Journal of Medical Virology 57:100–103 (1999)

# Modelling Long-Term Persistence of Hepatitis B Antibodies After Vaccination

**A. Vellinga,[1] P. Van Damme,[1]* L. Bruckers,[2] J.J. Weyler,[1] G. Molenberghs,[2] and A. Meheus[1]**

[1]*Center for the Evaluation of Vaccination, Epidemiology and Community Medicine, University of Antwerp, Antwerp, Belgium*

[2]*Biostatistics, Limburgs Universitair Centrum, Diepenbeek, Belgium*

Antibody response to hepatitis B vaccination was measured in 97 institutionalized, mentally handicapped patients after a 0-, 1-, 6-month vaccination schedule. Two groups were formed at month 7 according to the antibody response, which determined whether they needed an additional vaccine dose at month 12, to achieve an antibody titre of 100 IU/liter. All residents were followed up yearly for the first 5 years, after which, they received another booster dose. Another blood sample was taken 11 years after the start of the program. A linear mixed-regression model was used to analyze the data. Random and fixed effects were included to determine the generally known risk factors and the still unknown individual characteristics that influence the titre of hepatitis B surface antibodies (anti-HBs). The mean anti-HBs titre was a function of time, type of mental retardation (Down's syndrome or other types of mental retardation), the use of antiepileptic drugs, and the additional booster at month 12. The immediate and vigorous response of the immune system to booster vaccination shows that the immunologic memory is good after primary vaccination. For the maintenance of protection, the recommendation for mentally retarded patients in institutions is vaccination of all seronegative residents as well as new entrants, after which, no additional boosters will be necessary. ***J. Med. Virol. 57:100–103, 1999.*** © 1999 Wiley-Liss, Inc.

**KEY WORDS:** hepatitis B; mentally retarded; long term; linear mixed models

## INTRODUCTION

Hepatitis B virus (HBV) infection can be prevented by immunization resulting in the development of protective HBV antibodies (anti-HBs). After vaccination, the level of anti-HBs declines rapidly within the first year and more slowly thereafter [West and Calandra, 1996]. The reports on postvaccination anti-HBs decline are based generally on geometric mean titres (GMT) by which individual characteristics in response to vaccination are ignored [Coursaget et al., 1991; Da Villa et al., 1996; Gesemann and Scheiermann, 1995; Hadler et al., 1986; Nommensen et al., 1989; Tabor et al., 1993; Wainwright et al., 1997]. Other reports are based on individual declines by which risk factors are difficult to determine [Jilg et al., 1984; Jilg, 1990]. To characterize the long-term decline of anti-HBs titre after vaccination and to determine heterogeneity among subjects, a linear random-effects model has been proposed previously [Coursaget et al., 1991; Gilks et al., 1993]. This model included only the random variability of the individuals. A linear mixed-regression model is proposed that includes fixed as well as random effects, combining generally known risk factors and still unknown individual characteristics that can influence the anti-HBs titre.

## MATERIALS AND METHODS

The study population and serologic methods have been described previously [Vellinga et al., in press]. Institutionalized, mentally retarded patients (n = 105) were vaccinated in 1986 with a recombinant DNA hepatitis B vaccine (Engerix-B; Smith Kline Beecham Biologicals, Rixeusait, Belgium). According to the study protocol, group 1 (G1) received three doses (at 0, 1, and 6 months), and group 2 (G2) received four doses (at 0, 1, 6, and 12 months), because the anti-HBs titre did not reach 100 IU/liter at month 7. Eight patients required additional vaccine doses, because their immune responses did not reach 100 IU/liter at month 12, and they were not included in the study. The anti-HBs titres were recorded annually for 5 years. All individuals received a booster vaccination after 5 years. Eleven years after the start of the program, they were tested again for hepatitis B serologic markers.

*Correspondence to P. Van Damme, Center for the Evaluation of Vaccination, Epidemiology and Community Medicine, University of Antwerp, Universiteitsplein 1, B - 2610 Antwerp, Belgium.

Accepted 29 June 1998

TABLE I. Parameter Estimates and Standard Errors According to the Linear Mixed-Regression Model With the Anti-HBs titre as dependent Variable*

| Sample moment | Time | DS/OMR | Group |
|---|---|---|---|
| Time-dependent effects (SE) | | | |
| 1 | −6.859 (0.211) | 0.679 (0.693) | −1.305 (0.402) |
| 2 | −4.340 (0.214) | 0.419 (0.729) | −1.738 (0.434) |
| 7 | | 0.042 (0.601) | −2.395 (0.353) |
| 12 | −1.609 (0.178) | −0.258 (0.642) | −2.674 (0.371) |
| 13 | −0.440 (0.376) | | |
| 24 | −3.188 (0.178) | −1.505 (0.560) | −0.075 (0.326) |
| 36 | −3.386 (0.168) | −1.702 (0.491) | −0.226 (0.291) |
| 48 | −3.805 (0.203) | −1.450 (0.571) | 0.041 (0.339) |
| 60 | −4.144 (0.192) | −0.576 (0.528) | 0.254 (0.316) |
| 61 | 2.175 (0.243) | −0.780 (0.710) | −1.974 (0.422) |
| 132 | −0.671 (0.240) | −1.201 (0.666) | −1.990 (0.396) |
| Time-independent effects (SE) | | | |
| Intercept | 8.548 (0.257) | | |
| Gender | −0.080 (0.246) | | |
| Epilepsy | −0.577 (0.259) | | |

*Anti-HBs, hepatitis B surface antibodies; DS/OMR, Down's syndrome/other mentally retarded; SE, standard error.

A linear mixed-regression model was designed [Verbeke and Molenberghs, 1997] with the anti-HBs titre as a dependent variable. Because of the asymmetry of the data, they were log transformed and calculated as ln(anti-HBs+1) to avoid negative values. In this longitudinal model, four components are taken into account, the fixed-effects parameters and three sources of variability: random effects, which arise from between-subject variation; serial correlations, which are higher the closer in time measurements were taken; and measurement error. Time (sample moment in months), gender, age, group, duration of residency, age at admission, use of antiepileptic drugs, and type of mental retardation (Down's syndrome or other types of mental retardation) were entered as covariates. The variance of the measurement error was allowed to vary as a function of time. All covariates were tested for a time effect, i.e., a different effect at different time points. In the final model, month 7 was taken as the reference time point, because the groups were formed according to the immune responses of individuals at that month.

## RESULTS

After covariate selection, the mean anti-HBs titre was a function of time, type of mental retardation, use of antiepileptic drugs, and group (i.e., the immune response). The effect of immune response and type of mental retardation was time dependent (Table I). The use of antiepileptic drugs was a significant fixed effect. Gender remained in the model as a nonsignificant fixed effect for reasons of external comparison. Table I shows parameter estimates and standard errors. The time effect was the same for all subjects at each sample moment, but a simple linear or quadratic trend over time could not be detected.

The effect of Down's syndrome on anti-HBs titre was significant only at months 24, 36, and 48, indicating a more rapid decline in anti-HBs titre for Down's syndrome patients than for other mentally retarded patients. The immediate response to vaccination, however, was basically the same for Down's syndrome patients and other mentally retarded patients. Antiepileptic drugs also had a negative effect on antibody persistence, and this effect was independent of time. The additional booster at month 12 for G2 made G1 and G2 equal with respect to the anti-HBs titre from month 13 to month 48. After administration of the booster at month 60, G1 responded better again, and anti-HBs titres remained significantly higher in G1 than in G2 until year 11 (Fig. 1).

Figure 1 shows the combined effect at each sample moment of Down's syndrome patients/other mentally retarded patients and of group. For each individual, a parallel line could be drawn above or below, according to their age, gender, and use of antiepileptic drugs.

There was considerable random variation among subjects in their responses to vaccination, which represented the individual component of the immune response. These responses ranged from 2 IU/liter to 12 IU/liter at month 7 (which corresponds with an anti-HBs titre of 6–179,871 IU/liter). Despite this variation, however, responses to the 5-year booster were good and immediate for all individuals [range, 3–15 IU/liter for the ln(anti-HBs)].

## DISCUSSION

Response to vaccination can be attributed to a combination of known individual characteristics, such as gender, age, weight, and other individual but unknown characteristics. With linear mixed models, the unknown individual component is a (random) term in the calculation to determine the influence of other factors.

The use of antiepileptic drugs is a significant fixed linear effect that increases the rate of decline. The reason for this still is not clear. De Ponti et al. [1993] found that long-term administration of anticonvulsant drugs

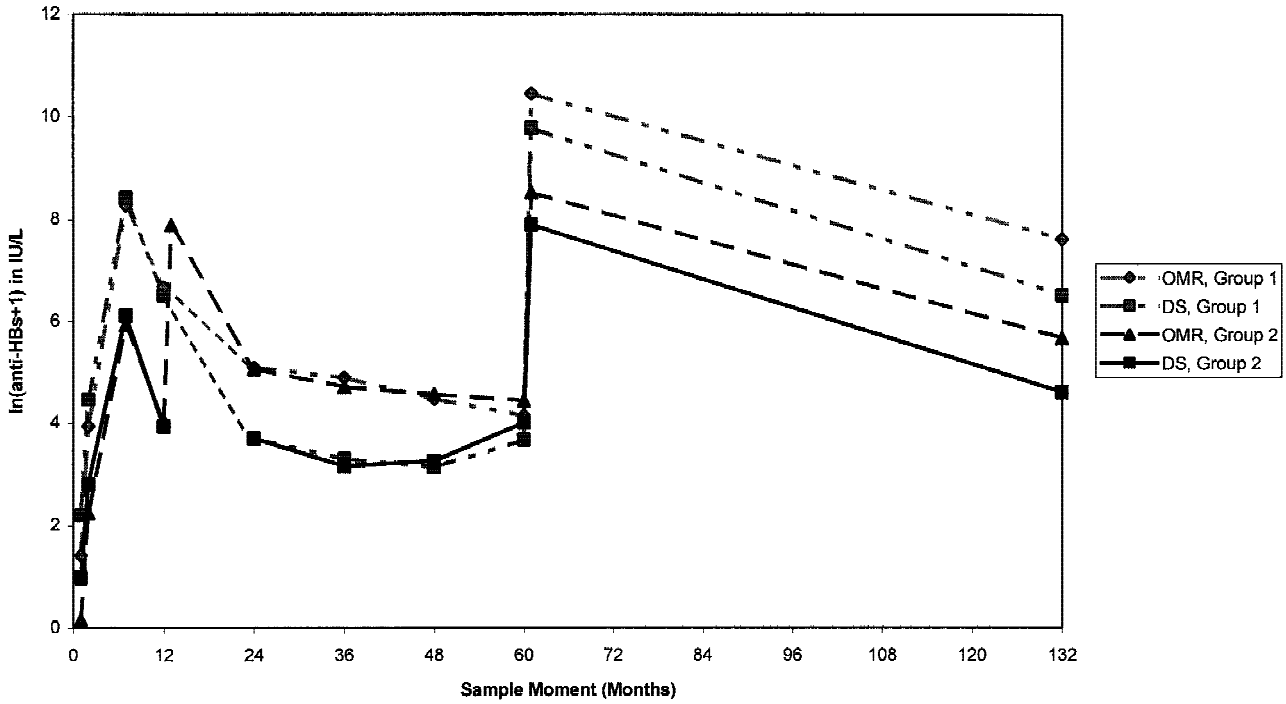


Fig. 1. The combined effect of the type of mental retardation and groups of immune response at each sample moment. Anti-HBs, hepatitis B surface antibodies; OMR, other mentally retarded patients; DS, Down's syndrome patients. Group 1 received no additional vaccine dose at month 12, and group 2 received an additional vaccine dose at month 12.

is sometimes associated with humoral and/or cellular immune response. However, whether this is due to the medication or to the epilepsy itself has not been determined. From our study, the only conclusion that can be drawn is that there seems to be an association between the response to vaccination and medication for epilepsy.

The response to vaccination was the same for Down's syndrome patients and other mentally retarded patients, but the decline in antibody was faster for Down's syndrome patients than for other mentally retarded. Down's syndrome patients have been found to have an impaired immune system [Nespoli et al., 1993] and a higher prevalence of hepatitis B carrier state than other mentally retarded patients [Vellinga et al., accepted]. Several studies have attempted to link this to anti-HBs response immediately after vaccination, but a difference between Down's syndrome patients and other mentally retarded patients could not always be demonstrated. Hayashi et al. [1991] found that Down's syndrome patients had the same response to vaccination as other mentally retarded patients, but the persistence of antibodies after 2 years in patients with Down's syndrome was significantly lower than for other mentally retarded patients. Also in our study, no difference could be found between Down's syndrome patients and other mentally retarded patients in their anti-HBs responses after vaccination; however, with the use of linear mixed models on the longitudinal data, a distinction could be made in the rate of decline of antibody titres to hepatitis B vaccination.

The additional booster that was given to G2 made the two groups equal in antibody response until both groups receive the 5-year booster. No additional vaccine dose was administrated to G2 after this booster, and the response of G2 is not as high as that of G1. This means that the initial response to vaccination is inherent to an individual and that additional vaccinations will improve this response but will not change the initial response itself.

The model presented here predicts the decline in anti-HBs titre over 11 years as a function of individual differences in immune response as well as other, known factors that are involved in this response. The heterogeneity between individuals has been shown to be of great importance; therefore, it should not be ignored in calculating long-term protection by means of the GMT.

Figure 1 shows that the response to the 5-year booster is very good and immediate. This rapid response of the immune system shows that the immunologic memory is good after the primary vaccination series. West and Calandra [1996] concluded from their review that, in healthy vaccinees, routine booster vaccination should not be required to sustain immunologic memory and protection within 5 years and perhaps longer after primary vaccination. This study confirms these findings, and, taking into consideration the titres at the moment of the 5 year booster as well as at year 11, the period of protection can be prolonged. Therefore, the recommendation for mentally retarded patients in institutions is to vaccinate all seronegative

residents as well as new entrants against hepatitis B: After such vaccination, no additional boosters will be necessary.

## REFERENCES


Coursaget P, Yvonnet B, Gilks WR, Wang CC, Day NE, Chiron JP, Diop-Mar I. 1991. Scheduling of revaccination against hepatitis B virus [see comments]. Lancet 337:1180–1183.

Da Villa G, Peluso F, Picciotto L, Bencivenga M, Elia S, Pelliccia MG. 1996. Persistence of anti-HBs in children vaccinated against viral hepatitis B in the first year of life: follow-up at 5 and 10 years. Vaccine 14:1503–1505.

De Ponti F, Lecchini S, Cosentino M, Castelletti CM, Malesci A, Frigo GM. 1993. Immunological adverse effects of anticonvulsants. What is their clinical relevance? Drug Safety 8:235–250.

Gesemann M, Scheiermann N. 1995. Quantification of hepatitis B vaccine-induced antibodies as a predictor of anti-HBs persistence. Vaccine 13:443–447.

Gilks WR, Wang CC, Yvonnet B, Coursaget P. 1993. Random-effects models, for longitudinal data using Gibbs sampling. Biometrics 49:441–453.

Hadler SC, Francis DP, Maynard JE, Thompson SE, Judson FN, Echenberg DF, Ostrow DG, O'Malley PM, Penley KA, Altman NL. 1986. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 315:209–214.

Hayashi J, Noguchi A, Nakashima K, Morofuji M, Kashiwagi S. 1991. Long term observation of the effect of intradermal hepatitis B vaccination on mentally retarded patients. Eur J Epidemiol 7:649–653.

Jilg W, Schmidt M, Deinhardt F, Zachoval R. 1984. Hepatitis B vaccination: how long does protection last? [letter]. Lancet 2:458.

Jilg W, Schmidt M, Deinhardt F. 1990. Decline of anti-HBs after hepatitis B vaccination and timing of revaccination [letter]. Lancet 335:173–174.

Nespoli L, Burgio GR, Ugazio AG, Maccario R. 1993. Immunologic features of Down's syndrome: a review. J Intellectual Dis Res 37: 543–551.

Nommensen FE, Go ST, MacLaren DM. 1989. Half-life of HBs antibody after hepatitis B vaccination: an aid to timing of booster vaccination [see comments]. Lancet 2:847–849.

Tabor E, Cairns J, Gerety RJ, Bayley AC. 1993. Nine-year follow-up study of a plasma-derived hepatitis B vaccine in a rural African setting. J of Med Virol 40:204–209.

Vellinga A, Van Damme P, Meheus A. Hepatitis B and C in institutions for the mentally retarded: a review. J Intellectual Dis Res (accepted, 1998)

Vellinga A, Van Damme P, Weyler JJ, Vraudex R, Meheus A. Hepatitis B vaccination in mentally retarded: effectiveness after 11 years. Vaccine (in press, 1999).

Verbeke G, Molenberghs G. 1997. Linear mixed models in practice: an SAS-orientated approach. Lecture notes in statistics, vol. 126. New York: Springer-Verlag.

Wainwright RB, Bulkow LR, Parkinson AJ, Zanis C, McMahon BJ. 1997. Protection provided by hepatitis B vaccine in a Yupik Eskimo population—Results of a 10-year study. J Infect Dis 175:674–677.

West DJ, Calandra GB. 1996. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination. Vaccine 14:1019–1027.