COST-EFFECTIVENESS OF HEPATITIS B VACCINATION IN HAEMODIALYSIS PATIENTS

M W Taal, R van Zyl-Smit

Background. Vaccination against hepatitis B virus is an important means of controlling the infection, but its role in haemodialysis patients has been questioned due to the latter's impaired immune response.

Methods. Forty-eight of 79 haemodialysis patients who were negative for antibodies to both hepatitis B surface and core antigens were entered into a vaccination programme. Standard doses of a plasma-derived vaccine were administered into the deltoid muscle at 0, 1, 2 and 4 months, and the antibody response was measured at 1 and 2 months after the third and fourth doses.

Results. The peak mean antibody titre of 372 IU/l was recorded at 1 month after the fourth dose, and the maximum response rate was achieved at 2 months after the final dose. Seroconversion occurred in 26 of 36 patients (72%) who completed the programme, and protective levels of antibody above 10 IU/l were found in 25 of 36 patients (69%). Cost analysis of the project revealed a net saving of ± R90/patient entered at the end of the first year, due to the reduced number of patients requiring monthly surveillance tests for hepatitis B surface antigen. After that, an annual saving of ± R380/patient is projected.

Conclusion. In view of the high prevalence of chronic hepatitis B carriers in the South African population, the reduction in the number of patients at risk of infection, combined with a net cost saving, makes it reasonable to recommend vaccination in all non-immune haemodialysis patients despite a reduced response rate.

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Hepatitis B virus (HBV) infection is a serious complication for the haemodialysis patient and the unit in which he or she receives treatment. The infection becomes chronic in about 50% of cases[1,2] and may progress to cause chronic liver disease, particularly following renal transplantation.[1,3-7] A high rate of nosocomial transmission means that all non-immune staff and patients in the unit are immediately placed at risk of infection.

Reports of HBV outbreaks in 19% of haemodialysis units in the UK, and an annual incidence of infection of 5.6% and 4.4% among British and American haemodialysis patients respectively,[8,9] prompted studies which demonstrated that regular screening of all patients for hepatitis B surface antigen (HBsAg) and isolation of positive patients to separate dialysis units were essential in controlling the spread of infection.[8,10,11] The development of a vaccine from HBsAg, obtained from the serum of chronic HBV carriers, provided an important new method for protecting patients against infection. However, although the vaccine induced antibodies in 93 - 100% of staff or normal controls,[12-15] an impaired response was found in haemodialysis patients and seroconversion rates varied from 55% to 83%.[14,16-23] Nevertheless, two placebo-controlled studies[12,19] demonstrated a reduction in incidence of infection from 45% to 21% and from 18% to 4% respectively.

The relatively low seroconversion rate and the associated cost have caused some to question the role of hepatitis B vaccine in haemodialysis patients. We report here the results of a study to investigate the response rate and cost-effectiveness of vaccination in local patients.

METHODS

Hepatitis B vaccination

Chronic haemodialysis patients at Groote Schuur Hospital are screened for HBsAg before starting dialysis and positive patients are treated in a separate unit. Before the introduction of vaccination, negative patients were tested monthly for HBsAg as a surveillance measure. In this study, all HBsAg-negative patients were tested for antibodies to HBsAg (anti-HBs) and immunoglobulin G (IgG) antibodies to hepatitis B core antigen (anti-HBc IgG), and those who were negative for both were included in the vaccination programme. A plasma-derived vaccine containing heat-inactivated HBsAg and aluminium phosphate was used (Hepaccine-B Vaccine, Cheil Foods and Chemicals Inc.). The standard dose of 3 µg was administered intramuscularly into the deltoid region at 0, 1, 2 and 4 months. Anti-HBs antibodies were measured at 1 and 2 months after the third dose, and at 1 and 2 months after the final dose (i.e. at 3, 4, 5 and 6 months after the first dose). Data from studies of homosexual men indicate that the minimum antibody level required for protection against HBV infection is 10 IU/l.[24] More recently, however, it has been suggested that vaccination protocols should aim to maintain antibody levels at > 100 IU/l or optimum protection.[25]

Patient folders were scrutinised and the following details recorded: age, race, gender, time on haemodialysis, number of previous blood transfusions and number of previous renal transplants.

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Assay techniques

HBsAg was detected using a radio-immunoassay (AUSRIA, Abbott Laboratories). Antibodies to HBsAg and anti-HBc IgG were both measured with microparticle enzyme immunoassays (IMx AUSAB and IMx CORE, Abbott Laboratories). All tests were performed by the virology laboratory at Groote Schuur Hospital.

Statistical analysis

Data for patient age were approximately normally distributed and Students *t*-test was used for testing differences between the means of groups. Data for other continuous variables were not normally distributed and the Mann-Whitney test was used instead. A chi-square (χ^2) test was used for 2×2 tables of frequency. *P*-values of < 0.05 were regarded as significant.

RESULTS

HBV antibodies before vaccination

At the time of pre-vaccination screening, there were 79 HBsAg-negative patients on chronic haemodialysis. Results of anti-HBs and anti-HBc IgG testing are shown in Fig. 1. Twenty-six patients (33%) were positive for both antibodies, indicating that they had previously been infected with HBV but had cleared the virus. Five patients (6%) were positive for anti-HBs but negative for anti-HBc, suggesting previous vaccination. An analysis of data to test for relationships between previous HBV infection and demographic or treatment-related factors is shown in Table I. The prevalence of previous infection was 40% in black patients, 35% in those of mixed racial origin, and 0% in white patients. There was no difference in the mean age of previously infected and uninfected patients. Males and females had a similar prevalence of previous infection. Means for time on haemodialysis, number of previous blood transfusions and number of previous renal transplants were also not significantly different.

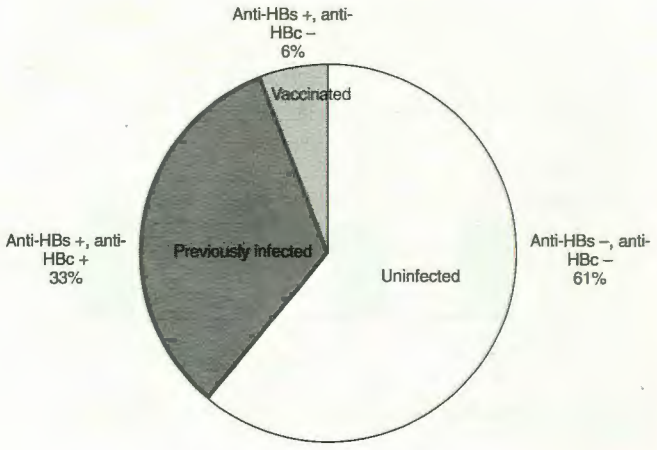

Fig. 1. HBV antibody status prior to vaccination.

Response to vaccination

Forty-eight patients were negative for both antibodies and therefore eligible for vaccination. Three received renal transplants before the vaccination was commenced and thus 45 received the first dose. One patient died, and 8 received renal transplants during the study, resulting in exclusion from the vaccination protocol. Therefore 36 received all four doses of vaccine and had their antibody response measured. No patients reported adverse effects related to vaccination.

Fig. 2 illustrates the mean antibody titres in those responding to the vaccine at different time intervals. After the initial three doses, the peak geometric mean titre (GMT) of 279 IU/l was recorded at 1 month after the third dose (month 3), although there was a further rise in antibody titre from month 3 to month 4 in 15 patients. Following the booster dose, the peak GMT (372 IU/l) was again noted at 1 month after administration (month 5). Most patients had a decline in antibody level from month 5 to month 6, and only 4 had a further increase.

Table I. Demographic data and possible risk factors for previous HBV infection in chronic haemodialysis patients

	Total	Anti-HBc +	Anti-HBc–	*P*-value
Number	79	26	53	
Black	20	8	12	0.046†
Mixed race	52	18	34	0.064†
White	7	0	7	
Female	38	11	27	0.47‡
Male	41	15	26	
Mean age (years)	43.2 (11.8)	44 (9.3)	42.8 (12.9)	0.68§
Months on HD*	35 (37.9)	38 (45)	33.5 (34.4)	0.70§
Transfusions (units)*	4.6 (7.9)	3.9 (9.3)	5 (7.3)	0.12§
Renal transplants*	0.81 (0.92)	0.65 (0.8)	0.89 (0.97)	0.42§

* Values for months on HD, transfusion units and renal transplants are expressed as mean (standard deviation).
† *P*-value for comparison with white patients.
‡ *P*-value for comparison with males.
§ *P*-value for comparison between anti-HBc-positive and negative patients.
HD = haemodialysis.

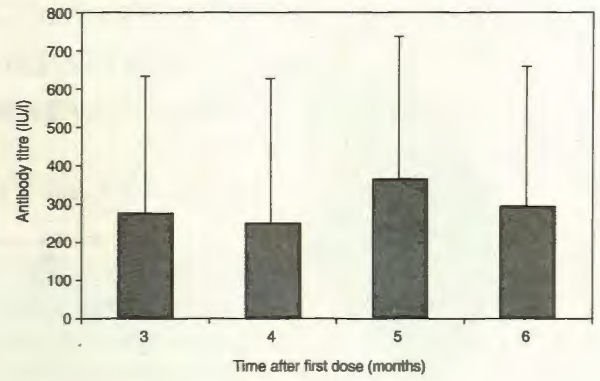

Fig. 2. Mean antibody titres ± standard deviation at different intervals post vaccination.

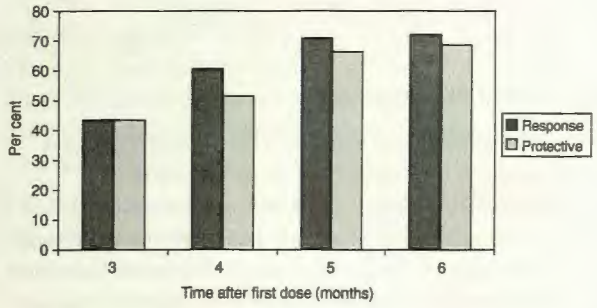

Fig. 3. Number of patients with antibody response and protective antibody levels at different intervals post vaccination.

Fig. 3 illustrates the number of patients who had responded and the number who had achieved the minimum protective antibody level of 10 IU/l at different times post-vaccination. There was a progressive increase in the number responding and the number achieving protective levels from month 3 to month 6. The maximum response rate was achieved at 2 months after the fourth dose of vaccine, when 26 of 36 patients (72%) were anti-HBs-positive and 25 of 36 (69%) had achieved protective levels.

Cost analysis of vaccination

A cost analysis of the vaccination programme was performed and results are shown in Table II. Prices for laboratory investigations were based on South African Institute for Medical Research (SAIMR) rates for public sector institutions. The cost of the vaccine was based on the tender price at Groote Schuur Hospital. The total cost of the vaccination programme was R19 763.00 (± R250/patient entered). However, this could be reduced to R12 853.70 (± R160/patient) in future by measuring antibody response only on one occasion at 2 months after the fourth dose of vaccine. Savings result from the fact that patients identified to have immunity following a previous infection and those who develop protective levels of antibodies after vaccination, no longer require monthly screening for HBsAg. Thus the programme will have resulted in a net saving of R7 223.90 (± R90/patient) at the end of the first year.

After the first year the cost of maintaining protective antibody levels in previously vaccinated patients consists of the cost of an annual anti-HBs level and booster doses of vaccine, which should be given to those whose levels have dropped below the recommended level of 100 IU/l. In the current analysis the figure of 16 is an estimate based on the number of patients with a titre of < 200 IU/l immediately after vaccination, who may be expected to have a titre of < 100 IU/l after 1 year. Therefore after the first year, antibody screening and vaccination of this cohort of patients can be expected to result in an annual net saving of R30 092.00 (± R380/patient entered).

Discussion

Response to vaccination

Using a standard dose of a plasma-derived vaccine given intramuscularly at months 0, 1, 2 and 4, we achieved a response rate (72%) and peak GMT (372 IU/l) similar to that reported by other centres. It is difficult to compare results directly because of the differences in vaccine type, dose, dosage schedule and patient population. However, our results are very similar to those of Benhamou *et al.*,[20] who used the same schedule, but a different plasma-derived vaccine. Previous studies suggest that response rates with plasma-derived (46 - 93%)[12,15,16,18-20] and recombinant vaccines (54 - 83%)[14,17,23] are similar.

The administration of a booster dose after the initial three doses led to an increase in seroconversion rate from 61% to 72% and an increase in the number of patients with protective antibody levels from 53% to 69%. The peak GMT rose from 279 IU/l to 372 IU/l. Although these differences are not statistically significant, a randomised controlled trial has previously demonstrated a significantly improved response when a four-dose schedule was compared with the standard three-dose schedule in haemodialysis patients.[20] Shortening the dosage schedule by giving the booster dose at 4 months instead of 6 months makes the vaccination programme slightly easier to manage, and does not appear to affect the response adversely. Determination of the optimum vaccine, dose and schedule in haemodialysis patients requires further randomised controlled trials.

Cost-effectiveness of vaccination

In this study the initial cost of antibody screening and vaccination was R250/patient. The largest component of this cost is the antibody assays, which were done repeatedly to determine the optimum time for testing in the future. Future vaccination programmes will require only pre-vaccination testing and a single post-vaccination assay at 2 months after the booster dose, which will reduce the cost to approximately R160/patient. The initial costs are offset by the large saving resulting from the reduced need for monthly HBsAg testing. Therefore by the end of the first year the current programme will have resulted in a net saving of R90/patient. With the use

Table II. Cost analysis of a hepatitis B vaccination programme

	Cost/item (Rand)*	Number	Total (Rand)
Cost			
Pre-vaccination testing			
Anti-HBs	59.20	79	4 676.80
Anti-HBc	59.20	79	4 676.80
			9 353.60
Post-vaccination testing			
Anti-HBs 1	59.20	42	2 486.40
Anti-HBs 2	59.20	38	2 249.60
Anti-HBs 3	59.20	37	2 190.40
Anti-HBs 4	59.20	36	2 131.20
			9 057.60
Vaccine			
Initial course (3 doses)	8.10	126	1 020.60
Booster dose	8.10	36	291.60
Incomplete courses	8.10	5	40.50
			1 352.70
Total cost			19 763.90
Total cost (1 post-vaccination anti-HBs level)			12 853.70
Annual cost (after first year)			
Annual anti-HBs level	59.20	25	1 480.00
Booster dose vaccine	8.10	16	129.60
			1 609.60
Saving			
First year			
HBsAg (vaccinated patients with protective levels)	51.80	209	10 826.20
HBsAg (patients with immunity after infection)	51.80	312	16 161.60
			26 987.80
Annual after first year			
HBsAg (vaccinated patients with protective levels)	51.80	300	15 540.00
HBsAg (patients with immunity after infection)	51.80	312	16 161.60
			31 701.60
Net cost			
First year			–7 223.90
First year (1 post-vaccination anti-HBs level)			–14 134.10
Annual after first year			–30 092.00

*The rand-dollar exchange rate was ±R8.1 to the dollar at the time of going to press.

of only one post-vaccination antibody level, the saving will be R180/patient. After the first year, the cost of maintaining protective antibody levels is relatively small, and therefore an annual saving of R380/patient can be expected. These figures do not take into account the fact that patients are constantly being transplanted and consequently leave the dialysis programme. However, the mean time on dialysis at the start of the programme was 35 months (Table I), indicating that the majority of patients will be on dialysis long enough for net saving to occur.

We observed a zero incidence of new HBV infections during the 40 months before the vaccination programme, demonstrating that existing measures to prevent the infection were effective. It would therefore be difficult to demonstrate an added benefit due to vaccination. Nevertheless, given the high prevalence of HBV carriers in South Africa,[26,27] haemodialysis patients remain at risk of acquiring HBV infection in the community and secondary transmission to other patients could have serious consequences for the individuals affected and for the unit as a whole. In order to contain an outbreak, all infected individuals would have to be transferred to an isolation unit and no new patients could be accepted into the unit until there was reasonable certainty that no further seroconversions would occur (i.e. for about 6 months). In addition, re-use of all

dialysers would have to be discontinued for the same period. These measures would sèverely disrupt the delivery of dialysis support to patients and would also lead to greatly increased costs (R200 000 - R300 000) due to the suspension of re-use. Therefore it would be important to consider any measure that could further reduce the risk of infection. The fact that hepatitis B vaccination has minimal adverse effects and results in cost saving means that it can be recommended even though the response rate is lower than in healthy subjects and additional benefit is difficult to prove in our setting.

We conclude that all patients should be screened for hepatitis B antibodies and vaccinated as required on or before commencement of haemodialysis.

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References

1. London WT, Drew JS, Lustbader ED, Werner BG, Blumberg BS. Host responses to hepatitis B infection in patients in a chronic hemodialysis unit. *Kidney Int* 1977; **12:** 51-58.
2. Szmuness W, Prince AM, Grady GF, *et al.* Hepatitis B infection. A point-prevalence study in 15 US hemodialysis centres. *JAMA* 1974; **227:** 901-906.
3. Dueymes JM, Bodenes-Dueymes M, Mahe JL, Herman B. Detection of hepatitis B viral DNA by polymerase chain reaction in dialysis patients. *Kidney Int Suppl* 1993; **41:** S161-166.
4. Josselson J, Kyser BA, Weir MR, Sadler JH. Hepatitis B surface antigenemia in a chronic hemodialysis program: lack of influence on morbidity and mortality. *Am J Kidney Dis* 1987; **9:** 456-461.
5. Harnett JD, Parfrey PS, Kennedy M, Zeldis JB, Steinman TI, Guttmann RD. The long-term outcome of hepatitis B infection in hemodialysis patients. *Am J Kidney Dis* 1988; **11:** 210-213.
6. Miller DJ, Williams AE, Le Bouvier GL, Dwyer JM, Grant J, Klatskin G. Hepatitis B in hemodialysis patients: significance of HBeAg. *Gastroenterology* 1978; **74:** 1208-1213.
7. Parfrey PS, Forbes RD, Hutchinson TA, *et al.* The impact of renal transplantation on the course of hepatitis B liver disease. *Transplantation* 1985; **39:** 610-615.
8. Polakoff S, Cossart YE, Tillett HE. Hepatitis in dialysis units in the United Kingdom. *BMJ* 1972; **3:** 94-99.
9. Garibaldi RA, Forrest JN, Bryan JA, Hanson BF, Dismukes WE. Hemodialysis-associated hepatitis. *JAMA* 1973; **225:** 384-389.
10. Polakoff S, Tillett HE. Decrease in the incidence of hepatitis in dialysis units associated with prevention programme. *BMJ* 1974; **4:** 751-754.
11. Najem GR, Louria DB, Thind IS, *et al.* Control of hepatitis B infection. The role of surveillance and an isolation hemodialysis center. *JAMA* 1981; **245:** 153-157.
12. Desmyter J, Colaert J, De Groote G, *et al.* Efficacy of heat-inactivated hepatitis B vaccine in haemodialysis patients and staff. Double-blind placebo-controlled trial. *Lancet* 1983; **2:** 1323-1328.
13. Crosnier J, Jungers P, Courouce AM, *et al.* Randomised placebo-controlled trial of hepatitis B surface antigen vaccine in French haemodialysis units: I, Medical staff. *Lancet* 1981; **1:** 455-459.
14. Jilg W, Schmidt M, Weinel B, *et al.* Immunogenicity of recombinant hepatitis B vaccine in dialysis patients. *J Hepatol* 1986; **3:** 190-195.
15. Lelie PN, Reesink HW, de Jong-van Manen ST, Dees PJ, Reerink-Brongers EE. Immunogenicity and safety of a plasma-derived heat-inactivated hepatitis B vaccine (CLB). Studies in volunteers at a low risk of infection with hepatitis B virus. *Am J Epidemiol* 1984; **120:** 694-702.
16. Stevens CE, Alter HJ, Taylor PE, Zang EA, Harley EJ, Szmuness W. Hepatitis B vaccine in patients receiving hemodialysis. Immunogenicity and efficacy. *N Engl J Med* 1984; **311:** 496-501.
17. Bruguera M, Cremades M, Mayor A, Sanchez Tapias JM, Rodes J. Immunogenicity of a recombinant hepatitis B vaccine in haemodialysis patients. *Postgrad Med J* 1987; **2:** 155-158.
18. Kohler H, Arnold W, Renschin G, Dormeyer HH, Meyer zum Buschenfelde KH. Active hepatitis B vaccination of dialysis patients and medical staff. *Kidney Int* 1984; **25:** 124-128.
19. Crosnier J, Jungers P, Courouce AM, *et al.* Randomised placebo-controlled trial of hepatitis B surface antigen vaccine in French haemodialysis units: II, Haemodialysis patients. *Lancet* 1981; **1:** 797-800.
20. Benhamou E, Courouce AM, Jungers P, *et al.* Hepatitis B vaccine: randomized trial of immunogenicity in hemodialysis patients. *Clin Nephrol* 1984; **21:** 143-147.
21. Lelie PN, Reesink HW, de Jong-van Manen ST, Dees PJ, Reerink-Brongers EE. Immune response to a heat-inactivated hepatitis B vaccine in patients undergoing hemodialysis. Enhancement of the response by increasing the dose of hepatitis B surface antigen from 3 to 27 micrograms. *Arch Intern Med* 1985; **145:** 305-309.
22. Bruguera M, Cremades M, Rodicio JL, *et al.* Immunogenicity of a yeast-derived hepatitis B vaccine in hemodialysis patients. *Am J Med* 1989; **87:** 30S-32S.
23. Guan R, Tay HH, Choong HL, Yap I, Woo KT. Hepatitis B vaccination in chronic renal failure patients undergoing haemodialysis: the immunogenicity of an increased dose of a recombinant DNA hepatitis B vaccine. *Ann Acad Med Singapore* 1990; **19:** 793-797.
24. Hadler SC, Francis DP, Maynard JE, *et al.* Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med* 1986; **315:** 209-214.
25. Eddleston A. Modern vaccines. Hepatitis. *Lancet* 1990; **335:** 1142-1145.
26. Schoub BD. Estimations of the total size of the HIV and hepatitis B epidemics in South Africa. *S Afr Med J* 1992; **81:** 63-66.
27. Tucker TJ, Kirsch RE, Louw SJ, Isaacs S, Kannemeyer J, Robson SC. Hepatitis E in South Africa: evidence for sporadic spread and increased seroprevalence in rural areas. *J Med Virol* 1996; **50:** 117-119.

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HISTORY OF MEDICINE

TUMOURS AND CANCERS IN GRAECO-ROMAN TIMES

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In Graeco-Roman times all tumours (Greek: *onkoi*, abnormal swellings) were considered to be of inflammatory origin, the result of unfavourable humoural fluxes, and caused by an extravascular outpouring of fluid into tissue spaces. The neoplastic nature of tumours is a more recent concept, barely two centuries old. In Hippocratic literature tumours were mainly classified as *karkinômata*, *phumata*, and *oidêmata*. *Phumata* included a large variety of tumours, inflammatory and neoplastic in origin, and mostly benign (in modern terms), while *oidêmata* were soft, painless tumours and even included generalised oedema (dropsy). Although all categories possibly included occasional cancers, the vast majority of what appears to have been malignant tumours were called *karkinoi karkinômata* (Latin: *cancrum/carcinoma*). There was, however, no recognition of benign and malignant, primary and secondary tumours, in the modern sense.

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Herodotus tells us that at the turn of the 6th century BC, Atossa, the wife of Darius the Great, was cured of a breast tumour (*phuma*) by a captive Greek physician, Democedes.[1] The readiness with which Democedes promised a cure and the ease with which he attained this, points to a benign breast tumour rather than a cancer.[2] The Hippocratic writings mention a woman from Abdera who had a breast tumour and a bloody discharge from the nipple; she was diagnosed as having a *karkinôma* and died of the lesion.[3] This was most likely a cancer as we know it today. However, the Graeco-Roman theories of tumour formation and carcinogenesis differed radically from our modern concepts, which originated as late as the 19th century. In the present study the theories of tumour formation in antiquity, and the nature of tumours reported, are reviewed.

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