus, almost 95% will recover most with no symptoms at all and all with life long immunity to the virus. Fewer than 5% will live essentially "symptom – free", with declining but continues infectiousness. About one fourth of this 5% will face life threatening liver complications decades later. [9]

It may be concluded that hepatitis-B virus infection s not a priority issue in India, as Indians have a lifetime risk of less than 0.1% of dying due to consequences of hepatitis-B infection. Today in the Indian situation there is no need to eradicate hepatitis-B infection, but rather should aim at reducing HBeAg pool. This is because the HBeAg positive, persons are

the ones which have much higher risk of developing serious liver disease and are the most infectious to others. Persistent presence of HBeAg in the hepatitis-B virus carrier is often associated with Chronic Active Hepatitis. [5]

Even if the Universal Vaccination of infants is done it will not eradicate the hepatitis-B virus infection in the near future, because it will take forty years to stop the vertical transmission. So after forty years of Universal Immunisation all the 'below forty' (i.e. childbearing population) would have been protected and hence vertical and also horizontal transmission would be stopped, in this age group. To stop the horizontal transmission amongst the above forty year-age group, it would take another twenty-five years of Universal Immunisation (as life expectancy in India is at present sixty-five years, though this figure is likely to increase, with further increase in the demand of the vaccine.)

As mentioned earlier vaccine cost for Universal Vaccination of only the newborn would be Rupees 1250 million (around 26 million US$), at Rupees 50 (around 1.04 US$) per child, for three doses. If all the children up to the age of two years (as covered by under EPI), the vaccine cost would be Rupees 3750 million (around 78 million US$) in the first year of the programme. Compare this with the cost involved in Highly Selective Vaccination, which would be around Rupees 287.5 million (around 6 million US$) in the first year and Rupees 101 million (around 2 million US$) per year there after. [6]

Though 152 countries have already introduced the hepatitis-B vaccine and 39 more countries will introduce it, the work of Phadke & Kale indicates that there is a need to have critical fresh look at this programme.

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