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DOI:
10.1016/j.bbi.2004.10.004

Document Version
Peer reviewed version

Citation for published version (Harvard):
Phillips, A, Burns, V, Carroll, D, Ring, C & Drayson, M 2005, 'The association between life events, social support and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults', *Brain, Behaviour, and Immunity*, vol. 19, pp. 325-333. https://doi.org/10.1016/j.bbi.2004.10.004

Cite this article as: Phillips, A.C., Burns, V.E., Carroll, D., Ring, C., & Drayson, M. (2005). The association between life events, social support and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. Brain, Behavior and Immunity,19, 325-333.

The Association between Life Events, Social Support and Antibody Status Following Thymus-Dependent and Thymus-Independent Vaccinations in Healthy Young Adults.

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Abstract

This study determined whether stressful life events and social support were related to antibody status following both thymus-dependent and thymus-independent vaccinations. Life events in the previous year and customary social support were measured in 57 healthy students at baseline. Antibody status was also assessed at baseline and at five weeks and five months following vaccination with the trivalent influenza vaccine and the meningococcal A+C polysaccharide vaccine. Taking into account baseline antibody titre, high life events scores prior to vaccination were associated with lower responses to the B/Shangdong influenza strain at both five weeks and five months and meningococcal C at five weeks. Life events scores were not associated with response to the other two influenza viral strains nor response to meningococcal A. Those with high social support scores had stronger 5-week and 5-month antibody responses to the A/Panama influenza strain, but not to any of the other strains. These associations could not be accounted for by demographic or health behaviour factors, and also emerged from analyses comparing those who exhibited a four-fold increase in antibody titre from baseline with those who did not. Life events and social support were related to antibody status following influenza vaccination in distinctive ways that may be partly determined by vaccine novelty and prior naturalistic exposure. Life events also predicted poor antibody response to meningococcal C polysaccharide vaccination after previous meningococcal C conjugate vaccination. Neither psychosocial factor was associated with response to primary meningococcal A polysaccharide vaccination.

Keywords: influenza vaccination, meningococcal polysaccharide A+C vaccination, primary response, secondary response, social support, stressful life events, thymus-dependent, thymus-independent.

Assessing antibody response to medical vaccination is now regarded as a useful model for the study of psychosocial influences on *in vivo* immune function (Burns, Carroll, Ring, & Drayson, 2003; Cohen, Miller, & Rabin, 2001; Vedhara, Fox, & Wang, 1999). The vast majority of studies using this model have examined thymus-dependent vaccinations that involve T-cells, and most have reported that psychological stress was associated with a relatively poor antibody response to vaccination (Burns, Carroll, Ring, Harrison, & Drayson, 2002; Glaser et al., 1992; Jabaaij et al., 1993; Petrie, Booth, Pennebaker, Davison, & Thomas, 1995). For example, an association between the stress of caregiving and antibody response to the thymus-dependent trivalent influenza vaccination has also been demonstrated (Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Vedhara, Cox et al., 1999), although the relationship is not necessarily manifest across all viral components of the vaccination (Vedhara et al., 1999a). More recently, the impact of life events exposure and perceived stress on the antibody response to an influenza vaccination has been examined in young healthy populations. In one study, participants with higher negative life event exposures and perceived stress were less likely to be protected against influenza at five-month follow-up. However, of the three strains, only the A/New Caledonia and A/Panama appeared to be susceptible to stress (Burns, Carroll, Drayson, Whitham, & Ring, 2003). A recent study of first semester college freshmen examined self-reported stress and feelings of being overwhelmed during the period around the time of vaccination including the two days prior to and up to ten days following inoculation with one of two influenza vaccinations (Miller et al., 2004). Participants who were classified as reporting higher levels of stress cumulatively across the initial 13 day period exhibited a blunted antibody response to the A/New Caledonia strain at one and four months following vaccination. Self-reported stress, however, was not related to antibody response to any of the remaining three viral strains, A/Panama, B/Victoria, and B/Yamanashi. In none of these studies was the strain specificity of effects easily attributable to a range restriction in the variance of response to some strains.

Currently it is unclear why the response to certain influenza vaccine strains, particularly A-strains, is perturbed by stress while others remain unaffected. It might be expected that psychological stress would have its major impact on response to more novel strains, given

that individuals are less likely to have built up substantial protection before vaccination. It is certainly the case that A strains are more subject to minor mutations (antigenic drift) than B strains, and tend to be associated with more frequent influenza outbreaks and more severe illness (Health, 1996). However, B strains are more likely to undergo major mutations (antigenic shift), and thus could be considered to comprise the more novel vaccine components.

Given such uncertainties regarding the strain specificity of the effects of stress on response to influenza vaccination, it was considered appropriate to re-visit this key vaccination. Since there are no clear structural or functional differences among influenza vaccine components that would make them differentially susceptible to stress (Miller et al., 2004), it is important to determine the reliability of the result that effects are limited to A-strains. In addition to re-examining the effects of stress on different viral strains of the influenza vaccination, the investigation of different types of vaccine within the same population is another important step in determining which aspects of the immune response to vaccination are vulnerable to psychosocial influence. Antibody responses to most proteins, including the influenza vaccine, are thymus-dependent, that is it is obligatory that T-cells can recognise components of the protein antigen that have been recognised, processed and presented by the activated B-cell. In contrast, for thymus-independent antibody responses against polysaccharide antigens (including pneumococcal and meningococcal polysaccharides), polysaccharide activated B-cells generate an antibody response without T-cell help. Indeed, T-cell help cannot be evoked unless the polysaccharide is conjugated to a substance that can be processed and presented to CD4 antigen specific T-cells (in polysaccharide conjugate vaccines this is often diphtheria toxoid). If, for example, the effects of stress are restricted to antibody responses to thymus-dependent vaccines, this would imply that T-cell dependent responses are more susceptible than T-cell independent responses (Burns, Carroll, Ring et al., 2003). There is supportive evidence from elsewhere; a recent meta-analysis suggested that T-lymphocytes were more consistently perturbed than B-lymphocytes by acute stress exposures (Segerstrom & Miller, 2004).

Thus far, only two studies have examined the association between psychosocial factors and response to thymus-independent vaccination: in both cases the pneumococcal vaccination. One study in 5-year old kindergarten children, ratings of problem behaviour, presumed to be a measure of stress, were not associated with antibody response to the pneumococcal vaccination administered one week previously (Boyce et al., 1995). In contrast, current caregivers exhibited relatively poor antibody titres, but only at 3 and 6 months after vaccination (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000). However, caregivers and controls did not differ significantly in self-reported stress, although caregivers reported poorer social support. Thus, it is difficult to determine whether stress, social support, or indeed another unmeasured variable such as physical strain effected the deterioration in antibody titre.

Lamentably, social support has received far less attention than stress in the context of antibody response to vaccination. Aside from the study cited above, we are aware of only two other studies that have examined the association between social support and vaccination response. Whereas students who had seroconverted after the first injection of the standard three-dose hepatitis B vaccination were less anxious and reported lower stress levels, those who reported greater social support demonstrated a stronger combined immune response to the booster third inoculation (Glaser et al., 1992). In a recent report from the college freshmen study, loneliness and smaller social network size were associated with a poorer antibody response to the A/New Caledonian strain of the influenza vaccination (Pressman et al., in press). Since there is pervasive evidence linking social support and health (Cohen, 1988; Schwarzer & Leppin, 1991; Smith, 1994), further examination of the association between support and the antibody response to vaccination is warranted.

Accordingly, the present study examined the association between psychological stress, social support, and antibody response to both the trivalent thymus-dependent influenza vaccination and the thymus-independent meningococcal A+C vaccination, which has not been investigated in this context. First, it was hypothesised that the effects of psychological stress would be more apparent with the thymus-dependent vaccine. Second, it was expected that psychosocial factors would not influence all influenza strains equally, but that there would be

strain specificity. Third, it was hypothesised that better social support would be associated with a better antibody response to vaccination.

Method

Participants

Fifty-seven University of Birmingham students (31 men and 26 women) were recruited from between November 2002 and January 2003. None of the participants had received an influenza vaccination in the past year or meningococcal A or A+C vaccinations ever, reported influenza in the winter prior to participation or meningitis ever, admitted to a history of negative reactions to blood sampling (e.g. fainting), or reported suffering from a current acute infection, chronic medical condition, or immune disorder (e.g. glandular fever); in addition, none had a history of vaccine-related allergies or side-effects, was pregnant or suspected to be pregnant, was breast-feeding, or was taking prescribed medication (excluding the contraceptive pill). The majority of participants (N=50) had received the conjugate meningitis C vaccination, 13 or more months prior to participation (96%), while at school or college (88%) as part of National Health Service policy. Participants' mean age was 19.8 (*SD* = 2.3) years and their mean body mass index, based on reported height and weight, was 23.9 (*SD* = 3.6). In terms of ethnicity, 50 described themselves as "white", four as "Asian", two as "black", and one as "other". Ninety-five percent of the sample reported being non-smokers. They were paid £10 for participating and had a chance of winning a further £50 from a random draw. The study was approved by the appropriate Research Ethics Committees, and all participants provided written informed consent.

Study Design

The study comprised three sessions. In December / January, participants attended an initial session for 45 min, during which time they completed demographic, health behaviour and psychological questionnaires and provided a single venous blood sample. They were then medically screened for eligibility for influenza and meningococcal A+C vaccinations. All were judged eligible and were duly vaccinated. At follow-up sessions, which took place five weeks and five months later, participants provided a further venous blood sample to measure antibody titre.

Questionnaires

At baseline, in addition to assessments of stressful life events, social support, and health behaviours, standard socio-demographic data including date of birth, height, and weight were gathered.

Psychological stress

Stressful life event exposure was assessed by the Life Events Scale for Students (LESS) (Linden, 1984). This is a student-specific life events inventory in which participants are required to select, from a list of 36, those life events that they had experienced in the last year and includes mainly major life events that are likely to be recalled accurately over such a time frame. Participants were also asked to rate each event on a four-point scale of severity, and in addition to the frequency of life events, a score weighted for self-rated severity was calculated. For analytic purposes, life events exposure was represented in two ways: a simple frequency count of events; and the score weighting events for perceived severity.

Social Support

At baseline, participants completed the Medical Outcomes Study Social Support Survey (MOSSSS) (Sherbourne & Stewart, 1991). This questionnaire provides an overall measure of structural support (number of close friends) and functional social support, which represents the aggregate of scores on four functional support dimensions: emotional/informational (e.g. someone to listen to you when you need to talk); tangible (e.g. someone to help you if you were confined to bed); affectionate (e.g. someone who hugs you); and positive social interaction (e.g. someone to get together with for relaxation). The questionnaire has a five-point Likert-type format ranging from none of the time to all of the time. Internal consistency is high, with all alphas exceeding 0.91, and one-year test-retest reliability values ranging from 0.72-0.78 have been reported for the four dimensions (Sherbourne & Stewart, 1991).

Health Behaviours

Health behaviours over the year preceding entry to the study were assessed using a questionnaire adapted from the Whitehall II study (Marmot et al., 1991). Participants were

asked, on average how much they smoked (0, 1-5, 6-10, 11-20, 21+ cigarettes per day); how much alcohol they drank (0, 1-5, 6-10, 11-20, 21-40, 40+ units per week)[1]; how long they slept (0-3, 4-5, 6-7, 8-9, 10-11, 12+ hours per night); and how often they take vitamin/mineral supplements (never, once a month, once a week, a few per week, every day, more than one per day). A simple categorical scoring system was used in all cases, for example if a participant indicated that they slept for 8-9 hours per night, they were allocated a score of 3. Participants also reported how much time they spent in activities of light, moderate and vigorous exercise intensity (0, 1-2, 2-5, 6-8, 9-10, 11+ hours per week). The category scores (0,1,2,3,4, or 5), derived from the above were multiplied by a weighting of 1,2, and 3 for light, moderate, and vigorous intensity activity respectively, and the products summed to yield a composite exercise score. From the dietary section of the questionnaire, two main measures were derived (Burns, Drayson, Ring, & Carroll, 2002): scores for fresh fruit and cooked vegetables were summed to give a measure of fruit and vegetable consumption; and scores for chips/fried food, crisps/similar, sweets/chocolate, biscuits/cakes/puddings, full fat dairy products, and processed meat were summed to provide an index of fat intake[2].

Blood samples, vaccinations and immunological assays

At the initial and the two follow-up sessions, venous blood was collected from an ante-cubital vein into two 6 ml plain tubes (BD Vacutainer, Meylan Cedex) and one 2ml tube containing potassium ethylene diaminetetraacetic acid (EDTA K3E 15 %, 0.054 ml, BD Vacutainer, Meylan Cedex). Following blood sampling in the initial session, participants received a Fluarix influenza vaccine (Glaxo SmithKline; Batch No: 18705B9) and an AC Vax meningitis A+C vaccination (Glaxo SmithKline; Batch No: N357A44D) via intramuscular injections into the upper arms. The Fluarix vaccine contained three viral strains: A/New Caledonia/20/99 (H1N1)-like strain - A/New Caledonia/20/99 (IVR-116); A/Moscow/10/99 (H3N2)-like strain - A/Panama/2007/99 (RESVIR-17); and B/Hong Kong/330/2001-like strain - B/Shangdong/7/97. The two 6 ml blood samples, which were allowed to clot for one hour, were centrifuged at 3500 rpm for 5 min and the separated serum was frozen at –20 °C until assayed for antibody titres. The serum samples were analysed separately for influenza and meningitis antibodies. Anti-influenza antibody titres were measured by the serology laboratory of Glaxo Smith Kline Beecham at Dresden, Germany, using a haemagglutination

inhibition test as described in the World Health Organisation Manual on Animal Influenza Diagnosis and Surveillance (*World Health Organisation Global Influenza Programme: Manual on Animal Influenza Diagnosis and Surveillance*). Wild type flu strains were used for the antigenic analysis; these were A/New Caledonia/20/99, A/Panama/2007/99, and B/Shangdong/7/97. Anti-meningococcal A and anti-meningococcal C antibodies were assayed at the Public Health Laboratory Service Meningococcal Reference Unit, Withington Hospital, Manchester. Serum Neisseria meningitidis serogroup A and C polysaccharide-specific immunoglobulin G (IgG) levels were determined quantitatively, in μg/ml, by a standardised enzyme-linked immunosorbent assay (ELISA). Fifty-five participants attended the five-week follow-up session, and 51 at five-month follow-up, and provided adequate serum for analysis.

Data Reduction and Analysis

Antibody levels at baseline, five-week, and five-month follow-up were subject to $\log_{10}$ transformation and then compared using MANOVA, followed, where appropriate, by post hoc testing using the Newman Keuls method. Effect sizes are reported in terms of η^2. Hierarchical regression was then conducted using log antibody titre at five weeks and five months to each vaccine component as the dependent variables. Log baseline titre was entered at step one to control for baseline antibody status. Each psychosocial independent variable was then entered at step two. Similar analyses were used for demographic and health behaviour variables. Any such variables associated with follow-up antibody titre were then entered in addition to baseline or five-week titre at step one, with the psychosocial independent variable again being entered at step two. Change in R^2 was taken as the measure of effect size. For analysis of the response to meningococcal C vaccine strain, only those participants (N=50) who had received the conjugate meningococcal C vaccination prior to recruitment to this study were included. Those who had previously received the meningococcal C conjugate vaccine had significantly higher $\log_{10}$ baseline titres than those who had not, $t(54) = 3.12$, $p = .003$; the geometric mean titres for those who had and had not been previously vaccinated were 7.76 and 1.64 μg/ml, respectively. In addition, MANOVA on the $\log_{10}$ titres at the two follow-ups, with baseline $\log_{10}$ titre as a covariate, yielded a significant interaction between prior vaccination status and follow-up period, $F(1,47) = 8.90$,

$p = .005$, $\eta^2 = .159$; those who had received the prior vaccination showed a more sustained response to the meningococcal C component. There were no effects of prior vaccination on any of the other strains.

Supplementary analysis was undertaken using logistic regression. Following convention (Al-Shamma & Al-Sa'ad, 1987; Burns, Carroll, Drayson et al., 2003; Vedhara, Cox et al., 1999), it was established whether or not participants registered a four-fold or greater increase in antibody titre from pre-vaccination baseline to five-week and five-month follow-ups for each vaccine component. A four-fold increase from pre-vaccination baseline is considered the clinical criterion of adequate protection. For each vaccine strain, participants were then classified either as responders or non-responders, on the basis of whether or not they had achieved a four-fold increase in titre from baseline. These classifications served as the dependent variables, with the psychosocial measures acting as the independent variables. Significant bivariate associations were then adjusted, where appropriate, for demographic variables and health behaviours. Throughout, the odds ratio (OR) is reported to indicate effect size.

Results

Questionnaire Data

The mean (*SD*) number of life events was 7.18 (2.56), and the life events score weighted for self-rated severity, was 16.28 (7.75). The mean (*SD*) number of close friends was 8.09 (4.22), and mean (*SD*) total functional social support score was 65.61 (13.74). For the social support sub-scales, participants' mean scores were: 13.00 (3.25) for tangible support, 14.20 (3.57) for emotional support, 13.84 (13.30) for informational support, and 10.30 (2.94) for affectionate support. Life events scores were not significantly correlated with number of close friends, total social support score, or any of the subscale scores, rs(53) = –.24 to .09, $p = .08$ to .52.

Vaccination Response

The geometric mean *(95%CI)* antibody titre for each of the vaccine components at each time point is displayed in Table 1. The number of participants with and without a four-fold increase to each of the three viral strains at five-week and five-month follow-up is presented

in Table 2. All participants responded with an initial increase in antibody titre from baseline at five weeks, which had declined to some extent by the five month measurement point, but remained above baseline levels.

[Insert Tables 1 and 2 about here]

Associations between Stressful Life Events and Follow-up Antibody Response

Taking into account baseline antibody status, statistically significant associations emerged between life events scores and follow up antibody titre for the thymus-dependent B/Shangdong influenza viral strain and thymus-independent meningitis C. Lower antibody titres for B/Shangdong at five-week follow-up were associated with life events, both in terms of the number of events, $B = –0.05$, *95%CI* = –0.10 to –0.01, $\beta = –.27$, $t = 2.39$, $p = .02$, $\Delta R^2 = .07$, and the weighted score, $B = –0.02$, *95%CI* = –0.04 to –0.01, $\beta = –.35$, $t = 3.11$, $p = .003$, $\Delta R^2 = .11$. The weighted life events score was also negatively related to five month B/Shangdong antibody titre, $B = –0.02$, *95%CI* = –0.04 to –0.01, $\beta = –.28$, $t = 2.68$, $p = .01$, $\Delta R^2 = .07$. The total number of stressful life events was also negatively associated with meningococcal C antibody titre at five weeks, $B = –0.04$, *95%CI* = –0.09 to 0.00, $\beta = –.24$, $t = 1.99$, $p = .05$, $\Delta R^2 = .06$, although not at five months. Life event scores were not significantly related to follow-up antibody titres for the other thymus-dependent influenza strains or the thymus-independent meningococcal A.

Associations between Social Support and Follow-up Antibody Response

There were significant positive associations between functional social support measures and antibody titre at five weeks and five months for the thymus-dependent A/Panama strain. Higher total social support scores predicted higher antibody titre at five weeks, $B = 0.01$, *95%CI* = 0.00 to 0.02, $\beta = .29$, $t = 2.06$, $p = .04$, $\Delta R^2 = .08$, but not at five months. Of the social support subscales, tangible social support was positively associated with A/Panama antibody titre at both five weeks, $B = 0.04$, *95%CI* = 0.01 to 0.07, $\beta = .34$, $t = 2.47$, $p = .02$, $\Delta R^2 = .11$, and five months $B = 0.05$, *95%CI* = 0.01 to 0.09, $\beta = .34$, $t = 2.45$, $p = .02$, $\Delta R^2 = .11$. There were no significant associations with any of the social support measures and the

A/New Caledonia and B/Shangdong antibody titres at either follow-up. Similarly, social support was not related to response to either meningococcal A or C vaccination.

Associations between Demographic and Health Behaviour Variables, and Follow-up Antibody Response

Age and BMI were not associated with the antibody response to any of the three influenza viral strains at either follow-up. There were also no consistent relationships between health behaviours and any of the three viral strains. However, sex (men = 0, women = 1) was significantly related to the A/Panama antibody titre at five weeks, B = –0.22, *95%CI* = –0.43 - –0.01, β = –.28, t = 2.07, p = .04, ΔR^2 = .08, and the B/Shangdong antibody titre at five months post-vaccination, B = –0.28, *95%CI* = –0.52 - –0.04, β = –.24, t = 2.36, p = .02, ΔR^2 = .06, such that women had lower antibody responses.

Consequently, sex was added to the regression models at step one, but the associations reported earlier remained statistically significant. Life event scores continued to be negatively related to B/Shangdong antibody titre at five weeks for both the number of life events, B = –.05, *95%CI* = –0.10 to 0.00, β = –.25, t = 2.18, p = .03, ΔR^2 = .06, and weighted score, B = –.02, *95%CI* = –0.04 to –0.01, β = –.32, t = 2.67, p = .01, ΔR^2 = .08. As before, at five months, only the weighted score was significantly associated with B/Shangdong antibody titre B = –.02, *95%CI* = –0.03 to 0.00, β = –.22, t = 2.00, p = .05, ΔR^2 = .04. Total, B = 0.01, *95%CI* = 0.00 to 0.02, β = .33, t = 2.43, p = .02, ΔR^2 = .10, and tangible, B = 0.04, *95%CI* = 0.00 to 0.07, β = .30, t = 2.20, p = .03, ΔR^2 = .08, social support scores remained positively associated with A/Panama antibody titre at five weeks. In addition, the significant associations between these social support variables and A/Panama were also evident at five-month follow-up for both total, B = 0.01, *95%CI* = 0.00 to 0.02, β = .32, t = 2.25, p = .03, ΔR^2 = .09, and tangible, B = 0.05, *95%CI* = 0.01 to 0.08, β = .32, t = 2.38, p = .02, ΔR^2 = .10, social support.

For response to meningococcal A+C vaccination, there were few significant associations with demographic or health behaviour variables. However, age was negatively related to five-week, B = –0.06, *95%CI* = –0.11 to –0.02, β = –.40, t = 2.82, p = .007, ΔR^2 = .15, and five-

month, B = –0.12, *95%CI* = –0.18 to –0.06, β = –.29, t = 4.09, $p < .001$, ΔR^2 = .08 meningitis C antibody titres. Older participants had lower antibody titres, although this could simply be a marker for when they received their previous meningococcal C vaccination. Consequently, age was added into the regression model linking life events with five-week meningococcal C antibody titre: the association remained significant, B = –0.04, *95%CI* = –0.08 to 0.00, β = –.23, t = 2.12, $p < .04$, ΔR^2 = .05. The only significant associations for meningitis A were for sleep, B = –0.24, *95%CI* = –0.47 to –0.02, β = –.25, t = 2.18, p = .03, ΔR^2 = .06, and fruit and vegetable consumption, B = 0.06, *95%CI* = 0.01 to 0.11, β = .30, t = 2.40, p = .02, ΔR^2 = .08, which both predicted five month antibody titre; individuals who slept longer and ate less fruit and vegetables had lower antibody titres.

Supplementary Analysis of Participants Exhibiting and Not Exhibiting a Four-Fold Increase from Baseline Titre

Of the influenza strains, only for A/Panama and B/Shangdong were there sufficient participants without a four-fold increase to permit analysis (see Table 2). Statistically significant associations with life event scores were again observed only for B/Shangdong. Those with higher life event scores were less likely to be four-fold responders at five weeks, for both the total number of events, OR = 1.45, *95%CI* = 1.02 to 2.06, p = .04, and the weighted score, OR = 1.19, *95%CI* = 1.05 to 1.34, p = .007. Again, at five months the weighted score predicted who would be four-fold responders to B/Shangdong relative to baseline, OR = 1.23, *95%CI* = 1.08 to 1.41, p = .002. In addition, in these analyses, the total number of events reported also predicted five-month antibody status, OR = 1.77, *95%CI* = 1.21 to 2.58, p = .003. These associations withstood adjustment for demographic variables and health behaviours. Participants with a high life events score were also more likely to exhibit a four-fold antibody response to meningitis C at five weeks, but this association was significant only following adjustment for age, OR = 1.38, *95%CI* = 1.22 to 5.11, p = .04. For social support, again effects emerged only for the A/Panama viral strain. Total social support score was positively related to antibody status at both five weeks, OR = 0.95, *95%CI* = 0.91 to 0.99, p = .04, and five months, OR = 0.95, *95%CI* = 0.91 to 0.99, p = .04. Similar associations emerged for tangible social support; at five weeks, OR = 0.81, *95%CI* = 0.67 to 0.99 p = .04, and at five months, OR = 0.74, *95%CI* = 0.59 to 0.93, p = .009. In addition,

these analyses indicated that those with high levels of emotional social support, OR = 0.84, *95%CI* = 0.71 to 1.00, $p = .05$, were more likely be four-fold responders at five-week follow-up. Again, the associations for social support withstood adjustment for demographic variables and health behaviours. No consistent associations emerged for meningococcal A. The key significant associations are presented in Figure 1.

Discussion

Participants who had higher life events scores over the previous year had lower antibody titres to the B/Shangdong viral strain of the trivalent influenza vaccine at both five-week and five-month follow-ups. In addition, those with higher life events scores were less likely to mount a four-fold response to this strain at five weeks and five months. These results add to the growing consensus that psychological stress has a negative impact upon the antibody response to influenza vaccination (Burns, Carroll, Drayson et al., 2003; Kiecolt-Glaser et al., 1996; Miller et al., 2004; Vedhara, Cox et al., 1999) and to the broader literature implicating stress in compromising the response to a range of thymus-dependent vaccine challenges (Burns, Carroll et al., 2002; Glaser et al., 1992; Jabaaij et al., 1993; Morag, Morag, Reichenberg, Lerer, & Yirmiya, 1999; Petrie et al., 1995).

In line with other studies of influenza vaccination, the present association between stress and antibody status did not occur for all strains. The present findings, though, challenge the notion that stress effects may be A-strain specific (Miller et al., 2004). Both the A/New Caledonian and A/Panama strains have been components of the Northern hemisphere influenza vaccine since 2000 (*World Health Organisation Global Influenza Programme: Manual on Animal Influenza Diagnosis and Surveillance*), and thus current rates of naturalistic exposure are likely to be high and novelty is likely to be lower in the present study, which used the 2002-03 vaccine, than the two earlier studies (Burns, Carroll, Drayson et al., 2003; Miller et al., 2004). In contrast, examination of the B strains comprising the influenza vaccination in previous years indicates that the B/Shangdong viral strain had not been a regular component of the Northern hemisphere influenza vaccine until winter 2002 (*World Health Organisation Global Influenza Programme: Manual on Animal Influenza Diagnosis and Surveillance*). Participants exhibited lower baseline antibody levels to

B/Shangdong than the two other viral strains. Thus, relative novelty may be what mainly determines whether or not stress effects will be observed with a thymus-dependent vaccine. Novelty and prior exposure have been cited previously to explain strain-specific associations (Vedhara, Cox et al., 1999).

Few studies have examined the impact of other psychosocial variables, such as social support, on antibody response following vaccination. The present study suggests that this would be a fruitful line for further enquiry, as there was evidence that high levels of functional social support, particularly tangible support, were associated with better antibody responses. This result is broadly in line with the findings from the two other vaccine studies which have shown that social support can influence vaccination response (Glaser et al., 1992; Pressman et al., in press). In the present study, the association between antibody status and social support appeared for a different influenza strain, A/Panama, from that which proved susceptible to the effects of stress. Thus, it would appear that the effects of different psychosocial variables may not necessarily be localized to the same influenza strain, and that variables such as social support can affect the antibody response to vaccination in a different way from stress. Whereas novelty and low baseline levels of exposure may increase the likelihood of observing stress effects on thymus-dependent vaccination response, it may be low novelty which affords the necessary conditions for social support to influence thymus-dependent vaccination response. This speculation receives support from the results of a previous study of hepatitis B vaccination. The effects of stress appeared following the initial administration of what would be a novel antigen, whereas the associations with social support only emerged later, following the third and less novel booster injection (Glaser et al., 1992). However, the results of the other recent study examining social support suggest that arguments in terms of low novelty and high likelihood of naturalistic exposure should be treated with caution at this stage (Miller et al., 2004).

Higher numbers of life events predicted lower antibody titres at five weeks to the C component of the thymus-independent meningococcal polysaccharide A+C vaccination. However, the vast majority of participants had already received a conjugate meningococcal C vaccination as part of a national vaccination programme. In this conjugate vaccination, the

meningitis C polysaccharide is conjugated to a protein molecule, diphtheria toxoid in order to evoke a thymus-dependent antibody response to a thymus-independent polysaccharide antigen. Thus, in the present study, the antibody response to the C component would have engendered a thymus-independent primary response and, in part, a secondary response utilising the memory B-cells induced by the previous meningococcal C conjugate vaccination. The present result can be interpreted as further evidence of the general susceptibility of secondary antibody responses to psychosocial influence (Cohen et al., 2001). There has only been one previous study of meningococcal C vaccination in this context (Burns, Drayson et al., 2002); high perceived stress and psychological distress levels were found to be associated with an increased risk of having low antibody levels against meningococcal C polysaccharide.

Responses to meningococcal A vaccination were not related to either stressful life events or social support in the present study. This implies that the effects of psychosocial factors, such as stress and social support, may be limited to antibody responses that either include a thymus-dependent element (Burns, Carroll, Ring et al., 2003) or are secondary. However, the finding that student examinees exhibiting higher anxiety and perceived stress failed to seroconvert following the first administration of a hepatitis B vaccination (Glaser et al., 1992) and the demonstration of stress effects for the primary keyhole limpet hemocyanin challenge (Snyder, Roghmann, & Sigal, 1990) lend more weight to the suggestion that it may be the thymus-dependent aspect of vaccines that render them susceptible to psychosocial influence.

Two previous studies have examined the effects of psychosocial factors on thymus-independent vaccines. Whereas one found no association between a behavioural measure of stress and antibody titre two weeks following pneumococcal vaccination in pre-school children (Boyce et al., 1995), the other reported that elderly caregivers exhibited a lower antibody titre between three and six months following pneumococcal vaccination than matched controls, which could be attributed to either chronic stress or poorer social support (Glaser et al., 2000). Taken together, these results can be interpreted as indicating that whereas psychosocial factors do not impact upon the initial formation of antibodies to thymus-independent vaccination, they may have consequences for the maintenance of antibody levels. However, the relatively long time course of the present study questions this

interpretation, since stress and social support were not associated with either the initial antibody response or later five-month antibody status. Nevertheless, variations between studies in population and the particular thymus-independent vaccine employed make direct comparison difficult.

A potential limitation of the present study was the relatively small sample size employed. However, it was of the same order as that used in the majority of previous studies of stress and medical vaccination (Burns, Carroll, Drayson et al., 2003; Burns, Drayson et al., 2002; Glaser et al., 1992; Glaser et al., 1998; Glaser et al., 2000; Jabaaij et al., 1996; Marsland, Cohen, Rabin, & Manuck, 2001; Miller et al., 2004; Petrie et al., 1995; Petry, Weems, & Livingstone, 1991; Pressman et al., in press). In addition, the inclusion of only one vaccine that exclusively elicited a primary response in this study makes it difficult to interpret the relative insensitivity of meningococcal A to psychosocial factors. Nevertheless, this is the first study that we know of to assess concurrently the effects of psychosocial factors on both thymus-dependent secondary responses, as well as thymus–independent primary and secondary responses, to vaccination.

In summary, stressful life events were significantly associated with a poorer antibody response to the B/Shangdong influenza strain and the C component, but not the A component, of the meningococcal polysaccharide vaccination. Social support was protective of antibody status following vaccination, but only for the A/Panama influenza viral strain. The observed relationships withstood adjustment for demographic variables and health behaviours. Such strain-specific effects for the influenza vaccination could reflect the influence of virus novelty and prior exposure on thymus-dependent responses. It is likely that our participants, because of prior vaccination, mounted a partially secondary response to meningococcal C. Thus, it would seem that it is thymus-independent antibody responses to vaccination are more resistant to psychosocial influence. Clarification of which specific immunological processes are sensitive to such influence will come only from further research using multiple vaccinations, including a range of thymus-independent and primary thymus-dependent challenges.

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Acknowledgement

The authors would like to acknowledge the valuable help of Ms Kate Edwards and Ms Jet Veldhuijzen van Zanten in the collection and processing of blood samples.

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[1] One unit is the equivalent of half a pint (284ml) of beer, one standard glass of wine (125ml), or a single shot of spirits (25ml).

[2] British-American dictionary: chips = French fries, crisps = chips, sweets = candies, biscuits = cookies.

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Table 1. *Geometric Mean (95% Confidence Intervals) Antibody Titres (μg/ml) for each Viral Strain Pre-Vaccination and at the Five Week and Five-month Follow-ups*

Viral Strain	Pre-vaccination	Five-week Follow-up	Five-month Follow-up	MANOVA (p<.001)
A/New Caledonia/20/99	26	1928[a]	1180[b, c]	F(2,49) = 156.18
	(1 – 477)	*(182 - 20417)*	*(132 - 10715)*	$\eta^2 = 0.864$
A/Panama/2007/99	35	314[a]	242[b, c]	F(2,49) = 52.33
	(3 – 437)	*(54 - 1820)*	*(35 - 1698)*	$\eta^2 = 0.681$
B/Shangdong/7/97	17	377[a]	161[b, c]	F(2,49) = 183.3
	(2 – 170)	*(40 - 3631)*	*(11 - 2344)*	$\eta^2 = 0.882$
Meningitis A	*2*	*21* [a]	*16* [b, c]	F(2,48) = 98.07
	(0-28)	*(1-372)*	*(1-309)*	$\eta^2 = 0.803$
Meningitis C	8	65 [a]	44 [b, c]	F(2,45) = 39.50
	(0-324)	*(8-501)*	*(5-355)*	$\eta^2 = 0.637$

[a] significant difference between pre-vaccination and 5-week follow-up

[b] significant difference between pre-vaccination and 5-month follow-up

[c] significant difference between 5-week and 5-month follow-up

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Table 2. *Number (%) of Participants With and Without a Four-Fold Response to Each Vaccine Strain at Five Weeks and Five Months*

Follow-up	Strain	Responders	Non-Responders
5 Weeks	A/New Caledonia/20/99	54 (98%)	1
	A/Panama/2007/99	36 (66%)	19
	B/Shangdong/7/97	49 (89%)	6
	Meningitis A	44 (80%)	11
	Meningitis C	28 (58%)	20
5 Months	A/New Caledonia/20/99	49 (94%)	3
	A/Panama/2007/99	31 (60%)	21
	B/Shangdong/7/97	43 (83%)	9
	Meningitis A	37 (74%)	13
	Meningitis C	22 (48%)	24

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Figure Caption

Figure 1. Associations between Psychosocial Factors and whether or not Participants Mounted a Four-fold Antibody Response.

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