

Intradermal Vaccination of Adults with Three Low Doses (2 µg) of Recombinant Hepatitis B Vaccine. I. Seroconversion Rate and Adverse Effects

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A total of 250 dentists (53.6% men and 46.4% women), with a mean age of 35.1 ± 9.8 years, were submitted to serological tests for the diagnosis of hepatitis B (HB) – HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe – using a radioimmunoassay. One or more of these markers were detected in 78 individuals (31.2%) who were excluded from the group to be vaccinated. Of the 172 HB-susceptible individuals, 135 (78.5%) responded to the call and were intradermally injected with three 2 µg doses of the Belgian HB recombinant vaccine, applied at an interval of one month between the 1st and 2nd dose and of five months between the 2nd and 3rd dose. A new determination of HB markers carried out 50 days after the 3rd dose showed that 110 (81.5%) individuals had become anti-HBs positive (65.5% good responders and 34.5% poor responders). Mean serum anti-HBs titer of these 110 dentists was 42.4 U S/N, similar in both sexes. The adverse effects analyzed in 106 dentists were: (a) local: pain (12.3%), burning sensation (14.1%), pruritus (25.5%), erythema (28.3%), local heat (18.9%), and a hypochromic spot (32.1%); (b) systemic (4.7%): discomfort in two patients, and fever, anorexia, and asthenia in one patient each. Intradermal administration of a fourth 2 µg vaccine dose to 39 dentists (poor or non-responders) increased the total number of anti-HBs-positive individuals from 110 (81.5%) to 114 (84.4%), with the number of good responders increasing from 72 (65.5%) to 85 (74.6%). We conclude that the Belgian recombinant vaccine applied in the scheme used here induces a high rate of seroconversion and causes only mild and transitory adverse effects.

Key words: hepatitis B vaccine - low-dose regimen - seroconversion - adverse effects

The identification and isolation of the etiological agent of hepatitis B (HB), as well as the subsequent discovery of safe and efficient vaccines, represent relevant scientific advancements obtained over the last few decades, which brought great benefits to humanity. However, HB continues to show a high incidence in many countries worldwide, remaining a significant medical-social problem that requires the design and implantation of treatment and prevention programs by public health authorities.

Hepatitis B virus (HBV) is one of the main agents of acute and chronic hepatitis worldwide (Evans & London 1998). According to these authors, 250 to 350 million chronic HBV carriers exist in the world, and more than 50 million individuals (about 5% of the world population) are estimated to be infected annually with this virus, while about one million people die as a consequence of the effects of the disease. Among chronic HBV carriers, 25% are at risk to develop chronic active HB, with eventual installation of cirrhosis and hepatocarcinoma (Zuckerman

1999). In addition to presenting these complications, chronic carriers serve as a source of infection for susceptible individuals (Shapiro 1993). In the United States, a country of low HB endemicity, about 300,000 new cases of infection are notified per year, most of them involving young adults; more than 10,000 individuals with acute HB are hospitalized per year, with about 300 of them dying of the disease (Robinson 2000). In Brazil, where notification of HB became compulsory only recently (Brasil, Ministério da Saúde 1999), the incidence of the disease is not precisely known. However, it is known that HB endemicity is high in the western Amazon region and in areas of the states of Espírito Santo, Santa Catarina and southeastern Paraná, intermediate in the eastern Amazon region, in the Northeast and Center-West, and low in the Southeast and South of Brazil (Costa et al. 1997).

The incidence and prevalence of HBV infection, as well as the rates of naturally acquired immunity or immunity provided by vaccination, are established based on the results of specific serological tests that permit the detection and, eventually, the quantification of antibodies (anti-HBs, anti-HBc, and anti-HBe) and antigens (HBsAg and HBeAg) in blood, also called serological markers or, simply, markers of HBV infection (Sjogren 1996, Mahoney 1999). Protection against HBV infection is conferred by the presence of anti-HBs in serum, an antibody responsible for the specific immunity resulting from natural infection or vaccination.

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The main current measure of HB prevention is re-presented by vaccines, which were introduced in routine use at the beginning of the 1980's. Active immunization against HB started with the utilization of a vaccine consisting of HB surface antigen or HBsAg – obtained from plasma of chronic HBV carriers – submitted to a process of purification and viral inactivation (human plasma vaccine). Still in the 1980's, another type of HB vaccine was developed using DNA technology (Troisi & Hollinger 1990, CDC 1990). The first recombinant vaccines against HB cloned in *S. cerevisiae* were licensed for commercialization in Belgium (SmithKline Beecham) in 1986, and in the United States (Merck, Sharp & Dohme) in 1989 (De Wilde et al. 1985, Hilleman 1986, McAleer et al. 1984, Zajac et al. 1986). Among immunocompetent adults younger than 40 years, intramuscular administration of three vaccine doses (20 µg and 10 µg of Belgian and North-American recombinant vaccines, respectively; 0, 1, and 6 month schedule) induced seroconversion in 90% to 95% of individuals (CDC 1990, Hadler & Margolis 1992, Krugman & Stevens 1994, Mahoney & Kane 1999). Using the above immunization scheme, these vaccines have demonstrated 80 to 95% protection efficacy in field studies (Stevens et al. 1987, CDC 1990).

The efficacy of a HB vaccine is directly related to the appearance of antibodies against HBsAg (anti-HBs) in serum of vaccinated susceptible people (CDC 1990, Krugman & Stevens 1994).

In 1992 the World Health Organization standardized universal immunization against HB (van Damme et al. 1997). Two complementary strategies were soon suggested to increase vaccine coverage, i.e., sensitization of health workers and a reduction in the costs of the immunizing agents (Krahn & Detsky 1992). One possibility to reduce the cost of HB vaccination is to decrease the amount of antigen in each dose. Numerous studies have been carried out with this objective, mainly involving adults receiving three intradermal injections of a tenth of the usually employed dose in different regimens (mainly the 0, 1, and 6 month scheme). The results obtained both with human plasma vaccines and recombinant vaccines were satisfactory in most studies (for reviews, see Bryan et al. 1992, Hadler & Margolis 1992), as well as in investigations mentioned in the discussion of this paper.

The objective of the present study was to determine the immune response to the Belgian recombinant vaccine of HB-susceptible adults receiving three low doses (2 µg) of the vaccine by the intradermal route, and to compare the results obtained, as well as the type and incidence of adverse effects, with those described in the literature.

PATIENTS AND METHODS

The 250 dentists included in this study were enrolled in the "Hepatitis B Prevention Program for Dentists from Londrina and Region", organized by the Associação Odontológica do Norte do Paraná.

Subjects received detailed information and gave written consent to participate in the Program. Data was collected using a standard questionnaire and blood samples were collected to carry out the serological tests for the diagnosis of the HBV infection, from December,

1989 to June, 1990. Another blood sample was collected from vaccinees 50 days after the application of the third dose, for immune response assessment.

The tests for the detection of serological markers of HBV infection (HBsAg, anti-HBs, total anti-HBc, HBeAg, and anti-HBe) were carried out at the Laboratory of Clinical Analyses, Regional University Hospital of Northern Paraná, State University of Londrina, by radioimmunoassay using reagents from Abbott Laboratories, US. The results were interpreted according to the criteria established by the manufacturer. With respect to HBsAg, total anti-HBc, HBeAg, and anti-HBe, we simply considered and reproduced the results provided by the laboratory (positive or negative, reactive or non-reactive), without taking into account the quantitative aspects of the results. The anti-HBs titer was calculated based on the comparison between the serum concentration of this antibody in each individual, expressed as counts per minute (cpm), and the cut-off corresponding to the mean titer of negative controls, also expressed as cpm, multiplied by 2.1. In the first blood sample collected before application of the first vaccine dose, the result was considered to be positive when the serum anti-HBs concentration was equal to or higher than the cut-off, and negative when it was lower than the cut-off.

Based on the test results of the first serum sample, the absence of any previous HBV infection (individuals susceptible to HB) was defined when none of the serological HB markers was detected in serum, and naturally acquired immunity against HB was defined when anti-HBs and anti-HBc, associated or not with anti-HBe, were present in serum (Decker 1998). For dentists receiving the three vaccine doses, we adopted the criterion that natural HBV infection had occurred during vaccination when anti-HBc antibodies, associated or not with HBsAg or anti-HBs, were present in serum (Decker 1998).

The complete vaccine scheme was indicated only to dentists who were susceptible to viral infection. They were submitted to three 2 µg doses of the Belgian recombinant vaccine administered intradermally in the left deltoid region in October and November 1990 and in April 1991. The vaccine doses were administered at an interval of one month between the first and second dose and of five months between the second and third dose (0, 1, and 6 month scheme), based on the knowledge that the usual dose of this vaccine indicated for adults is 20 µg administered intramuscularly in the same regimen (CDC 1990).

An immune response (seroconversion) was considered to be present when only anti-HBs antibodies at a concentration equal to or higher than 2.1 U S/N were detected by radioimmunoassay in the blood sample collected 50 days after application of the third dose (Szmunes et al. 1980). The following criterion was adopted for interpretation of the results: an anti-HBs titer lower than 2.1 U S/N indicates the absence of seroconversion (susceptibility), a titer between 2.1 and 10 U S/N indicates seroconversion with a low response, corresponding to poor responders or hyporesponders, and a titer higher than 10 U S/N indicates the development of solid immunity, corresponding to good responders (Peard 1986, Ferraz et al. 1992). In the radioimmunoassay,

S (sample) corresponds to the anti-HBs titer of the sample, in cpm, and *N* (negative) corresponds to the mean count obtained for negative controls, also in cpm.

Vaccinated dentists who did not show seroconversion and those considered to be poor responders were advised to take a fourth 2 µg dose of the same vaccine by the intradermal route. These individuals were again submitted to all serological tests for the diagnosis of HBV infection one month after application of the fourth vaccine dose.

Adverse effects were characterized based on a standard questionnaire applied to individuals who received all three vaccine doses.

The chi-square test or Fisher exact test was used to establish correlations between qualitative variables and to compare proportions. Quantitative variables were compared between samples using the Student t-test or the Wilcoxon Rank Sum test for two samples. The level for significance was set at 0.05 for all tests. Statistical analysis was performed with a microcomputer using the Epi Info system (Dean et al. 1990) for tabulation and analysis of the data.

RESULTS

Of the 250 dentists, 134 (53.6%) were males and 116 (46.4%) were females. The age of the 250 dentists ranged from 22.1 to 85.2 years, with a mean age of 35.11 ± 9.79 years. Age ranged from 22.1 to 85.2 years (37.92 ± 11.16) among males, and from 22.9 to 50.9 years (31.87 ± 6.61) among females; 191 (76.4%) individuals were white and 59 (23.6%) were of Asian origin.

According to the results of the serological tests performed on 250 dentists before application of the first vaccine dose, 78 (31.2%) presented one or more HB markers. Four (1.6%) subjects showed HBsAg in association with anti-HBc and anti-HBe, a result that was reproducible more than six months later. The presence of anti-HBs in serum was demonstrable in 68 (27.2%) dentists, and was associated with anti-HBc in 61 of them (31 of whom also presented anti-HBe). Serum anti-HBc alone was detected in five dentists (results confirmed upon a second test) and in simple association with anti-HBe in one. These six dentists were instructed to receive a usual dose regimen of the HB vaccine. None of the 78 dentists was positive for HBeAg. The four dentists with an HBsAg-positive serological test were referred for clinical evaluation. The 61 dentists with positive serological tests for anti-HBs and anti-HBc were informed that they had been naturally infected with HBV and that they were immune to HB. All 78 patients with a positive serological test for one or more markers were excluded from the study group used to assess the immune response to vaccination.

The anti-HBs titer of the 61 dentists who presented serum anti-HBs and anti-HBc (i.e., those with naturally acquired hepatitis B immunity) ranged from 2.5 to 194.7 U S/N, with a mean titer of 57.8 U S/N and with the mean anti-HBs concentration being similar in both sexes.

The 172 dentists in whom no marker of HBV infection was detected in serum were included in the group of patients who should receive the HB vaccine. Of these, 135 (78.5%) responded to the call, received the complete regimen and carried out the serological tests (HBsAg, anti-

HBs, total anti-HBc, HBeAg, and anti-HBe) 50 days after application of the third vaccine dose. At the time of the application of each vaccine dose against HB, none of the patients complained of disease and all were apparently healthy. The age of the 135 individuals ranged from 22.1 to 60.3 years (mean = 33.78 ± 8.42); the age of the 71 male dentists ranged from 22.1 to 60.3 years (mean = 36.31 ± 9.48), while the age of the 64 female dentists ranged from 22.9 to 46.6 years (mean = 30.97 ± 5.98). The mean age was significantly higher in male than in female dentists ($p < 0.05$). Ninety seven (7.9%) of the dentists were white and 38 (28.1%) were of Asian origin.

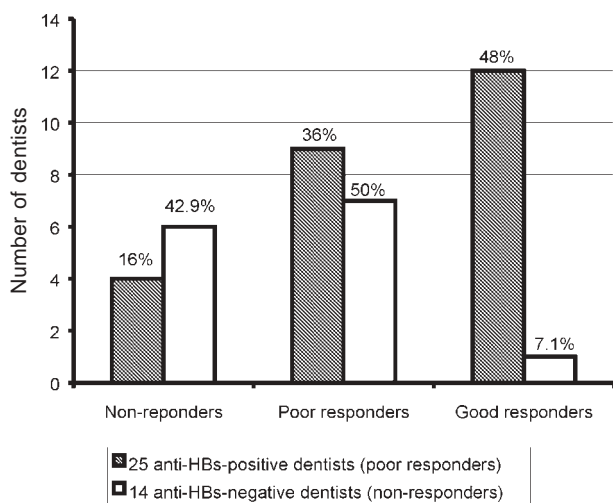
The distribution of the 135 dentists according to the type of response to vaccination and sex is shown in the Table. The proportion of individuals among the three groups (good responders, poor responders, and non-responders) was similar for the two sexes. As can be seen in this Table, a response to vaccination was observed in 110 (81.5%) of the 135 vaccinees, with only anti-HBs being present at protective titers. Among the 110 dentists who responded to the vaccination, 72 (65.5%) showed a good response and 38 (34.5%) a poor response. No significant difference in the frequency of the presence or absence of a vaccination response was observed between sexes. Among responders, mean age was significantly higher in men (36.2 ± 9.4 vs 30.7 ± 5.6 for men and women, respectively; $p < 0.05$). The same was not true among male and female poor responders (34.2 ± 8.5 vs 32.9 ± 5.1) and non-responders (36.6 ± 8.4 vs 32.8 ± 8.4).

Mean serum anti-HBs concentration of the 110 dentists who responded to vaccination ranged from 2.3 to 256.4 U S/N, with a mean titer of 42.4 U S/N, and with a similar mean anti-HBs concentration being observed for the two sexes.

Of the 135 vaccinees, 106 (78.5%) – 59 (55.7%) men and 47 (44.3%) women – responded to a questionnaire about adverse effects of vaccination. The occurrence of local adverse effects was reported 139 times, 60 times (44.1%) by male dentists and 79 times (56.8%) by female dentists. The dose after which the local adverse effects occurred was not reported by all dentists. The proportion of dentists of each sex who presented the local adverse effects cited was similar, at least with respect to those in whom the observed frequency permitted statistical analysis. Local pain, burning sensation, pruritus, erythema, and heat manifested on the same day of vaccine application. Pain was reported by 13 (12.3%) of the 106 vaccinees. A burning sensation was reported by 15 (14.1%) vaccinees, with five of them not reporting after which dose this symptom occurred. Pruritus was observed in 27 (25.5%) vaccinees, with four not reporting after which dose the symptom occurred. Erythema was reported by 30 (28.3%) vaccinees, with two of them not reporting after which dose this symptom occurred. Twenty (18.9%) of the vaccinated dentists complained of local heat, with one dentist not reporting after which dose this symptom occurred. Thirty-four (32.1%) vaccinees reported the presence of a small hypochromic persistent spot at the site of application; 11 of them did not report after which dose this sign occurred; the hypochromic spot appeared after the three doses in 16 (69.6%), after the first dose in 4

(17.4%), and in one (4.3%), after the second, after the third and after the first and second doses, respectively. Systemic adverse effects were only observed in 5 (4.7%) of the 106 vaccinated dentists, all of them females. Fever and general discomfort were reported by one and by two dentists, respectively, after the first and the second vaccine doses in all cases. In addition to these systemic adverse effects, two dentists reported other reactions: one showed a clinical picture which was called "rhinitis" (together with general discomfort after the first and second dose, and local pain after the third dose), and the other reported signs and symptoms of "fatigue", together with pain at the injection site. Only one female subject of the 106 dentists reported a decrease in productivity during work on the day when receiving the first vaccine dose.

A fourth intradermal 2 µg dose of the same vaccine was applied six months after the third dose to the 39 dentists previously vaccinated who responded to the call, i.e., 14 (56%) of 25 dentists without seroconversion (non-responders) and 25 (80%) of 38 poor responders. The response to the fourth vaccine dose was evaluated by the detection and quantification of anti-HBs in serum one month after its application (Figure). Twelve (48%) of the 25 poor responders became good responders, 9 (36%) continued to be poor responders, and 4 (16%) became anti-HBs-negative, whereas 6 (42.9%) of the 14 non-responders continued to be anti-HBs negative and 8 (57.1%) became anti-HBs positive, one showing a good response and seven showing a poor response. None of the other HBV infection markers (HBsAg, anti-HBc, HBeAg, and anti-HBe) was detected in the serum of any of the dentists who received the fourth vaccine dose one month after its application. Administration of the fourth intradermal 2 µg dose to the previously vaccinated 39 non-responding and poorly responding dentists who responded to the call increased the total number of vaccine responders from 110 (81.5%) to 114 (84.4%), with the number of good responders raising from 72 (65.5%) to 85 (74.6%).



Hepatitis B (HB) immunity status of the 25 anti-HBs-positive dentists (poor responders) and of the 14 anti-HBs-negative dentists (non-responders) one month after intradermal application of the fourth 2 µg vaccine dose.

DISCUSSION

The proportion of men and women was similar among the 250 dentists included in the present study (134 vs 116, $p > 0.05$); the mean age of male and female dentists was also similar, although there was a significant predominance ($p < 0.05$) of female professionals in the ≤ 40 -year age range and of male dentists in the > 40 -year age range. White dentists were more frequent than dentists of Asian origin, with a significant difference in the proportion of white and Asian dentists being observed for the groups aged more than 40 years and 40 years or less. However, the proportion of white and Asian dentists was similar for the two sexes in these two age groups.

Sixty-five (26%) of the 250 dentists studied presented serological HB markers that indicated the presence of naturally acquired immunity in 61 and persistent HBV infection resulting from a past natural HBV infection in four.

Seroconversion was observed in 110 (81.5%) of the 135 dentists who received three HB vaccine doses (Table). The mean age of responders and non-responders was similar for male and female dentists. Among the responders, 72 (65.6%) showed a good response and 38 (34.5%) showed a poor response, with the type of response being similar in the two sexes, as was the mean anti-HBs concentration in those who seroconverted. The mean anti-HBs titer of the 110 vaccinees who showed seroconversion was 42.4 U S/N, a value only slightly lower than the mean serum titer (57.8 U S/N) observed for the 61 dentists with naturally acquired immunity to HB.

The results of the present investigation were similar to those reported in most published studies carried out with recombinant HB vaccines applied in small doses by the intradermal route. Intradermal application of the North-American recombinant vaccine (Merck, Sharp & Dohme) in 1 µg or 2 µg doses at 0, 1, and 6 months or 0, 1, and 5 months to 748 adults showed seroconversion rates ranging from 55% to 94% (mean 78.5%) in five of the studies analyzed by Hadler and Margolis (1992) and by Bryan et al. (1992). The mean serum anti-HBs titer of seroconverted individuals determined by ELISA was 432.7 mIU/ml in three of the studies in which it was quantified. The results of quantitative ELISA for anti-HBs are considered to be positive when the serum titer of this antibody is equal to or higher than 10 mIU/ml, with a good response corresponding to an anti-HBs concentration higher than 100 mIU/ml and a poor response to a concentration between 10 and 100 mIU/ml (Hadler et al. 1986, Peard 1986). In the three studies cited by Hadler and Margolis (1992) and by Bryan et al. (1992) involving the intradermal application of 2 µg of the Belgian recombinant vaccine at 0, 1, and 6 months to 295 adults, the seroconversion rate ranged from 78% to 87% (mean 82%) and the anti-HBs titer of seroconverted individuals was 126 and 600 mIU/ml (mean of 363 mIU/ml) in the two studies in which it was quantified.

Brink and Murray (1991), administering the Belgian recombinant vaccine to 152 young adults using the same route and dose regimen employed here, obtained seroconversion in 123 (80.9%) patients, including 90 (73.2%)

TABLE
Distribution of the 135 hepatitis B-vaccinated dentists according to the type of immune response to vaccination and sex

Type of immune response ^a	Sex				Total	
	Male		Female		Nr	%
	Nr	%	Nr	%		
Good response	37	52.1	35	54.7	72	53.3
Poor response	18	25.4	20	31.2	38	28.2
Lack of response	16	22.5	9	14.1	25	18.5
Total	71	100	64	100	135	100

a: good response: > 10 U S/N; poor response: 2.1 |—| 10 U S/N; lack of response: < 2.1 U S/N

good responders, and 33 (26.8%) poor responders. Using the same vaccination procedure, Payton et al. (1993) administered the same vaccine to 282 adults and observed seroconversion in 228 (80.8%) of them, including 144 (51.1%) good responders and 84 (29.8%) poor responders. In the study by Struve et al. (1992) conducted on adults receiving three doses of the Belgian recombinant HB vaccine at 0, 1, and 6 months, 286 subjects received 20 µg doses by the intramuscular route and 383 received 2 µg doses by the intradermal route, with seroconversion being observed in 94% of vaccinees in the first group and in 89% in the second group. The mean serum anti-HBs concentration was five times higher in the group vaccinated by the intramuscular route. Cardell et al. (1999) demonstrated seroconversion in 89% of 1406 adults receiving three or four 2 µg doses of the Belgian recombinant vaccine by the intradermal route (at 0, 1, and 6 months or 0, 1, 6, and 8 months), and calculated that vaccination with three doses leads to a 85% sero-conversion rate. Henderson et al. (2000) reported 99% seroconversion in 370 adults receiving three 3 µg doses of the Belgian recombinant vaccine by the intradermal route at 0, 1, and 6 months. In Brazil, Turchi et al. (1997) carried out a randomized study on 359 university students divided into three groups receiving three doses of the Belgian recombinant HB vaccine (month 0, 1, and 6): the first group received three 20 µg doses intramuscularly, the second group received three 10 µg doses intra-muscularly, and the third group received three 2 µg doses intradermally. The anti-HBs seroconversion rates were similar in the first two groups (99.1 and 94.6%, respectively, with a high mean serum anti-HBs concentration), and lower (78.6%) in the third group, which showed a very low mean serum anti-HBs concentration. Söyletir et al. (1992) demonstrated a 100% seroconversion rate in 21 adults injected intradermally with 2 µg doses of the Belgian recombinant vaccine at 0, 1, and 6 months, with the mean serum anti-HBs titer reaching 1390 mIU/ml.

With respect to adverse effects determined in 106 (78.5%) of the 135 dentists who received three vaccine doses, mainly local reactions were relatively common, reported 139 times, but were of low clinical significance.

In fact, despite the occurrence of a persistent hypochromic spot, erythema, pruritus, heat, burning sensation, and pain at the site of vaccine application in 32.1%, 28.3%, 25.5%, 18.9%, 14.1%, and 12.3% of cases, respectively, especially after the first and second dose and often after the third dose, these manifestations did not cause any significant discomfort since all participants completed the proposed vaccination scheme. The incidence of local adverse effects was similar for men and women. Systemic adverse effects were uncommon, and were only reported on four occasions by female dentists. Struve et al. (1992), in a study conducted on 293 Swedish adults using the same vaccine, the same number of doses and the same route and regimen employed here, observed local reactions (nodule, edema, pruritus, skin discoloration, pain, etc.) in 45.7% of cases. Post-vaccination systemic manifestations were detected by these authors in 10% of cases, with the most common being headache and general discomfort (6.1%), fever (1.7%), and generalized pruritus (1%). In the same study, the authors determined the adverse effects induced by intramuscular administration of the same recombinant vaccine in the same regimen (0, 1, and 6 months) to 241 health care workers, and found a lower incidence of adverse effects with this conduct. Thompson et al. (1993), using the four-dose schedule cited below, reported the occurrence of poorly significant local adverse effects (pain, pruritus, transitory nodules, and a persistent pigmented stain), as also observed by Brink and Murray (1991).

In the present study, a fourth vaccine dose was administered to 39 dentists. Analysis showed that 8 (57.1%) of the 14 vaccinees who had not responded to the three vaccine doses acquired immunity (1 good responder and 7 poor responders), while 19 (76%) of the 25 poor responders continued to be anti-HBs positive (12 became good responders and 9 continued to be poor responders), and 4 (16%) became non-responders (Figure). Struve et al. (1995) also observed the occurrence of non-protective anti-HBs titers (< 10 mIU/ml) in 5 (9.8%) of 51 adults – who had previously seroconverted with a serum anti-HBs concentration between 10 and 99 mIU/ml (poor responders) after intradermal application of three 2 µg doses of the Belgian recombinant vaccine at 0, 1, and 6 months – receiving a 2 µg booster dose of the vaccine by the same route 18 months later. In the present study, intradermal administration of a fourth vaccine dose increased the total number of seroconverted individuals from 110 (81.5%) to 114 (84.4%), with the number of good responders increasing from 72 (65.5%) to 85 (74.6%) and the number of poor responders from 38 (34.5%) to 41 (36%). Struve et al. (1994) also observed the occurrence of anti-HBs at protective titers in 7 (46.7%) of 15 non-seroconverted adults after an additional dose of the same vaccine and the same route and regimen employed in our study. Thompson et al. (1993), who administering intradermally four 2 µg doses of the Belgian recombinant vaccine to 227 adults using different regimens (0, 4, 9, and 22 months, 0, 3, 7, and 20 months, and 0, 5, 9, and 22 months), observed seroconversion in 214 of them (94.3%). McMaster III et al. (1993), administering the same vaccine in four intradermal 2 µg doses (0, 1, 2, and 6 months), obtained

seroconversion in 90.5% of 411 adults completing the scheme.

The results of the present study are in accordance with most similar studies published in the literature. This fact led us to conclude that intradermal HB vaccination with three 2 µg doses of the Belgian recombinant vaccine at 0, 1, and 6 months of immunocompetent adults in the age range studied here induces a high rate of seroconversion. This result, however, was observed at a lower frequency and with lower mean serum anti-HBs titers than those induced by intramuscular administration of three 20 µg doses of the same vaccine in the same regimen (Hadler & Margolis 1992, Struve et al. 1992, Turchi et al. 1997). If the persistence of immunity and, in particular, the development of the immunologic memory after vaccination using the route and scheme employed here were confirmed, its routine use in active HB immunoprophylaxis would become a valid alternative for the age groups studied, especially in large populations of poor countries due to the extraordinary reduction in vaccination costs.

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