



Immunogenicity and safety of yeast-derived recombinant hepatitis B vaccine (Heberbiovac HB) in South African children

To the Editor: Infection with hepatitis B virus (HBV) remains a serious public health concern worldwide, and immunisation is the most effective way to control and prevent disease caused by HBV.¹ In countries where hepatitis B vaccination started many years ago, there is a reduction in the incidence of new HBV infections, HBV chronic carriers, HBV-induced cirrhosis and/or hepatocellular carcinoma.² In South Africa, HBV is the main cause of liver-related diseases, especially among black people.³ In April 1995, South Africa integrated the hepatitis B vaccine into the Expanded Programme on Immunisation (EPI),⁴ and the vaccine has been shown to be highly effective in both controlled and field studies, leading to elimination or marked reduction of hepatitis B surface antigen (HBsAg) carriage in vaccinated cohorts of children.^{5,6}

Hepatitis B vaccination in the South African EPI has been conducted with either a plasma-derived Hepaccine-B (which contains products of pre-S1, pre-S2 and S genes) (Cheil Foods and Chemicals), or yeast-derived recombinant Engerix-B (which contains only products of the S gene) (GlaxoSmithKline). Hepatitis B vaccine is given at 6, 10 and 14 weeks of age, along with monovalent oral polio vaccine (OPV), diphtheria-tetanus-pertussis (DTP) vaccine, and *Haemophilus influenzae* type b (Hib) vaccine. South Africa is one of the few sub-Saharan countries responsible for self-funding of both hepatitis B and Hib vaccines, in addition to other EPI vaccines. The major determinant in the choice of hepatitis B vaccine appears to be affordability.⁴ Consequently, the hepatitis B vaccine that has been widely used in the EPI to date is Hepaccine-B, which is a low-cost, low-dose vaccine. However, plasma-derived vaccines will not be available indefinitely, and this necessitates testing of alternative, recombinant HBV vaccines. Heberbiovac HB vaccine (Centre for Genetic Engineering and Biotechnology, Havana, Cuba) is a preparation of yeast (*Pichia pastoris*)-derived recombinant small hepatitis B surface antigen (sHBsAg). The vaccine has been tested and licensed in several countries for use according to schedules other than that used in the South African EPI.⁷ This study reports on the safety and immunogenicity of Heberbiovac HB administered according to the World Health Organisation (WHO) accelerated schedule, viz. at 6, 10 and 14 weeks of age.

This was a phase IIIb, open, uncontrolled, multicentre study. The study protocol was independently approved by the Medicines Control Council of South Africa and the Research and Ethics Committee of the Medical University of Southern

Africa (MEDUNSA). Informed consent was obtained from 100 mothers or guardians of previously unvaccinated 6-8-week-old babies; 18 from Phedisong 1 Clinic at Ga-Rankuwa located in North West province, 59 from Hebron Clinic also located in North West, and 23 from Soshanguve Clinic III, which is in Gauteng. Babies were screened for eligibility following inclusion and exclusion criteria. All babies were then administered an intramuscular dose (right thigh) of Heberbiovac HB (10 µg/0.5 ml), together but separately with DTwP-Hib (left thigh), and OPV vaccines, at 6, 10, and 14 weeks of age. Local (pain/tenderness, redness, hardness and swelling) and systemic (e.g. fever) reactions were recorded 30 minutes after each immunisation at the clinic and thereafter daily for 7 days. In addition, a brief physical examination was conducted at enrolment and at each visit. Adverse events (AEs) were recorded during each visit throughout the trial. A sample of venous blood (2-3 ml) was drawn 4-5 weeks after the third dose, tested and quantified for antibodies to hepatitis B surface antigen (anti-HBs) (AUSAB assay, Abbott Laboratories).^{4,5} Samples with anti-HBs titres > 1 000 and > 10 000 mIU/ml were diluted 1:10 and 1:100 respectively, and re-tested. Statistical analysis for descriptive statistics for immunogenicity and safety was performed using SAS, run under Microsoft Windows NT.

A total of 93 of 100 babies received all three doses, and of these, 89 babies returned for anti-HBs testing, forming the basis of the immunogenicity results. The seroconversion rate (i.e. per cent of babies with any detectable anti-HBs) was 100% for the 89 babies, while the seroprotection rate (i.e. per cent of babies with anti-HBs ≥ 10 mIU/ml) was 97.8%, with a 95% confidence interval (CI) of 94.8 - 100% (Table I). The minimum level of anti-HBs observed was 5.0 mIU/ml and the maximum level was 15 510.0 mIU/ml. The geometric mean titre (GMT) was 1 145.2 mIU/ml, with a 95% CI of 860.2 - 1 524.5 mIU/ml.

Safety analysis was conducted on all 100 babies. Overall, the vaccine was well tolerated. A total of 37 AEs were reported from 18 babies. AEs included vomiting, diarrhoea, fever, coughing, breathing problems, blocked nose, flu, stomach cramps, sneezing and irritability. Of these AEs, 35 were remotely related to the vaccine and only 2 (both of which were fever) were considered to be probably related to the study vaccine. All post-immunisation reactions and AEs were mild or moderate and resolved without complications. No serious AEs were reported.



Table I. Distribution of anti-HBs levels and GMT values

Group	Frequency		Anti-HBs titre (mIU/ml)	GMT (mIU/ml)
	N	(%)		
Non-responders	2	(2.2)	< 10	5.7
Male	0	(0.0)	0	0
Female	2	(2.2)	5.0 - 6.5	5.7
Responders*	87	(97.8)	≥ 10	1 293.6
Male	41	(46.1)	57.7 - 1 3870.0	1 164.3
Female	45	(50.6)	70.5 - 1 5510.0	1 380.4
Low responders	2	(2.2)	10 - 99.9	63.8
Good responders	37	(41.6)	100 - 999.9	535.0
Hyper-responders	48	(53.9)	1 000	2 896.4
Total	89	(100)	< or > 10	1 145.2

*One baby had ambiguous external genitalia.

This study demonstrated that Heberbiovac HB is safe, immunogenic, and compatible with other EPI antigens, within the South African EPI schedule. In addition, Heberbiovac HB appears to be more immunogenic than other hepatitis B vaccines. The current hepatitis B vaccine being used in the South African EPI, Hepacacine-B, has previously shown a seroprotection rate of 93% and a GMT of only 257.6 mIU/ml.⁴ In contrast, the seroprotection of Heberbiovac HB was 97.8% and the GMT was 1 145.2 mIU/ml (Table I). A highly immunogenic hepatitis B vaccine is desirable for a number of reasons. First, it will reduce the number of non-responders, which is a problem with most currently available hepatitis B vaccines. Second, such a vaccine is likely to induce a heightened response with a persistent anti-HBs titre of over 10 mIU/ml. A previous study conducted among South African children showed that gradual waning of anti-HBs titre with time depends on the initial peak of anti-HBs response after the primary course of vaccination; the majority of babies who developed anti-HBs > 100 mIU/ml after the primary immunisation retained protective antibodies for a longer period,⁸ an observation in line with other findings.⁹ Third, the strong immunogenicity suggests that Heberbiovac HB could potentially be combined with other common EPI antigens (DTP-Hib) without compromising immunogenic potency. Finally, the use of hepatitis B vaccines with strong potency may induce optimal response in HIV-infected babies and may benefit at-risk patients with underlying immuno-suppression and genetic disorders. A recent review has reported that serological responses to hepatitis B vaccines are generally lower for HIV-infected children and adults than for uninfected individuals, and that individuals who respond well to the initial three-dose regimen experience a more rapid decline in antibody titre than uninfected persons.¹⁰ This would be highly

relevant in sub-Saharan Africa, where there is a high background of HIV infection, and the majority of babies are exposed to HIV through vertical transmission.

In conclusion, one other study has shown a strong protective immune response in neonates using half the licensed dosage of Heberbiovac HB. No significant differences were observed in seroprotection rate and GMT values between the licensed dosage (10 µg) and the experimental dosage (5 µg).⁷ Although this observation needs to be investigated and verified further, especially in an HIV endemic country like South Africa, the implication is that Heberbiovac HB can potentially be used as a low-dose, low-cost hepatitis B vaccine by reducing the dosage. Affordable hepatitis B vaccines will help most developing countries to sustain hepatitis B immunisation programmes, especially those countries currently relying on temporary financial aid from the Global Alliance for Vaccines and Immunisation (GAVI).

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