

# Effects of Massage on Antibody Responses After Hepatitis B Vaccination

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**Objective:** The aim of this study was to examine whether participation in a 4-week massage intervention is associated with reduced distress and enhanced antibody responses after hepatitis B vaccine in students embarking on academic examinations. **Methods:** Seventy medical student volunteers (36 women, 34 men) were randomly assigned to intervention or control groups. Baseline assessments were made of distress, health behaviors, and prevaccination antibodies to hepatitis B surface antigen. Intervention participants received weekly 45-minute massages before an examination period. At the end of the intervention and 1 week before commencing the examination period, all participants received an intramuscular hepatitis B vaccination and repeated the assessments completed at baseline. Serum antibody responses to hepatitis B surface antigen were measured at 2 and 6 weeks postvaccination. **Results:** Examinations were associated with increased distress in both the massage and the control groups: perceived stress ( $F(1,67) = 10.64, p = .002$ ), anxiety ( $F(1,67) = 15.72, p < .001$ ) and negative affect ( $F(1,66) = 5.80, p = .019$ ); these increases did not differ between the massage and the control groups. Furthermore, massage was associated with lower levels of antibody to hepatitis B surface antigen after vaccination at both time points ( $F(1,63) = 6.29, p = .015$ ). **Conclusions:** These findings indicate that a brief massage intervention did not attenuate emotional distress during an examination period but did result in lowered antibody responses to vaccination. Further research is required to establish whether these effects were attributable to the nature of intervention (i.e., duration and type of massage) and/or its limited relevance to a healthy population confronting a relatively acute stressor such as examinations. **Key words:** Massage, hepatitis B vaccination, perceived stress, examinations, antibodies.

NK = natural killer; anti-HBs = antibody to hepatitis B surface antigen; PSS = Perceived Stress Scale; PANAS = Positive and Negative Affect Scale; STAI = State-Trait Anxiety Inventory; HBV = hepatitis B virus; ANOVA = analysis of variance.

## INTRODUCTION

Observational studies suggest that immune responses after vaccination are influenced by psychological stress (for a review, see Ref. (1)). These findings have stimulated interest in the potential for psychological and behavioral interventions to reduce stress and enhance the immune response to vaccinations.

There is evidence in support of a range of interventions (e.g., emotional disclosure, cognitive behavioral stress management, and exercise) modulating immune responses to vaccines such as hepatitis B and influenza. For example, one of the first published studies in this area examined the effects of written emotional expression of traumatic events on immune responses to hepatitis B vaccination in young healthy volunteers. Compared with control participants, individuals who received the intervention exhibited significantly higher antibody levels at 4 and 6 months postvaccine (2). Kohut and colleagues (3) extended this early work by examining the effects of a 10-month aerobic exercise intervention on immune responses to influenza in the elderly. They reported that their intervention was associated with enhanced antibody levels to influenza vaccination. Similarly, Vedhara et al. (4) examined the effects of a stress management intervention on antibody responses to influenza

vaccination in spousal carers of patients with dementia. Their intervention was associated with a significantly greater likelihood of the vaccine being effective: with protection against influenza (denoted by a four-fold increase in antibody levels) achieved in 50% of carers who received the intervention compared with only 7% of carers who did not receive the intervention and 29% of a noncarer control group. However, not all studies have observed beneficial effects of psychobehavioral interventions on immunity. For example, in a study examining the effects of emotional disclosure about racist experiences in black participants, the authors observed that antibody responses to influenza vaccine were significantly lower for two of three of the viral strains in the vaccine (5). These data clearly find evidence in support of modulation but not in the expected direction. Notwithstanding these latter results, the aim of the present study was to examine if massage therapy could be added to the armory of nonpharmacological interventions that can enhance the immune response.

A growing literature suggests that massage therapy can promote physical and psychological well-being. Reported effects include enhanced mood and reduced perceived stress (6) as well as reduced cortisol and heart rate activity (7,8). A small number of studies have looked at the effects of massage on immune responses, although with mixed results. For example, Zeitlin and colleagues (9) reported evidence of lowered anxiety and perceived stress, decreased respiratory rate, and increased lymphocyte numbers and natural killer (NK) cell activity after a single 1-hour massage administered before an academic examination. Similarly, Diego et al. (10) examined the effects of 12 biweekly sessions of massage therapy versus progressive muscle relaxation on mood and immunity in HIV-positive adolescents. They observed that the massage group reported less anxiety and depression and enhanced immunity as evidenced by increased NK numbers, CD4 cells, and the CD4/CD8 ratio. In contrast, a recent study with women with breast cancer reported that ten 20-minute sessions of effleurage massage therapy had no effect on a range of outcomes including NK cells, cortisol, oxytocin, or mood (11).

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# MESSAGE AND HBV VACCINATION ANTIBODY RESPONSES

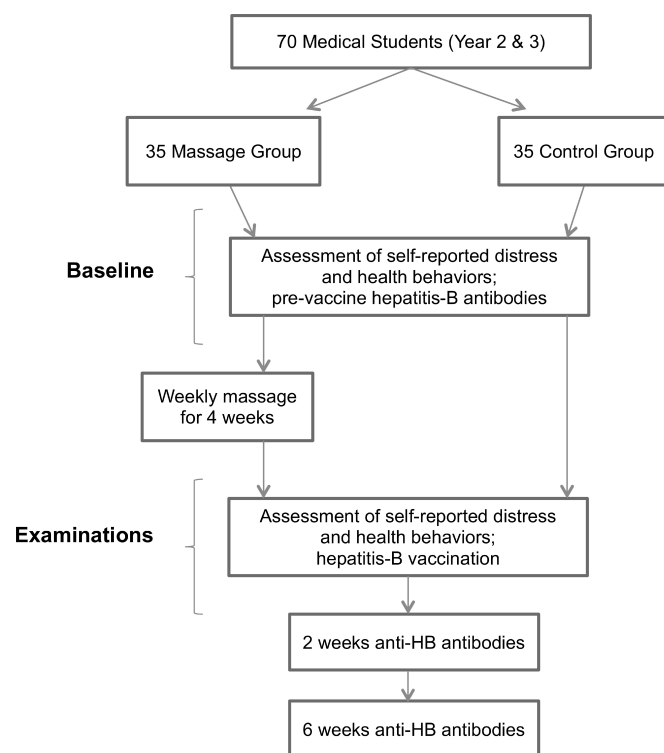


Figure 1. Study overview. Anti-HB = antibody to hepatitis B.

A few studies that have examined the effects of massage on immune responses to vaccine have also had mixed results. For example, Hsu and colleagues (12) reported on the effects of a 1-minute massage on infants after diphtheria-tetanus-pertussis vaccine. They observed that although pain and fever were greater in the massage group, antibody responses were enhanced and remained enhanced up to 19 months of age in infants who received the massage. This group extended this work a few years later, examining the effects of a more intense massage, but again immediately after diphtheria-tetanus-pertussis vaccine (13). However, this time, they observed that massage had no effect on antibody responses to the vaccine antigens. Thus, the effects of massage on immune responses to vaccine remain unclear, and to our knowledge, no previous studies have examined the effects of massage when administered before vaccination.

Thus, the present study examined whether participation in a massage intervention was associated with reduced distress and enhanced antibody responses to hepatitis B vaccine in students about to embark on academic examinations. In keeping with previous research, the vaccination was administered after the intervention (2–5). Furthermore, examination stress was considered an appropriate stressor because previous research has shown that examinations are associated with impaired immunity and that immune responses during an examination period are amenable to modulation by psychobehavioral interventions (14,15).

## METHODS

### Participants

Undergraduate medical students were invited to participate in a study looking at whether massage altered antibody responses to a hepatitis B vac-

cination. Seventy-two students agreed to participate; however, 2 withdrew before baseline. Thus, a total of 70 students participated: 36 women and 34 men, aged 18 to 34 years (mean [standard deviation] = 21 [3.5] years), 57% European, 23% were Asian, and 20% from other ethnic groups.

### Procedure

The study was approved by the University of Auckland Human Participants Ethics Committee and was conducted over a 5-month period (March to July) in a single semester in 2007. All participants provided written informed consent and were paid NZ\$50. The study protocol is summarized in Figure 1. In brief, participants were randomly assigned to one of two groups: intervention ( $n = 35$ ) or control ( $n = 35$ ). Characteristics of the participants in each group are summarized in Table 1. Randomization was performed independently of the principal investigators. Participants were numbered 1 to 70 based on their order of entry into the study, and each number was randomly allocated the words “massage” or “control” by a random assignment computer program. At baseline, all participants, regardless of group allocation, completed self-report instruments measuring emotional distress and health behaviors and provided a blood sample for the measurement of antibody to hepatitis B surface antigen (anti-HBs). The intervention group then participated in a weekly massage program for 4 weeks. After the intervention, in the week preceding examinations (examination phase), all assessments completed at baseline were repeated, and participants received a single intramuscular dose of a hepatitis B vaccine and provided blood samples 2 and 6 weeks later for the measurement of anti-HBs.

### Emotional Distress and Health Behaviors

Emotional distress was measured using the Perceived Stress Scale (PSS) (16); the negative affect scale of the Positive and Negative Affect Scale (PANAS) (17) and the state scale of the State-Trait Anxiety Inventory (STAI) (18). Cronbach  $\alpha$  values for these scales in the present study ranged from 0.77 to 0.92. Participants also rated on a 0- to 5-point Likert scale the amount of exercise, fruit and vegetable intake, vitamin intake, alcohol consumption, and frequency of adequate sleep (from never [0], once a month [1], once a week [2], two to three times a week [3], four to five times a week [4], and every day [5]) and indicated the number of cigarettes smoked per day over the last month.

### Massage Intervention

The massage group underwent the weekly massage intervention in the period before an examination phase. All participants completed all massage sessions. The massages were administered individually by six professionally registered massage therapists. All massages were based on a standardized 45-minute massage protocol designed to induce relaxation. Each step of the standardized massage was listed and displayed on the wall to remind the therapists of the massage protocol. Participants rested in a prone position on a standard massage table and grape seed oil was used to enhance the strokes. The 45-minute firm relaxation massage protocol consisted of 30 minutes of effleurage on the upper body, back, shoulders, neck, arms, and hands;

TABLE 1. Summary of Participant Characteristics in Each Group

	Control Group	Intervention Group
Men/Women	16/19	18/17
Age, M (SD)	21.51 (4.17)	20.57 (2.37)
Previous vaccination	28	21
Ethnicity		
European	19	21
Maori/Maori mixed	7	3
Pacific Island/Pacific Island mixed	1	—
Asian	5	11
Other	3	—

M = mean; SD = standard deviation.

10 minutes on the legs; and 5 minutes of pectoral stretch and shoulder and neck massage.

### **Hepatitis B Virus Vaccination and Antibody Measurement**

All participants received a single 1-ml intramuscular injection of a recombinant hepatitis B virus (HBV) vaccine (ENGERIX-B; GlaxoSmithKline) containing 20 µg of anti-HBs adsorbed on 0.5 mg of aluminium hydroxide. All participants received their vaccinations 3, 6, or 7 days (mean = 6 days) before their first examination. The standard HBV vaccine schedule involves three vaccinations. We chose, however, to focus our assessment on the immune response after the first vaccination because we thought that the exponential phase of the response would be more likely to reveal group differences. In contrast, responses assessed after the second and third vaccinations would probably have achieved broadly similar maximal titers and would have been nonlinear.

Participants provided three 5-ml blood samples during the study period. The first was collected at baseline (i.e., prevaccine), followed by two further samples collected at 2 and 6 weeks after HBV vaccination. Data on primary and secondary antibody responses to hepatitis vaccines suggest that most individuals will produce a measurable immune response, which peaks at 2 weeks for the secondary immune response and at 4 weeks for the primary immune response (19–22). Thus, we elected to collect postvaccine blood samples at 2 and 6 weeks postvaccine to maximize the likelihood of capturing peak antibody responses in all participants.

Levels of total serum anti-HBs antibody (immunoglobulins M and G) were analyzed by microparticle enzyme immunoassay using AxSYM AUSAB assay kits (Abbott Laboratories, Abbott Park, IL, USA) at Labplus, Auckland City Hospital, New Zealand. All serum samples were initially assayed to a maximal anti-HBs titer of 1000 mIU/ml, and specimens with anti-HBs titers over this threshold were further diluted 1 in 25 to enable the measurement of anti-HBs titers up to 25,000 mIU/ml. Eighteen of the 2-week postvaccine samples (6 in the control group, 12 in the intervention group) were assayed for titers up to 1000 mIU/ml but were then inadvertently discarded and were therefore not available to be reassayed to 25,000 mIU/ml. The exclusion of these individuals' data from the analyses did not affect the results pertaining to antibody responses. Nevertheless, we present the results from the analyses, which included and excluded these participants. Antibody data were available for all participants at baseline, 65 at week 2 and 67 at week 6.

Participants were not selected into this study based on vaccine history. This decision was predicated on several considerations. First, it was our expectation that the sample would be relatively homogenous in their previous exposure to the vaccine because hepatitis B vaccination has been a routine component of the New Zealand immunization schedule since 1988, with a catch-up program offered to all children younger than 16 years in 1990. Thus, the expectation was that for most participants, we would be assessing a secondary immune response. Second, notwithstanding the effects of public health policy, it is known that vaccine history is a relatively unreliable method of establishing prior exposure to the pathogen. Furthermore, there is considerable variability in the approach that has been taken in previous research with this vaccination, with authors reporting and not reporting the vaccine history of their participants (23,24). Thus, we considered it most appropriate to not restrict our recruitment based on vaccine history but to expect a largely homogenous group, with any baseline variations being addressed by randomization.

### **Data Analysis**

Repeated-measures analyses of variance (ANOVAs) examined within- and between-participant effects of the intervention on distress, health behaviors, and anti-HBs levels in both groups preintervention and postintervention. Post hoc univariate analyses (one-way ANOVAs) were conducted as appropriate to investigate significant interaction effects. All analyses were conducted in SPSS 19.

## **RESULTS**

Descriptive data summarizing participants' scores on all study variables are presented in Table 2.

**TABLE 2. Descriptive Results for Massage and Control Groups at Baseline and Examinations**

	Control Group ( <i>n</i> = 35), <i>M</i> ( <i>SE</i> )	Intervention Group ( <i>n</i> = 35), <i>M</i> ( <i>SE</i> )
<b>Exercise</b>		
Nonexamination	3.60 (0.19)	3.35 (0.19)
Examination	3.15 (0.19)	3.00 (0.17)
<b>Vitamins</b>		
Nonexamination	1.09 (0.24)	1.21 (0.30)
Examination	1.18 (0.24)	1.17 (0.29)
<b>Fruit/vegetable intake</b>		
Nonexamination	3.57 (0.22)	3.82 (0.17)
Examination	3.41 (0.20)	3.66 (0.17)
<b>Alcohol</b>		
Nonexamination	2.11 (0.21)	1.44 (0.17)
Examination	1.79 (0.18)	1.20 (0.14)
<b>Sleep</b>		
Nonexamination	3.50 (0.19)	3.56 (0.19)
Examination	3.47 (0.17)	3.41 (0.17)
<b>Cigarettes</b>		
Nonexamination	0.34 (0.29)	0 (0)
Examination	0.32 (0.30)	0 (0)
<b>PANAS</b>		
Nonexamination	15.91 (0.53)	15.97 (0.84)
Examination	17.35 (0.73)	17.17 (0.85)
<b>PSS</b>		
Nonexamination	21.57 (0.87)	22.94 (1.07)
Examination	24.68 (1.18)	24.69 (1.44)
<b>STAI</b>		
Nonexamination	31.03 (1.45)	33.49 (1.57)
Examination	36.88 (1.59)	35.46 (1.61)
Baseline hepatitis B titers	1065.45 (710.30)	495.29 (246.41)
Hepatitis B titers, 2 wk	12,328.47 (1979.54)	5020 (1577)
Hepatitis B titers, 6 wk	15,769.88 (1881.16)	11,213.38 (1931.87)

*M* = mean; *SE* = standard error; PANAS = Positive and Negative Affect Scale; PSS = Perceived Stress Scale; STAI = State-Trait Anxiety Inventory.

### **Effects of Examination Stress and Massage on Emotional Distress**

The analyses revealed significant within-participant effects on responses to the PSS, STAI, and PANAS, indicating that, for all measures, the examination phase was associated with an increase in distress in both groups (PSS:  $F(1,67) = 10.64$ ,  $p = .002$ ,  $d = 0.14$ ; STAI:  $F(1,67) = 15.72$ ,  $p < .001$ ,  $d = 0.19$ ; PANAS:  $F(1,66) = 5.80$ ,  $p = .019$ ,  $d = 0.08$ ). The between-participant effects revealed, however, no main effect of group on any measure; that is, levels of distress did not differ significantly between the groups after the massage intervention, as shown in Table 2.

### **Effects of Massage on Anti-HBs Levels**

Repeated-measures ANOVA revealed a significant within-participant effect, with both groups exhibiting an increase in antibody postvaccination ( $F(2,126) = 51.67$ ,  $p < .001$ ,  $d = 0.45$ ),

## MASSAGE AND HBV VACCINATION ANTIBODY RESPONSES

a significant antibody  $\times$  group interaction ( $F(2,126) = 3.74$ ,  $p = .03$ ,  $d = 0.06$ ), and a significant between-participant effect, with antibody levels in the intervention group being persistently lower than the levels in the control group ( $F(1,63) = 6.29$ ,  $p = .015$ ,  $d = 0.09$ ; see Fig. 2). The analyses of these data excluding participants whose week 2 samples were not analyzed up to 25,000 mIU/ml showed comparable results: significant within-participant effect ( $F(2,90) = 41.97$ ,  $p < .001$ ,  $d = 0.48$ ), significant antibody  $\times$  group interaction ( $F(2,90) = 4.14$ ,  $p = .02$ ,  $d = 0.08$ ), and a significant between-participant effect ( $F(1,45) = 4.65$ ,  $p = .04$ ,  $d = 0.09$ ). Post hoc analyses demonstrated that although there were no differences between the groups at baseline ( $F(1,68) = 0.58$ ,  $p = .45$ ), the massage group had significantly lower antibody responses at week 2 postvaccine ( $F(1,63) = 8.40$ ,  $p = .005$ ) and lower levels at week 6, which approached significance ( $F(1,65) = 2.85$ ,  $p = .096$ ). Additional analyses excluding all smokers revealed a significant within-participant effect ( $F(2,118) = 50.21$ ,  $p < .001$ ,  $d = 0.46$ ), significant antibody  $\times$  group interaction ( $F(2,118) = 4.82$ ,  $p = .01$ ,  $d = 0.08$ ), and a significant between-participant effect ( $F(1,59) = 6.96$ ,  $p = .01$ ,  $d = 0.11$ ). Thus, indicating that the main findings were not affected by smoking status.

Further analyses were conducted to examine whether the change in negative mood from baseline to the examination phase influenced antibody responses to the vaccination. This was again explored using repeated-measures ANOVA in which the between-participant variable was the intervention or control group and changes in the PSS, PANAS, and STAI were included as covariates. The inclusion of these covariates did not change the previously observed effects. In particular, a significant within-participant effect was sustained, with both groups exhibiting an increase in antibody postvaccination ( $F(2,118) = 39.93$ ,  $p < .001$ ,  $d = 0.40$ ). The significant antibody  $\times$  group interaction was retained ( $F(2,118) = 3.35$ ,  $p = .04$ ,

$d = 0.05$ ), as was the significant between-participant effect ( $F(1,59) = 4.53$ ,  $p = .04$ ,  $d = 0.07$ ). However, no significant between-participant effects (PANAS:  $F(1,59) = 0.22$ ,  $p = .64$ ,  $d = 0.00$ ; PSS:  $F(1,59) = 0.85$ ,  $p = .36$ ,  $d = 0.01$ ; STAI:  $F(1,59) = 1.86$ ,  $p = .18$ ,  $d = 0.03$ ) or antibody  $\times$  negative mood interaction effects (PANAS:  $F(2,118) = 1.60$ ,  $p = .21$ ,  $d = 0.03$ ; PSS:  $F(2,118) = 0.24$ ,  $p = .79$ ,  $d = 0.00$ ; STAI:  $F(2,118) = 0.27$ ,  $p = .77$ ,  $d = 0.00$ ) were observed for any of the mood measures, thus indicating that change in negative mood did not affect the antibody response to vaccination in either group.

Finally, to examine the potential effects of vaccine history on our results, we conducted post hoc analyses to explore whether the pattern of findings was affected by participants' baseline levels of antibody. Specifically, we distinguished participants into two groups based on whether their baseline levels of antibody suggested prior exposure. Levels of 1 IU/ml or less at baseline were assumed to indicate no prior exposure ( $n = 12$ ), whereas levels higher than 1 IU/ml were assumed to indicate prior exposure ( $n = 58$ ). We then repeated our main analyses for each of these two groups separately. In the first analysis, we examined the effects of the intervention on those participants who were assumed to have had no prior exposure to the virus (baseline levels  $\leq 1$  IU/ml) and thus were likely to be mounting a primary immune response. For this group, we observed the same general pattern of findings as observed for the main analysis with the cohort as a whole, although some results only approached significance because of the reduced power: within-participant effect of antibody ( $F(2,20) = 4.51$ ,  $p = .02$ ,  $d = 0.31$ ), between-participant effect of group ( $F(1,10) = 3.09$ ,  $p = .11$ ,  $d = 0.24$ ), and group  $\times$  antibody interaction ( $F(2,20) = 3.36$ ,  $p = .06$ ,  $d = 0.25$ ). Similarly, for the analysis with only those participants who were assumed to have had some prior exposure to the virus (baseline levels  $>1$  IU/ml) and who were thus likely to be mounting a secondary immune response, we again observed the same general pattern of findings as observed for the cohort as a whole: within-participant effect of antibody ( $F(2,102) = 55.70$ ,  $p \leq .001$ ,  $d = 0.52$ ), between-participant effect of group ( $F(1,51) = 2.61$ ,  $p = .11$ ,  $d = 0.05$ ), and group  $\times$  antibody interaction ( $F(2,102) = 2.75$ ,  $p = .07$ ,  $d = 0.05$ ). Figure 3 displays the antibody responses over time for these four groups (control group versus massage group and  $\leq 1$  IU/ml at baseline versus  $>1$  IU/ml at baseline).

### Massage Effects on Health Behaviors

Repeated-measures ANOVAs examined if the groups differed in their health behaviors before and after the massage intervention. The groups only differed significantly on alcohol consumption, with the control group exhibiting a slightly greater reduction in alcohol intake in the examination phase ( $F(1,66) = 8.45$ ,  $p = .005$ ,  $d = 0.11$ ). No other significant between-group differences were observed.

### DISCUSSION

This study examined the effects of massage intervention on distress and immune responses after HBV vaccination. The

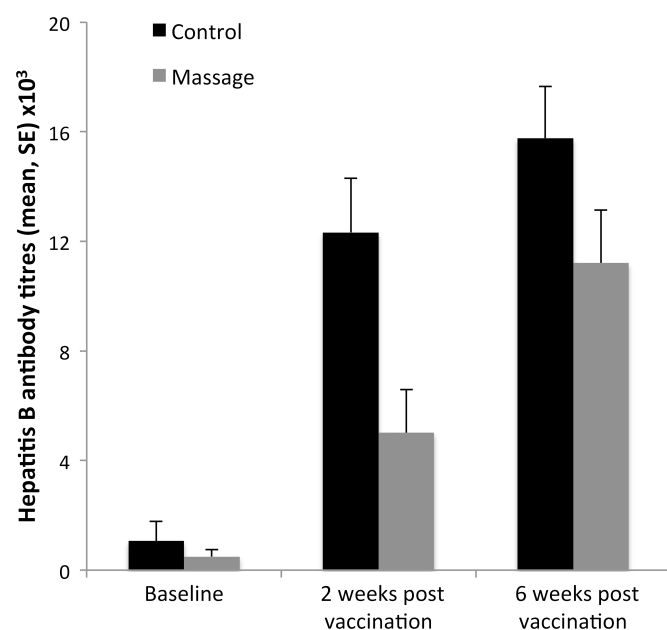


Figure 2. Hepatitis B antibody levels over observation period. SE = standard error.

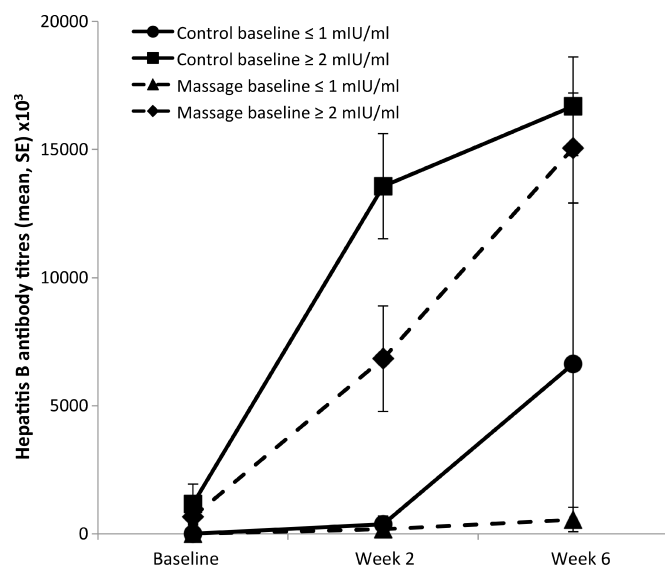


Figure 3. Antibody levels of control and massage participants with and without antibody levels denoting protection prior to vaccination. SE = standard error.

results revealed that the examination period was associated with greater emotional distress in both groups; that is, the massage intervention was not associated with reduced distress in the examination period. Furthermore, massage was associated with an attenuated, rather than enhanced, antibody response after HBV vaccination.

These data provide further evidence that psychological and behavioral interventions can significantly modulate immune responses after vaccinations. It is, however, relevant to examine why massage may not have enhanced the immune response and the mechanisms that gave rise to the observed results. With regard to the former, possible explanations may relate to the duration/intensity of the massage intervention. Previous studies have varied considerably in the intensity of their interventions (ranging from single sessions to two per week for 24 weeks: (7,10)) and beneficial effects on immunity have been observed with both very limited intensity/single session interventions (7,12) and also intensive interventions (10). In contrast, medium-intensity interventions (e.g., 10 × 20-minute sessions) (11), such as in the present study, have not been found to be beneficial. Further research is clearly required on the intensity of massage interventions, as conducted by Edwards and colleagues (25) in the context of exercise interventions, to establish the dose-response relationship between massage and antibody responses to vaccination.

Another explanation may relate not to the massage intervention per se but to its appropriateness to a healthy population confronting a relatively immediate stressful situation such as examinations. Unfortunately, existing research examining the effects of massage is unable to illuminate this issue because these studies have exhibited considerable variation in their target populations (e.g., individuals with breast cancer, individuals with HIV infection, healthy volunteers: (7,10,11)), and to our knowledge, the present study is the first to examine the effects of massage in a healthy adult population confronting a relatively immediate naturalistic stressor. However, related re-

search has suggested that acute stressors can enhance, rather than diminish, immune responses to vaccination (26). Thus, it is possible that these data highlight an enhancement of the immune response, attributable to examination stress, an effect that was tempered by the intervention.

Notwithstanding these reflections, it is relevant to consider the mechanisms that gave rise to the observed attenuated antibody response after massage. Our data allow us to consider both emotional and behavioral mechanisms. With regard to the former, the results revealed that massage did not result in a lowering of distress postintervention. Thus, the observed effects on immunity would initially seem to be unrelated to negative mood. However, our measures of mood were restricted to the periods before and after the massage intervention. It is possible, therefore, that increases in negative mood during the intervention period itself may have been missed, that is, changes in mood attributable to the massage protocol (e.g., due to the additional pressure associated with participating in the intervention during an already stressful period, or a reduction in the time available for revision). If such increases in negative mood had occurred in the intervention group, it is possible that they could have affected antibody responses to the vaccination, without affecting the self-report measures of mood collected postintervention. This proposal further advocates the future use of ecological momentary assessment techniques (27). Such techniques have typically been used to provide a detailed and regular assessment of mood during stressors. The same methods could clearly be used during interventions to elucidate the precise nature and direction of changes in mood.

With regard to behavioral mechanisms, our data on health behaviors revealed a significant change in alcohol consumption, with a greater decrease in consumption observed in the control group (baseline = 2.11, postintervention = 1.79). However, median scores were 2 (i.e., once a week) at both times, indicating that changes in this behavior were unlikely to have made a large contribution to the observed differences in immune responses to the vaccine.

Finally, it is relevant to examine potential limitations with the current study. In particular, it should be noted that we did not restrict our recruitment to participants who were vaccine naive or who had a history of vaccination. This decision was predicated on a number of considerations. First, we expected the sample to be relatively homogenous in their previous exposure to the vaccine because hepatitis B vaccine is provided routinely in New Zealand. Second, we expected that randomization would accommodate any baseline differences in antibody levels. Indeed, the groups were found not to differ on antibody levels at baseline. Third, there has been considerable variability in how the issue of prior exposure/vaccine history has been accommodated in previous research (23,24). Nevertheless, to give consideration to the consequences of not selecting participants according to vaccine history or prior exposure, we examined the data according to participants' baseline levels of antibody. Specifically, we identified whether individuals had evidence of antibody levels that were indicative of prior exposure (>1 IU/ml) or not (≤1 IU/ml). This was considered a

more accurate measure of vaccine history than participant recall of history, and also, it did not restrict us to only those participants who were able to recall this information (6% were unable to report their vaccine history). The results of the post hoc analyses on these two groups and Figure 3 suggest, first, as might be expected, that the antibody response was persistently lower in individuals whose baseline levels indicated no prior exposure, compared with those whose baseline levels were suggestive of prior exposure. Second, regardless of individuals' prior exposure status, massage was associated with an attenuated antibody response. These findings would tend to suggest that, despite not selecting participants according to vaccine history/prior exposure, our observations regarding the effects of massage on antibody responses to hepatitis B vaccine are robust. In particular, both primary and secondary immune responses to the vaccination seem to have been blunted after massage.

In sum, this study failed to find evidence in support of massage exerting a beneficial effect on immunity. Our results may have been related to the nature and/or duration of the massage or, indeed, the appropriateness of massage to a healthy population confronting a relatively immediate stressful situation. Thus, we propose that it may be premature to conclude that massage can be used to enhance immunity (28) and that further research is required before the effects of massage on immune function can be established.

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