Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination.

Gallagher, S; Phillips, Anna; Drayson, Mark; Carroll, Douglas

DOI:
10.1016/j.bbi.2008.05.006

Document Version
Peer reviewed version

Citation for published version (Harvard):
Gallagher, S, Phillips, A, Drayson, M & Carroll, D 2009, 'Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination.', *Brain, Behaviour, and Immunity*, vol. 23, no. 3, pp. 338-46. https://doi.org/10.1016/j.bbi.2008.05.006

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination.

Stephen Gallagher[1,*], Anna C. Phillips[1], Mark T. Drayson[2], and Douglas Carroll[1]

[1] School of Sport and Exercise Sciences, University of Birmingham, Birmingham, England

[2] Division of Immunity and Infection, Medical School, University of Birmingham, Birmingham, England

[*]Corresponding author. Fax: ++44 121 414 4121. *E-mail address:* sxg598@bham.ac.uk (Stephen Gallagher)

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

Abstract

In older populations, caregiving for a spouse with dementia has been associated with a poor antibody response to vaccination. The present study examined whether younger caregivers, specifically the parents of children with developmental disabilities, would also show a diminished antibody response to vaccination. At baseline assessment, 30 parents of children with developmental disabilities and 29 parents of typically developing children completed standard measures of depression, perceived stress, social support, caregiver burden, and child problem behaviours. They also provided a blood sample and were then vaccinated with a pneumococcal polysaccharide vaccine. Further blood samples were taken at 1- and 6-month follow-ups. Caregivers mounted a poorer antibody response to vaccination than control parents at both follow-ups. This effect withstood adjustment for a number of possible confounders and appeared to be, at least in part, mediated by child problem behaviours. The negative impact of caregiving on antibody response to vaccination is not restricted to older spousal caregivers, but is also evident in younger parents caring for children with developmental disabilities. The behavioural characteristics of the care recipients may be a key consideration in whether or not immunity is compromised in this context.

Keywords: Antibody response; Caregiving; Children with developmental disabilities; Child problem behaviours; Chronic stress; Pneumococcal vaccination

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

Antibody response to vaccination provides a useful model for studying psychosocial influences on *in vivo* immune function (Burns et al., 2003a; Phillips and Burns, 2008; Vedhara et al., 1999a). Stress, whether measured as life events exposure, perceived stress, or negative affect has been found to be inversely associated with the antibody response to a variety of medical vaccinations (Burns et al., 2003b; Burns et al., 2002; Gallagher et al., 2008a; Marsland et al., 2001; Phillips et al., 2005; Phillips et al., 2006), implying that those experiencing stress have a reduced capacity to fight viral and bacterial infections. In humans, the effects of chronic stress on immunity have mainly been studied by comparing non-routine caregivers and broadly matched controls (Kiecolt-Glaser et al., 1991; Kiecolt-Glaser et al., 1987; Mills et al., 2004; Redwine et al., 2004; Vedhara et al., 1999b; Vitaliano et al., 1998). There is now reasonable consensus that older spousal caregivers of dementia patients have a relatively poor response to both influenza and pneumococcal vaccinations (Glaser et al., 2000; Kiecolt-Glaser et al., 1996; Vedhara et al., 1999a). However, younger caregivers have rarely been studied in this context.

The only published vaccination study to target younger caregivers found no differences in antibody response to influenza vaccination between those caring for a spouse with multiple sclerosis and controls (Vedhara et al., 2002). This raises the issue of whether the poor antibody response observed in older caregivers is, to an extent, a function of an interaction between chronic stress exposure and immuosenescence, and accordingly will be less likely to occur in younger caregivers (Graham et al., 2006; Kiecolt-Glaser et al., 2003). Indeed, a recent study from our group supports such a notion (Gallagher et al., 2008b). S-IgA secretion rates were found to be lower in non-routine caregivers relative to controls, but only for the oldest of three distinct age cohorts. Nevertheless, analysis within the caregiving group indicated that for the youngest and the middle-aged cohorts, S-IgA secretion rates varied negatively with caregiving burden and strain.

There is, however, an alternative explanation for the discrepancy in outcomes among the caregiver vaccination studies. Rather than immuosenescence, it is possible that it is

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

the intensity of the chronic stress experienced that determines whether caregiving becomes an issue for immunity (Vedhara et al., 2002). Dementia is a disease characterised by much more severe cognitive and behavioural disturbances than multiple sclerosis (Gregory and Hodges, 1996; Keegan and Noseworthy, 2002; Neary et al., 1998; Poser et al., 1983). Accordingly, the precise caregiving experience will vary between those caring for patients with multiple sclerosis and dementia. Indeed, older spousal caregivers of dementia patients have been found to report greater distress than younger multiple sclerosis caregivers (Vedhara et al., 2002). Further, the results of two recent meta-analyses indicate that caregivers of dementia patients generally experience greater burden and report more symptoms of depression than those caring for non-dementia, e.g., cancer patients, (Pinquart and Sorensen, 2003a, b). Thus, it might be hypothesized that, irrespective of the caregiver's age, caring for someone with severe cognitive and behavioural problems will compromise immunity.

A model which would allow us to shed light on these competing propositions is young parents caring for children with developmental disabilities. Dealing with severe cognitive difficulties and behaviours that are problematic and distressing are the main challenges of such caring (Floyd and Gallagher, 1997; Hastings et al., 2006; Higgins et al., 2005; Maes et al., 2003). Few previous studies have examined the impact of caregiver stress on immunity in relatively young caregivers *per se*, let alone in parents caring for a child with a developmental disability. Table 1 provides a summary of the studies of young caregivers and the immune outcomes. As can be seen, caregivers were daughters, mothers, adult children, and spouses. Not all studies employed a case-control design and, in those that did, there were few differences between caregivers and controls in immune function. Exceptions were the observation that mothers of pre-term infants showed a poorer *in vitro* proliferative response to mitogens than mothers of full-term infants (Gennaro et al., 1997) and that mothers of children with cancer had lower glucocorticoid sensitivity than parents of healthy children (Miller et al., 2002). For the most part, these studies examined the consequences for immunity of caring for someone with a physical rather than a mental health problem. In only one was the care-recipient a

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

child with an developmental disability; caregivers had a lower T helper: suppressor ratio than controls (Pariante et al., 1997).

[Insert Table 1 about here]

Although possible physiological mediators of the diminished antibody responses in elderly caregivers have received some attention (Kiecolt-Glaser et al., 1996; Li et al., 2007; Vedhara et al., 1999a), consideration of psychological and circumstantial mediators has been sparse (Vitaliano et al., 2003). Research has identified caregiver burden as a potent contributor to psychological distress in various caregiver groups (Beach et al., 2000; Cooper et al., 2007; Garand et al., 2005). For those parents caring for children with developmental disabilities, child problem behaviours emerge as an additional factor (Gallagher et al., in press,d; Hastings and Brown, 2002). Further, perceived stress and depression have been associated with a reduced antibody response in older caregivers (Li et al., 2007), and caregivers almost invariably differ from controls in the social support they can draw on; those who are socially isolated appear to suffer poorer immunity (Baron et al., 1990; Kiecolt-Glaser et al., 1987). Consequently, it is possible that a poor antibody response to vaccination will be particularly evident in parental caregivers who are more distressed, socially isolated, burdened, and report more child problem behaviours.

The present study compared the responses to pneumococcal vaccination of relatively young parents caring for a child with a developmental disability and parents caring for a typically developing child. As such, it is the only study that we know of that has examined antibody response to vaccination in parents caring for a child with a developmental disability. In addition, these particular caregivers provide an optimal model for testing whether the poorer antibody response to vaccination observed in older caregivers of dementia patients is specific or generalizes to younger caregivers with similar or even greater caregiving demands, i.e., is it the age of the caregiver that mainly matters or the characteristics of the care recipient? Finally, by measuring psychological and caregiving characteristics of our participants in greater detail than previous caregiving studies, we also

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

aspired to shed light on the psychosocial determinants of any impairment in antibody response in the present caregivers. It was hypothesized that parents of children with developmental disabilities would report substantially more distress and exhibit a poorer antibody response. We also explored whether it was distress, social support, burden, or the child's problem behaviours that was most strongly associated with any impairment in vaccination response.

2. Methods

2.1. Participants

Thirty-two parents caring for children with developmental disabilities and 29 parents of normally developing children attended the baseline session. Developmental disabilities is the term used to describe conditions including but not limited to Autism spectrum disorders and Downs syndrome (National Institute of Child Health and Development, National Institute of Health- http://www.nih.gov/icd/). These parental caregivers were recruited via invitation letters distributed by their respective associations and by advertising in syndrome newsletters, and by direct contact with family support groups. Inclusion criteria for these parents were: caring for at least one child with Autism, Downs, Cornelia de Lange, or Smith-Magenis syndromes. Since the emotional reaction of parental caregivers is highly influenced by the diagnostic process (Graungaard and Skov, 2007), we aimed to avoid this particular event and focus on the parents' stressful experiences of caring *per se.* Thus, in keeping with existing research (Hastings et al., 2006), children with developmental disabilities had to be aged between 3 and 19 years and living at home during the school term. These children attended either 'special needs' schools or had 'special need provision' in main stream school. The majority of parents reported caring for a child with Autism (66%); the remainder were caring for a child with Downs (22%) or with other syndromes (12%). Controls, i.e. parents of typically developing children who were in the same age range as the disabled sample, were recruited via local schools, media campaigns and newspaper advertisements. One caregiver parent reported that he had previously received the

pneumococcal vaccine and was thus was excluded from participation. No other parents had received the pneumococcal vaccine previously or had a history of negative reactions to blood sampling (e.g., fainting). None reported suffering from a current acute infection, chronic medical condition, or immune disorder (e.g., glandular fever), or taking prescribed medication (excluding the contraceptive pill). None of the female participants reported that they were pregnant. Attempts were made to match the groups as closely as possible on age, sex, socioeconomic position, ethnicity, and marital status, by recruiting individual parents of normally developing children that matched as near as possible individual parents of children with developmental disabilities.

2.2. Study design and procedure

This was a prospective case-control study involving three testing sessions: baseline, 1-month and 6-month follow-up. At baseline, parents completed questionnaires and then provided a blood sample to determine baseline antibody status. After medical screening, they were vaccinated with the 23-valent polysaccharide pneumococcal (Pneumovax II; Sanofi Pasteur MSD) vaccine via subcutaneous injection in the upper arm. Following vaccination, parents were asked to return one month later (mean lag = 31, SD = 4, days) and six months later (mean lag =183, SD = 5, days) to provide a further venous blood sample for measurement of antibody titre. Antibody data were available for 59 participants at the first follow-up and 56 at the later follow-up. One caregiving parent relocated and was therefore unable to attend their next appointments; the remaining three parents who were not available for the final follow-up cited issues of family commitments as the main reason for non-attendance. The choice of follow-up times was dictated by wishing to capture both the peak IgG response and the subsequent decay.

2.3. Questionnaires

2.3.1. Depression

Parental depression was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The scale contains 14 four-point items, from 0,

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

not present, to 3, considerable, with seven assessing largely the anhedonic rather than somatic aspects of depression (e.g., 'I have lost interest in my appearance') and seven assessing anxiety (e.g., 'I feel tense or wound up'). The item scores were added to yield sub-scale scores for depression and anxiety from zero to 21. In the present study, only the depression subscale was used. The HADS has good concurrent validity (Bramley et al., 1988; Herrmann, 1997). For the present sample, Cronbach's α was .86 for the depression subscale.

2.3.2. Perceived stress

Psychological stress over the previous month was measured using the 14-item Perceived Stress Scale (Cohen et al., 1983). This scale used extensively in caregiver research (Glaser et al., 2000; Vedhara et al., 2002), measures the degree to which individuals appraise situations in their lives as stressful over the last month. Scale responses ranged from 0, never, to 4, very often, with higher scores indicating greater perceived stress. This scale shows good test–retest reliability (r = .80) and internal reliability (Cronbach's α = .75). In the present study, a high internal consistency was observed, α = .88.

2.3.3. Social support

Social support was assessed using the 12-item Support Functions Scale (Dunst et al., 1988). Parents rated each source of support available to them including practical (e.g. 'someone to help take care of my child') and emotional (e.g. 'someone to talk to about things that worry me') support on a 5-point Likert scale ranging from 1, never, to 5, quite often. This scale has been shown to be reliable (Cronbach's α = .86) and has been used previously in developmental disability research (White and Hastings, 2004). A high internal consistency (α = .89) was also evident for the present sample.

2.3.4. Caregiver Burden

As a measure of parental caregiver burden, an adapted version of the 22-item Caregiver Burden Index was used (Zarit et al., 1986). This index was designed to assess the stresses experienced by family caregivers of elderly and disabled persons. Questions

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

were amended replacing 'your relative' with 'your child'. Examples of items include 'Do you feel that because of the time you spend with your child that you don't have enough time for yourself?', 'Are you afraid what the future holds for your child?', and 'Overall, how burdened do you feel in caring for your child?'. Responses ranged from 0, never, to 4, nearly always. The scale has also been used previously in caregiver research (Vedhara et al., 2002). Internal consistency in the current sample was .94.

2.3.5. Child problem behaviour

The 25-item Strengths and Difficulties Questionnaire (Goodman, 1997), was used to screen for child problem behaviour. The measure has five subscales, with one assessing prosocial behaviour (e.g. 'kind to younger children') and four assessing problem behaviour; emotional symptoms (e.g. 'often unhappy, downhearted or tearful'), conduct disorder (e.g. 'often argumentative with adults'), hyperactivity (e.g. easily distracted, concentration wanders'), and peer relationships (e.g. rather solitary, tends to play alone'). Parents are asked to rate whether a behaviour is 1, true, to 0, somewhat true or 2, certainly true, of their child with higher scores indicating more problem behaviour. Some items are reversed scored (e.g. generally obedient, usually does what adults request). The scale has been shown to be reliable (Cronbach's $\alpha = .76$) and effective at identifying behavioural problems in children (Goodman and Scott, 1999). Further, it has been used extensively in research with children with developmental disabilities (Hastings et al., 2006). Internal consistency for the whole scale in this study was .88. For the purpose of our analyses both total and subscale scores were used.

2.4. Control and confounding variables

2.4.1. Health behaviours

As in our previous research (Burns et al., 2003a; Phillips et al., 2005; Phillips et al., 2006) typical health behaviours were assessed at baseline, 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, and 21+ cigarettes per day); how much alcohol they drank (0, 1–5, 6-10, 11–20, 21–40, and 40 + units per week). A simple

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

categorical scoring method was used in all cases. Participants were also asked how much time they spent in activities of light, moderate and vigorous exercise intensity which were summed to yield a composite exercise score. They also indicated how regularly they ate certain foods from a standard list, and this information was summed to give a measure of fruit and vegetable consumption and fat intake.

2.4.2. Sleep Quality

Sleep quality was measured by the 19-item Pittsburgh Sleep Quality Index (Buysse et al., 1989). This index has seven components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction with scores ranging from 0, no problems in area, to 3, high problem area. By summing component scores a total sleep quality score was obtained that ranges from 0, good sleep quality, to 21, poor sleep quality.

2.4.3. Time spent caregiving

Amount of time spent caregiving was assessed using a modified version of the Caregiver Activity Survey (Davis et al., 1997). Rather than asking parents how much time they spend providing care each day to their child, this survey asks parents how much time on five specific (e.g. transport, dressing, eating, bathing and supervision) caring roles in any one. Hours for each caring role were summed together to yield a total daily score for time spent caregiving.

2.5. Blood sampling and antibody analysis

Venous blood specimens were collected from an ante-cubital vein into two 7-ml plain tubes (BD Vacutainer, Meylan Cedex) to assess antibody titres. Samples were allowed to clot at room temperature for 1 h and centrifuged at 3500 rpm for 5 min. The separated serum was frozen at −20°C until assayed. Luminex technology was used to assess seven pneumococcal (Pn) IgG antibody serotypes (types 1, 3, 6, 9, 14, 19 and 23) contained in the pneumococcal vaccine. Assessment and selection of these specific Pn serotypes were based on clinical observations linking these common serotypes to invasive disease in

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

Europe (Denham and Clarke, 2005; Sleeman et al., 2001). Further details of this assay are described elsewhere (Ferraro et al., 2008; Gallagher et al., 2008a; Lal et al., 2005). Serum samples were diluted 1:4000 in diluent buffer that additionally contained 5μg/ml purified pneumococcal serotype 22F in accordance with the WHO protocol for ELISA detection of Pn antibody (http://www.vaccine.uab.edu/#), were run in duplicate, and read on a Luminex 100 machine (Luminex Corp, TX, USA). Acquisition software (BioPlex Software Manager (version 4, BioRads, Labs, CA, USA) was used to generate serotype antibody concentrations from a 5 parameter logistic curve fit. Serum Pn IgG levels are reported in μg/L.

2.6. Statistical analyses

Analysis of variance (ANOVA) and chi-square were employed to assess group differences in demographics, health behaviours, and psychosocial status. Prior to statistical analyses, the antibody data were checked for assumptions of fit and normality. Screening revealed two outliers and skewed antibody data. One outlier (caregiver) was removed for the type 1 strain and one (control) for the type 23 strain and both were removed from the average titre. These two participants registered biologically unfeasible values for at least one of the follow-ups. For one, this took the form of registering a 700-fold increase in titre relative to a 12-fold mean increase for the participants as a whole and for the other, an 80-fold increase relative to a 4-fold increase. These exclusions are reflected in the slight variations in degrees of freedom. Given the skew of the data, antibody titres were subjected to $\log_{10}$ transformation for the main analyses. Partial eta-squared (η^2_p) is reported as a measure of effect size. Analysis of covariance (ANCOVA) was used to test for group differences in antibody titre at each follow-up separately; baseline antibody titre was always entered as a covariate. We have used the analytic strategy of representing antibody response as the follow-up antibody titre adjusted for the baseline titre throughout our previous studies (Gallagher et al., 2008a, 2008c; Phillips et al., 2005; Phillips et al., 2006). The approach of analyzing the two follow-ups separately is also identical to the one we have used in previous vaccination research (Gallagher et al., 2008a, 2008c; Phillips et al., 2005; Phillips et al., 2006). It was in this case further

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

justified by the results of Glaser et al., (2000), who found caregiver control differences only at six months following vaccination, and by, in a small study with some attrition, our desire to optimize our degrees of freedom and hence our power to detect effects. Where significant group effects emerged, subsequent ANCOVAs were undertaken to adjust for potential confounding variables. The major dependent variables were the average IgG titres of the seven strains at the two follow-ups. However, sensitivity analyses using the seven individual Pn polysaccharide serotypes were also undertaken. A clinically adequate response to the 23-valent pneumococcal vaccine has been determined as a two-fold or greater rise in aggregate antibody titre (Center for Disease Control, 1989). For illustration purposes, this criterion was adopted and the number of non-responders in each group compared using chi-square. Hierarchical linear regression analyses were used to determine whether any of the caregiving or psychosocial variables predicted $\log_{10}$ antibody level at each follow-up. In these regression models, antibody levels at baseline were entered at step one, parental groups at step 2 and caregiving and psychosocial variables entered separately at step three. Mediation analysis was then conducted to determine whether the caregiving or psychosocial variables mediated any variation between groups in antibody response.

3. Results

3.1. Demographic, childcare and psychosocial characteristics of parental groups

The demographic and summary childcare characteristics of the two parental groups are presented in Table 2. It is evident that the groups are reasonably well matched on most variables. However, parents of children with developmental disabilities were slightly older on average, their child was older; they were less likely to be currently employed outside the home and spent more time caregiving. They also reported poorer sleep quality. Where appropriate, the analyses adjusted for these variables. There were no differences between groups in health behaviours such as alcohol consumption and smoking. As might be expected, parents caring for a child with a developmental disability had much higher levels of depressive symptomatology and perceived stress,

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

reported poorer social support, greater caregiving burden, and more child problem behaviour than parents of typically developing children (see Table 2)

[Insert Table 2 about here]

3.2. Antibody response to vaccination

The mean (SE) actual antibody levels (μg/L) for the average pneumococcal titre, and for each of the seven targeted individual strains, at each time point for each of the groups is displayed in Table 3. The average antibody titre rose from baseline to 1-month follow-up for both groups and, although there was some subsequent decline, antibody levels were still higher at the 6-month follow-up than at baseline. A broadly similar pattern was observed for each of the individual strains for each of the groups. There was no significant difference between groups in average pneumococcal titre at baseline, but baseline antibody levels were higher in the caregivers for the type 3 and type 19 strains.

[Insert Table 3 about here]

3.3. Caregiving and antibody response

After adjusting for baseline $\log_{10}$ antibody levels, the aggregate $\log_{10}$ antibody titre at both follow-ups differed significantly between parental groups. Parents caring for children with developmental disabilities had a much poorer antibody response than parents of typically developing children, at both the 1-month, $F(1, 57) = 5.65$, $p = .02$, $\eta^2_p = .095$, and the 6-month follow-up, $F(1, 50) = 7.14$, $p = .01$, $\eta^2_p = .125$. The η^2_p values signify medium to large effects (Cohen, 1988; Pierce et al., 2004). A repeated measures ANCOVA, with both follow-ups included, confirmed these group differences, $F(1, 50) = 6.86$, $p = .01$, $\eta^2_p = .121$. As an indicator of a clinically protective antibody response, a two-fold increase in antibody titre from baseline to follow-up was used; individuals not achieving a two fold response were classified as non-responders. Parents of children with developmental disabilities were more likely to be non-responders than parents of

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

typically developing children at both the 1-month (20% *versus* 4%) and the 6-month (48% *versus* 4%) follow-up (see Figure 1). Health behaviours including smoking, diet, exercise, and alcohol consumption were unrelated to antibody response. It is thus unsurprising that the differences reported above withstood adjustment for these variables in ANCOVA. Further, because age of parents and care recipient, work outside the home, time caregiving and sleep quality differentiated groups, these were also entered as covariates. The main outcomes also remained unchanged following adjustment for these variables.

[Insert Figure 1 about here]

3.4. Sensitivity analysis for caregiving and antibody response to individual strains

Sensitivity analysis was undertaken to establish which pneumococcal serotypes differed between parental groups. At both follow-ups, parents of children with developmental disabilities had a poorer response to the type 1 strain, $F(1, 55) = 6.97$, $p = .01$, $\eta^2_p = .112$, and $F(1, 51) = 6.68$, $p = .02$, $\eta^2_p = .100$, respectively, and the type 6 strain, $F(1, 55) = 4.59$, $p = .04$, $\eta^2_p = .112$ and $F(1, 51) = 12.57$, $p > .001$, $\eta^2_p = .198$, respectively. At 6-month follow-up, the group difference in response to type 3 strain approached significance, $F(1, 52) = 3.62$, $p = .06$, $\eta^2_p = .065$, with parental caregivers tending to mount a poorer response.

3.5. Contribution of depression, perceived stress, social support, caregiver burden and child problem behaviour to group differences in antibody titre

In hierarchical linear regression analysis in which baseline titre was entered at step 1 and parental group at step 2, and each psychosocial variable entered individually at step 3, only child problem behaviour, $\beta = -.29$, $t = 2.33$, $p = .02$, $\Delta R^2 = .03$, abolished the between group effect for the 1-month antibody response. In these analyses, the β for parental group changed from -.20 at step 2 to .04 at step 3. Accordingly, we tested for mediation using the Goodman test (Goodman, 1960). This revealed evidence of

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

mediation, $z = 3.09$, $p < .001$. Thus, it would seem that child problem behaviour was not only associated with the 1-month antibody titre independently of parental group in this model, but also appeared to account for the caregiver/control group differences in antibody response. The outcome of the mediation analysis is presented in Figure 2. Further, analysis of the questionnaire subscales indicated that it was conduct behaviours that were primarily responsible; the β for parental group changed from -.20 at step 2 to -.09 at step 3. Similar analyses were undertaken with the 6-month antibody titre as the dependent variable. In these analyses no associations emerged between the psychosocial variables and antibody titre. In addition, the associations reported above withstood adjustment for demographic variables, other caregiving variables, and health behaviours, including sleep quality.

[Insert Figure 2 about here]

3.6. Within case group antibody analyses

In hierarchical linear regression analyses, again adjusting for baseline titre, no significant associations emerged between any of the psychosocial variables and antibody response of parents caring for a child with developmental disabilities. However, although not meeting the conventional criterion for statistical significance, there were indications of a negative association between child problem behaviour and 1-month antibody response, $\beta = -.19$, $t = 1.57$, $p = .12$, $\Delta R^2 = .04$. Again, it was conduct problems that tended to be associated 1-month antibody response, $\beta = -.20$, $t = 1.61$, $p = .12$, $\Delta R^2 = .04$. Moreover, when these parents were divided into those reporting high and low conduct problems in their children using a median split, ANCOVA revealed a significant effect, $F(1, 25) = 4.51$, $p = .04$, $\eta^2_p = .153$; parents caring for a child with developmental disabilities who reported that their children showed more conduct problem behaviours mounted a poorer antibody response at 1-month (see Figure 3). No associations emerged between any of the psychosocial and circumstantial factors for the 6-month antibody titre.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

[Insert Figure 3 about here]

4. Discussion

Parents caring for children with developmental disabilities exhibited a poorer antibody response to a pneumococcal vaccination than parents caring for typically developing children at both 1-month and 6-month follow-ups. Of the variables considered it would appear to be child problem behaviour which mediated this effect. In addition, within the parental caregiving group, parents reporting more child conduct problems, a component of the child problem behaviour measure, mounted a poorer antibody response at 1-month than parents reporting less conduct problems.

Adopting the criterion of a two-fold antibody response as indicative of clinical protection, 20% of parents caregiving for a child with a developmental disability failed to mount an adequate response compared to only 4% of controls at 1-month follow-up. At 6-months, almost half (48%) did not meet the two-fold criteria compared with 4% of controls. Thus, a negative impact of caregiving on vaccination response would not appear to be restricted to older individuals caring for spouses with dementia (Glaser et al., 2000; Kiecolt-Glaser et al., 1996; Vedhara et al., 1999a), and, accordingly, would not seem to require an ageing immune system in order to manifest itself. Rather, our results suggest that it is the characteristics of the caregiving experience *per se* that is the key determinant of its impact on immunity. Variations in caregiving experience could also explain the discrepancy in outcomes between the present study and the earlier finding that younger spousal caregivers of multiple sclerosis patients did not differ from controls in antibody response (Vedhara et al., 2002). A cursory comparison of the two studies reveals that the present caregivers reported much higher perceived stress (Mean 30.33 $\pm$ 8.40) and caregiver burden (Mean 44.0 $\pm$ 14.26), than those caring for spouses with multiple sclerosis (Mean 25.42 $\pm$ 8.45) and (Mean 29.00 $\pm$ 14.80) respectively, $t(70) = 2.46$, $p = .01$, and, $t(70) = 4.31$, $p < .001$. Although neither perceived stress nor caregiver burden accounted for the differences between groups in antibody responses they correlated highly with child behaviour problems in the sample as a whole, as well as within the caregiving group (r =

.49 to .76). It is also possible that differences in vaccination, pneumococcal *versus* influenza, might also have contributed to the differences in results. However, it is worth noting that responses to both vaccinations have been found to be compromised in those caring for spouses with dementia (Glaser et al., 2000; Kiecolt-Glaser et al., 1996; Vedhara et al., 1999a).

The present study is not only the first to study caregivers of children with developmental disabilities in this context, it is also only the second to examine the responses of caregivers to pneumococcal vaccination. In the previous study, older spousal caregivers showed a poorer response to pneumococcal vaccination relative to former caregivers and non-caregiving controls, but only at the final 6-month follow-up (Glaser et al., 2000). Although, the difference between caregivers and controls in the present study was larger at the later follow-up, the groups still differed significantly at the earlier 1-month follow-up. More demanding caregiving could again provide an explanation for the earlier effect in the present study. In support of this, perceived stress, measured on the truncated scale, was much higher among the present parental caregivers than that reported for the spousal caregivers of patients with dementia (Mean 22.23 $\pm$ 7.27 *versus* Mean 16.73 $\pm$ 2.82), t (39) = 3.52, p <.001. Again caution is warranted, since perceived stress did not account for the differences between groups in vaccination response.

In analyses of the individual pneumococcal IgG antibody serotypes, parents of children with developmental disabilities mounted a poorer response to type 1 and type 6 strains at both follow-ups, and to type 3 at 6-months. It appears that some Pn serotypes are more susceptible to psychosocial influence. Such specificity has also been reported from other studies using polyvalent vaccinations (Phillips et al., 2005; Phillips et al., 2006; Pressman et al., 2005; Vedhara et al., 1999a). Indeed, in a recent study of students, social support was associated with antibody response to pneumococcal vaccination and it was types 1 and 3 again which appeared to be particularly sensitive (Gallagher et al., 2008a; 2008c). One explanation for such specificity is that antigens that are less immunogenic are more susceptible to exogenous influence (Cohen et al., 2001). It is worth noting in this regard that some of the smallest antibody titres at follow-up were observed for the types 1 and 3 strains.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

We also explored whether it was distress, social support, burden or the child's problem behaviour that was most strongly associated with any impairment in vaccination response. Despite group differences on all psychosocial and circumstantial measures, no associations emerged between depression, perceived stress, social support, or caregiver burden and antibody responses at either follow-up. However, child problem behaviour was a significant predictor of 1-month antibody response and a formal test of mediation confirmed it as a candidate mediator. Thus, it appears that child problem behaviour was not only associated with antibody titre independently of parental group, but also contributed substantially to the caregiver/control group differences in the antibody response. In addition, subscale analysis indicated that conduct behaviours (e.g., often has temper tantrums, often fights with other children) were primarily responsible for this effect. Further, within the caregiving group, those parents reporting more problems with conduct behaviour showed a poorer response to vaccination compared to those reporting less conduct behaviours. The negative association between care recipients' problem behaviour and antibody responses is broadly in line with the results of research on caregivers of patients with mental health difficulties using other health outcomes. For example, not only have problem behaviours been associated with caregivers' psychological distress (Mausbach et al., 2006; Pinquart and Sorensen, 2003a, b), they have also been linked to increased incidence of infectious illness (Dyck et al., 1999) and the onset of cardiovascular disease (Mausbach et al., 2007). The current findings reinforce the importance of targeting child problem behaviours in interventions for those caring for a child with a developmental disability. There is preliminary evidence that managing behaviour problems in dementia patients can enhance caregivers' *in vitro* immunity immediately after intervention and 6-months later (Garand et al., 2002).

The current study has a number of limitations. First, our sample size might be regarded as small. Nevertheless, it is of a similar order of magnitude to that of other published case-control studies (Glaser et al., 2000; Vedhara et al., 2002). Second, it is possible that our sample was biased and included more parents from support groups, who were particularly stressed. However, contacted but non-participating parents almost invariably cited geographical distance from the University, or an unwillingness to give blood or receive a

vaccination as their reasons for not participating. Third, there were group differences in baseline titre, but these were not significant for the average pneumococcal titre or for five of the seven strains. There has been speculation on the effects or prior antigenic exposure on subsequent capsular polysaccharide vaccination responsiveness, with some studies finding higher antibody concentration and others lower (see Artz, et al., 2003; Davison et al., 1994; O'Brien et al., 2007). Importantly, in the present study, the strains that differed significantly between groups in vaccination response (types 1 and 6) were not among those showing a significant group difference at baseline. Thus, our results for vaccination response are unlikely to be an artifact of baseline antibody status. Fourth, there is also the possibility of confounding as a result of unmeasured or poorly measured variables. However, our main findings survived statistical adjustment for the more common health behaviours and any group differences that emerged as a result of imperfect matching. Finally, in the absence of appropriate measurement we can only speculate about underlying biological mechanisms. Nevertheless, in caregivers of dementia patients a higher cortisol awakening response was found for those reporting high versus low levels of behavioral problems in the care recipients (de Vugt et al., 2005). Further, secretion of this stress hormone was inversely associated with antibody response to influenza vaccination in caregivers of dementia patients (Vedhara et al., 1999b). Such variations in cortisol may provide one pathway through which problem behaviours exert an influence on antibody response to vaccination.

In conclusion, the negative impact of caregiving on antibody response to vaccination is not restricted to older spousal caregivers, but is also evident in younger parents caring for children with developmental disabilities. Relative to parents of typically developing children, such caregivers mounted a poorer response than controls to a pneumococcocal vaccine at 1-month and showed poorer maintenance at 6-months. The strongest and most consistent predictor of group differences in antibody response, as well as individual variations in response within the group of parents of children with developmental disabilities, was child problem behaviour. Analyses of its subscales indicated that it was conduct behaviours that underlay these effects. Thus, the behavioural characteristics of the

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

care recipients may be a key determinant of whether or not immunity is compromised in this context.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

Acknowledgements

The authors would like to express their appreciation to Autism West-Midlands, the Down Syndrome Association, and Baljit Nhal from Birmingham Children's Hospital and Sara Walton from Birmingham City Council's Education Department for their help with the recruitment process. A special thanks is also extended to the parents caring for children with developmental disabilities and the parents caring for typically developing children who made this research possible.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

References

Artz, A.S., Ershler, W.B., Longo, D.L., 2003. Pneumococcal Vaccination and Revaccination of Older Adults. Clin. Microbiol. Rev. 16, 303-318.

Baron, R.S., Cutrona, C.E., Hicklin, D., Russell, D.W., Lubaroff, D.M., 1990. Social support and immune function among spouses of cancer patients. J. Pers. Soc. Psychol. 59, 344-352.

Beach, S.R., Schulz, R., Yee, J.L., Jackson, S., 2000. Negative and positive health effects of caring for a disabled spouse: longitudinal findings from the caregiver health effects study. Psychol. Aging 15, 259-271.

Bramley, P.N., Easton, A.M.E., Morley, S., Snaith, R.P., 1988. The Differentiation of Anxiety and Depression by Rating-Scales. Acta Psychiatrica Scandinavia 77, 133-138.

Burns, V.E., Carroll, D., Ring, C., Drayson, M., 2003a. Antibody response to vaccination and psychosocial stress in humans: relationships and mechanisms. Vaccine 21, 2523-2534.

Burns, V.E., Carroll, D., Drayson, M., Whitham, M., Ring, C., 2003b. Life events, perceived stress and antibody response to influenza vaccination in young, healthy adults. J. Psychosom. Res. 55, 569-572.

Burns, V.E., Drayson, M., Ring, C., Carroll, D., 2002. Perceived stress and psychological well-being are associated with antibody status after meningitis C conjugate vaccination. Psychosom. Med. 64, 963-970.

Buysse, D.J., Reynolds, C.F., 3rd, Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28, 193-213.

Centre for Disease Control., 1989. Pneumococcal Polysaccharide Vaccine. MMWR 38.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd Eds, Lawrence Erlbaum Associates, Hillsdale.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385-396.

Cohen, S., Miller, G.E., Rabin, B.S., 2001. Psychological stress and antibody response to immunization: a critical review of the human literature. Psychosom. Med. 63, 7-18.

Cohen, M., Pollack, S., 2005. Mothers with breast cancer and their adult daughters: the relationship between mothers' reaction to breast cancer and their daughters' emotional and neuroimmune status. Psychosom. Med. 67, 64-71.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

Cooper, C., Balamurali, T.B., Livingston, G., 2007. A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. Int. Psychogeriatr. 19, 175-195.

Davidson, M., Bulkow, L.R., Grabman, J., Parkinson, A.J., Chamblee, C., Williams, W.W., Lanier, A.P., Schiffman, G., 1994. Immunogenicity of pneumococcal revaccination in patients with chronic disease. Arch. Intern. Med. 154, 2209 - 2214.

Davis, K.L., Marin, D.B., Kane, R., Patrick, D., Peskind, E.R., Raskind, M.A., Puder, K.L., 1997. The Caregiver Activity Survey (CAS): development and validation of a new measure for caregivers of persons with Alzheimer's disease. Int. J. Geriatr. Psychiatry 12, 978-988.

Denham, B.C., Clarke, S.C., 2005. Serotype incidence and antibiotic susceptibility of Streptococcus pneumoniae causing invasive disease in Scotland, 1999-2002. J. Med. Microbiol. 54, 327-331.

de Vugt, M.E., Nicolson, N.A., Aalten, P., Lousberg, R., Jolle, J., & Verhey, F.R. (2005). Behavioral problems in dementia patients and salivary cortisol patterns in caregivers. J Neuropsychiatry Clin. Neurosci. 17, 201-207.

Dunst, C.J., Trivette, C.M., Deal, A.G., 1988. Enabling and Empowering Families: Principles and Guidelines for Practice. Brookline Books :Cambridge, MA

Dyck, D.G., Short, R., Vitaliano, P.P., 1999. Predictors of burden and infectious illness in schizophrenia caregivers. Psychosom. Med. 61, 411-419.

Epel, E.S., Blackburn, E.H., Lin, J., Dhabhar, F.S., Adler, N.E., Morrow, J.D., Cawthon, R.M., (2004). Accelerated telomere shortening in response to life stress. Proc. Natl. Acad. Sci. U S A, 101, 17312-17315.

Ferraro, A.J., Drayson, M.T., Savage, C.O., MacLennan, I.C., 2008. Levels of autoantibodies, unlike antibodies to all extrinsic antigen groups, fall following B cell depletion with Rituximab. Eur. J. Immunol. 38, 292-298.

Floyd, F.J., Gallagher, E.M., 1997. Parental stress, care demands, and use of support services for school-age children with disabilities and behavior problems. Family Relations 46, 359-371.

Gallagher, S., Phillips, A.C., Ferraro, A.J., Drayson, M.T., Carroll, D., 2008a. Psychosocial factors are associated with the antibody response to both thymus-dependent and thymus-independent vaccines. Brain Behav. Immun. 22, 456–460.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

Gallagher, S., Phillips, A.C., Evans, P., Der, G., Hunt, K., Carroll, D., 2008b. Caregiving is associated with low secretion rates of immunoglobulin A in saliva. Brain Behav. Immun. 22, 565-572.

Gallagher, S., Phillips, A.C., Ferraro, A.J., Drayson, M.T., Carroll, D., 2008c. Social support is positively associated with the immunoglobulin M response to vaccination with pneumococcal polysaccharides. Biol. Psychol. 78, 211–215.

Gallagher, S., Phillips, A.C., Oliver, C., Carroll, D., in press, d. Predictors of Psychological Morbidity in Parents of Children with Intellectual Disabilities. J. Pediatr. Psychol.

Garand, L., Buckwalter, K.C., Lubaroff, D., Tripp-Reimer, T., Frantz, R.A., Ansley, T.N., 2002. A pilot study of immune and mood outcomes of a community-based intervention for dementia caregivers: the PLST intervention. Arch. Psychiatr. Nurs. 16, 156-167.

Garand, L., Dew, M.A., Eazor, L.R., DeKosky, S.T., Reynolds, C.F., 3rd, 2005. Caregiving burden and psychiatric morbidity in spouses of persons with mild cognitive impairment. Int. J. Geriatr. Psychiatry 20, 512-522.

Gennaro, S., Fehder, W., Nuamah, I.F., Campbell, D.E., Douglas, S.D., 1997. Caregiving to very low birthweight infants: a model of stress and immune response. Brain Behav. Immun. 11, 201-215.

Glaser, R., Sheridan, J., Malarkey, W.B., MacCallum, R.C., Kiecolt-Glaser, J.K., 2000. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosom. Med. 62, 804-807.

Goodman, R., 1997. The Strengths and Difficulties Questionnaire: a research note. J. Child Psychol. Psychiatry 38, 581-586.

Goodman, R., Scott, S., 1999. Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: is small beautiful? J. Abnorm. Child Psychol. 27, 17-24.

Graham, J.E., Christian, L.M., Kiecolt-Glaser, J.K., 2006. Stress, age, and immune function: toward a lifespan approach. J. Behav. Med. 29, 389-400.

Graungaard, A.H., Skov, L., 2007. Why do we need a diagnosis? A qualitative study of parents' experiences, coping and needs, when the newborn child is severely disabled. Child Care Health Dev. 33, 296-307.

Gregory, C.A., Hodges, J.R., 1996. Clinical features of frontal lobe dementia in comparison to Alzheimer's disease. J. Neural Transm. Suppl. 47, 103-123.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

Hastings, R.P., Brown, T., 2002. Behavior problems of children with autism, parental self-efficacy, and mental health. Am. J. Ment. Retard. 107, 222-232.

Hastings, R.P., Daley, D., Burns, C., Beck, A., 2006. Maternal distress and expressed emotion: cross-sectional and longitudinal relationships with behavior problems of children with intellectual disabilities. Am. J. Ment. Retard. 111, 48-61.

Herrmann, C., 1997. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. J. Psychosom. Res. 42, 17-41.

Higgins, D.J., Bailey, S.R., Pearce, J.C., 2005. Factors associated with functioning style and coping strategies of families with a child with an autism spectrum disorder. Autism 9, 125-137.

Keegan, B.M., Noseworthy, J.H., 2002. Multiple sclerosis. Ann. Rev. Med. 53, 285-302.

Kiecolt-Glaser, J.K., Dura, J.R., Speicher, C.E., Trask, O.J., Glaser, R., 1991. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. Psychosom. Med. 53, 345-362.

Kiecolt-Glaser, J.K., Glaser, R., Gravenstein, S., Malarkey, W.B., Sheridan, J., 1996. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc. Natl. Acad. Sci. U S A. 93, 3043-3047.

Kiecolt-Glaser, J.K., Glaser, R., Shuttleworth, E.C., Dyer, C.S., Ogrocki, P., Speicher, C.E., 1987. Chronic stress and immunity in family caregivers of Alzheimer's disease victims. Psychosom. Med. 49, 523-535.

Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B., Glaser, R., 2003. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc. Natl. Acad. Sci. U S A 100, 9090-9095.

Lal, G., Balmer, P., Stanford, E., Martin, S., Warrington, R., Borrow, R., 2005. Development and validation of a nonaplex assay for the simultaneous quantitation of antibodies to nine Streptococcus pneumoniae serotypes. J. Immunol. Methods 296, 135-147.

Li, J., Cowden, L.G., King, J.D., Briles, D.A., Schroeder, H.W., Jr., Stevens, A.B., Perry, R.T., Chen, Z., Simmons, M.S., Wiener, H.W., Tiwari, H.K., Harrell, L.E., Go, R.C., 2007. Effects of chronic stress and interleukin-10 gene polymorphisms on antibody response to tetanus vaccine in family caregivers of patients with Alzheimer's disease. Psychosom. Med. 69, 551-559.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

Maes, B., Broekman, T.G., Dosen, A., Nauts, J., 2003. Caregiving burden of families looking after persons with intellectual disability and behavioural or psychiatric problems. J. Intellect. Disabil. Res. 47, 447-455.

Marmot, M.G., Dowey Smith, G., Stansfeld, S., Patel, C., North, F., Head, J., White, I., Brunner, E., Feeney, A., 1991. Health inequalities among British civil servants: the Whitehall II study. Lancet 337, 1387–1393.

Marsland, A.L., Cohen, S., Rabin, B.S., Manuck, S.B., 2001. Associations between stress, trait negative affect, acute immune reactivity, and antibody response to hepatitis B injection in healthy young adults. Health Psychol. 20, 4-11.

Mausbach, B.T., Aschbacher, K., Patterson, T.L., Ancoli-Israel, S., von Kanel, R., Mills, P.J., Dimsdale, J.E., Grant, I., 2006. Avoidant coping partially mediates the relationship between patient problem behaviors and depressive symptoms in spousal Alzheimer caregivers. Am. J. Geriatr. Psychiatry 14, 299-306.

Mausbach, B.T., Patterson, T.L., Rabinowitz, Y.G., Grant, I., Schulz, R., 2007. Depression and distress predict time to cardiovascular disease in dementia caregivers. Health Psychol. 26, 539-544.

Mills, P.J., Adler, K.A., Dimsdale, J.E., Perez, C.J., Ziegler, M.G., Ancoli-Israel, S., Patterson, T.L., Grant, I., 2004. Vulnerable caregivers of Alzheimer disease patients have a deficit in beta 2-adrenergic receptor sensitivity and density. Am. J. Geriatr. Psychiatry 12, 281-286.

Miller, G.E., Cohen, S., Ritchey, K.A., 2002. Chronic Psychological Stress and the Regulation of Pro-Inflammatory Cytokines: A Glucocorticoid-Resistance Model. Health Psych. 21, 531-541.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F., 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51, 1546-1554.

O'Brien, K.L., Hochman, M., Goldblatt, D., 2007. Combined schedules of pneumococcal conjugate polysaccharide vaccines: is hyporesponsiveness an issue. Lancet 7, 597-606.

Pariante, C.M., Carpiniello, B., Orru, M.G., Sitzia, R., Piras, A., Farci, A.M., Del Giacco, G.S., Piludu, G., Miller, A.H., 1997. Chronic caregiving stress alters peripheral blood immune parameters: the role of age and severity of stress. Psychother. Psychosom. 66, 199-207.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

Phillips, A.C., Burns, V.E., 2008. Why are vaccinations interesting to psychologists? The Psychologist 21, 202-204.

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, Behav. Immun. 19, 325-333.

Phillips, A.C., Carroll, D., Burns, V.E., Ring, C., Macleod, J., Drayson, M., 2006. Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. Brain, Behav. Immun. 20, 279-289.

Pierce, C.A., Block, R.A., Agunis, H., 2004. Cautionary note on reporting eta-squared values from multifactor ANOVA designs. Educ. Psych. Meas. 64, 916-924.

Pinquart, M., Sorensen, S., 2003a. Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. J. Gerontol. B Psychol. Sci. Soc. Sci. 58, P112-128.

Pinquart, M., Sorensen, S., 2003b. Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. Psychol. Aging. 18, 250-267.

Poser, C.M., Paty, D.W., Scheinberg, L., McDonald, W.I., Davis, F.A., Ebers, G.C., Johnson, K.P., Sibley, W.A., Silberberg, D.H., Tourtellotte, W.W., 1983. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann. Neurol. 13, 227-231.

Pressman, S.D., Cohen, S., Miller, G.E., Barkin, A., Rabin, B.S., Treanor, J.J., 2005. Loneliness, social network size, and immune response to influenza vaccination in college freshmen. Health Psychol. 24, 297-306.

Provinciali, M., Moresi, R., Muzzioli, M., Tarabelli, D., Sirolla, C., Melchiorre, MG., Tucci, MG., Panerai, A., Sacerdote, P., Mengani, M., Lamura, G., (2004). Psychological, neuroendocrine and immune measures in non spousal carers of disabled elderly in Italy. Neuro. Endocrinol. Lett. 25, 391-396

Redwine, L., Mills, P.J., Sada, M., Dimsdale, J., Patterson, T., Grant, I., 2004. Differential immune cell chemotaxis responses to acute psychological stress in Alzheimer caregivers compared to non-caregiver controls. Psychosom. Med. 66, 770-775.

Sleeman, K., Knox, K., George, R., Miller, E., Waight, P., Griffiths, D., Efstratiou, A., Broughton, K., Mayon-White, R.T., Moxon, E.R., Crook, D.W., 2001. Invasive

pneumococcal disease in England and Wales: vaccination implications. J. Infect. Dis. 183, 239-246.

Vedhara, K., Fox, J.D., Wang, E.C., 1999a. The measurement of stress-related immune dysfunction in psychoneuroimmunology. Neurosci. Biobehav. Rev. 23, 699-715.

Vedhara, K., Cox, N.K., Wilcock, G.K., Perks, P., Hunt, M., Anderson, S., Lightman, S.L., Shanks, N.M., 1999b. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet 353, 627-631.

Vedhara, K., McDermott, M.P., Evans, T.G., Treanor, J.J., Plummer, S., Tallon, D., Cruttenden, K.A., Schifitto, G., 2002. Chronic stress in nonelderly caregivers: psychological, endocrine and immune implications. J. Psychosom. Res. 53, 1153-1161.

Vitaliano, P.P., Scanlan, J.M., Ochs, H.D., Syrjala, K., Siegler, I.C., Snyder, E.A., 1998. Psychosocial stress moderates the relationship of cancer history with natural killer cell activity. Ann. Behav. Med. 20, 199-208.

Vitaliano, P.P., Zhang, J., Scanlan, J.M., 2003. Is caregiving hazardous to one's physical health? A meta-analysis. Psychol. Bull. 129, 946-972.

White, N., Hastings, R.P., 2004. Social and professional support for parents of adolescents with severe intellectual disabilities. J. Appl. Res. Int. Dis. 17, 181-190.

Zarit, S.H., Todd, P.A., Zarit, J.M., 1986. Subjective burden of husbands and wives as caregivers: a longitudinal study. Gerontologist 26, 260-266.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavia 67, 361-370.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

Table 1. Caregiving and immunity in relatively young (< 60 years) caregiving samples

Author	Care recipient + carers	Age		Psychological measures	Immune measures	Results
		CG	CO			
Baron et al., (1990)	Cancer patients + spouses	48.2	-	Depression, social support, life events	Response to mitogens: Con A, PHA, NK activity and enumerative cell counts	Within CG better social support = greater proliferation to PHA, and NK activity
Cohen & Pollack (2005)	Mothers with breast cancer + daughters	37.5	-	Emotional symptom checklist. Life disruption and time helping	Response to mitogens: PHA, LPS; IL-2, IL-12, cortisol and catecholamines	Within CG: high distress (advanced disease) = lower cytokines secretion
Epel et al., (2004)	Chronically ill children + mothers	Both groups 38 Range 20-50		Perceived stress and years since diagnosis (chronicity)	Telomere length and telomerase function and oxidative stress	Group differed only on stress Within CG, time caregiving = shorter telomere length + lower activity and higher oxidative stress
Gennaro et al., (1997)	Preterm infants + mothers	27	24	Anxiety and depression	Response to mitogens: Con A, PHA and PWM and NK activity	No difference in distress CG less responsive to mitogens Immune response ≠ to distress
Miller et al., (2002)	Children with cancer + parents	36.5	37	Perceived stress, depression, affect and social support	Cortisol , Glucocorticoid sensitivity, cytokines	CG reported higher psychological distress No difference in baseline cytokine levels; CG had flatter cortisol slopes Reduced glucocorticoid sensitivity to IL-6, but not IL-1β or TNF-α CG sensitivity improved with tangible support
Pariante et al., (1997)	Developmentally disabled children + mothers	44	45	Burden, dependence behaviors, anxiety, depression and personality	Enumerative cell count/ratios Humoral response to latent viruses	CG more anxious CG less % of T-cells; higher ratio of T suppressor/cytotoxic cells; lower T helper/suppressor ratio. Age + severity of stress -ve immunity
Provinciali et al., (2004)	Disabled older adults + adult children and grandchildren	54	58	Level of disability, depression, anxiety, stress, QoL , caregiver burden	ACTH, cortisol, prolactin, NK activity and number, β-endorphins. Incidence and severity of influenza	No group effect CG unable to leave disabled person alone had lower NK count + activity
Vedhara et al., (2002)	Multiple Sclerosis patients + spouses	46	33	Perceived stress, anxiety, depression and caregiver burden.	Antibody response to influenza, IFN-γ and IL-4, cortisol and DHEA	CG reported more stress. No differences in antibody or cytokine responses CO had higher cortisol

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

CG (Care giver); CO (Control); = associated with; ≠ not associated with; -ve = negatively associated;

Table 2. Demographics, childcare and psychosocial characteristics of each parental group

	Caregivers (N = 30)	**Controls (N = 29)**	**Test of difference**
Sex (Female)	23 (76%)	20 (69%)	χ^2 (1) = 0.14, p = .70
Marital status (Partnered)	26 (87%)	20 (70%)	χ^2 (1) = 1.76, p = .19
Ethnicity (Caucasian)	29 (91%)	26 (90%)	χ^2 (1) = 0.00, p = 1.00
Occupational status (Professional)	14 (47%)	16 (55%)	χ^2 (1) = 0.15, p = .70
Currently employed outside the home	22 (73%)	28 (96%)	χ^2 (1) = 6.56, p = .005
Alcohol (1-20 units per week)	28(100%)	25(93%)	χ^2 (1) = 0.557, p = .45
Smoking (non- smoker)	23 (93%)	25 (79%)	χ^2 (1) = 1.08, p = .30
Body Mass Index (SD)	26.7 (4.33)	24.7 (4.10)	F (1,54) = 2.91, p =.09
Hour spent caregiving (SD) per day	10.6 (8.19)	3.5 (3.53)	F (1,56) = 17.89, p <.001
Sleep quality (SD)	10.0 (2.55)	7.1 (2.09)	F (1,57) = 23.08, p <.001
Mean age (SD) years	42.8 (5.95)	39.9 (4.35)	F (1,57) = 4.44, p = .04
Mean age of main care recipient (SD) years	11.5 (3.41)	8.8 (4.22)	F (1,57) = 7.18, p = .01
Mean depression score (SD)	8.4 (3.86)	3.2 (2.31)	F (1,57) = 38.40, p <.001
Mean perceived stress score (SD)	30.33 (8.40)	22.2 (7.48)	F (1,57) = 15.52, p <.001

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

Mean social support score (SD)	31.7 (9.82)	37.9(10.37)	F (1,57) = 5.62 , p =.02
Mean caregiver burden score (SD)	44.0 (14.26)	22.9 (10.67)	F (1,57) = 40.94, p <.001
Mean child behaviour problem score (SD)	23.0 (5.97)	9.9 (4.89)	F (1,57) = 84.64, p <.001

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

Table 3. Mean (SE) antibody titres (ug/L) for the average and the individual pneumococcal serotypes at baseline, 1-month and 6-month follow-up.

Pneumococcal titre	**Baseline**		**1-Month**		**6-Month**	
	Caregivers	**Controls**	**Caregivers**	**Controls**	**Caregivers**	**Control**
Average	327 (82)	201 (99)	856 (109)	937 (111)	576 (76.9)	847 (78.3)
Type 1	42 (19)	14 (2)	162 (157)	534 (157)	132 (99)	353 (99)
Type 3	22 [a] (8)	4 (1)	63 (24)	78 (25)	42 (24)	72 (25)
Type 6	1125 (328)	1052 (674)	1823 (396)	2355 (411)	1021 (282)	1539 (294)
Type 9	135 (80)	23 (11)	285 (62)	390 (63)	169 (52)	302 (53)
Type 14	598 (274)	189 (70)	2004 (417)	1899 (424)	1732 (298)	1669 (304)
Type 19	181 [a] (59)	43 (17)	788 (244)	542 (248)	556 (144)	537 (147)
Type 23	134 (59)	34 (9)	332 (83)	363 (86)	199 (66)	319 (69)

[a] Significant difference ($p < .05$) between caregivers and controls at baseline. The follow-up titres are adjusted for baseline.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity,* 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006

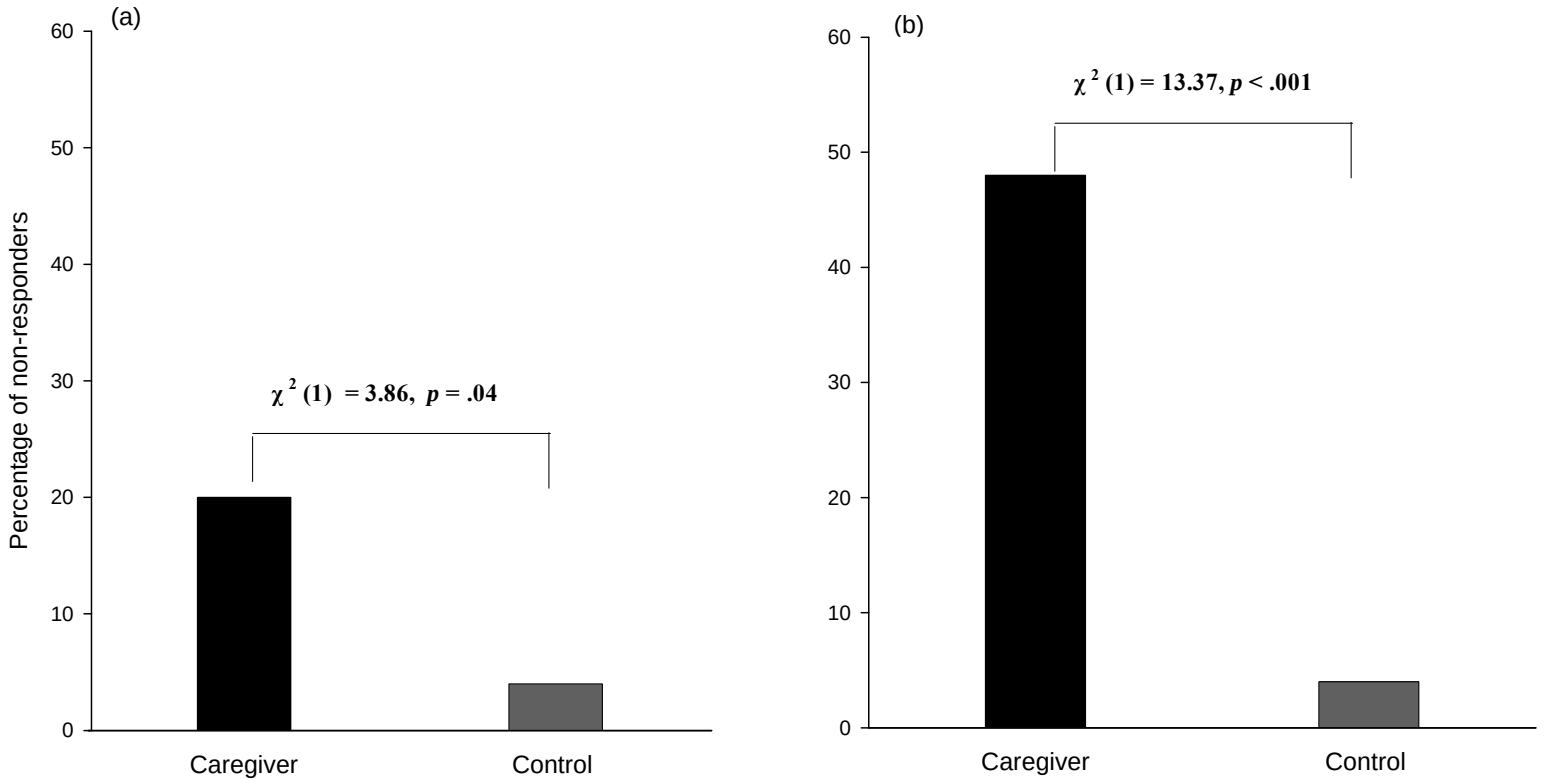
Figure captions

Figure 1. Percentage of non-responders (less than two-fold increase) from baseline at 1-month follow-up (a) and from baseline to 6-month follow-up (b) for each parental group

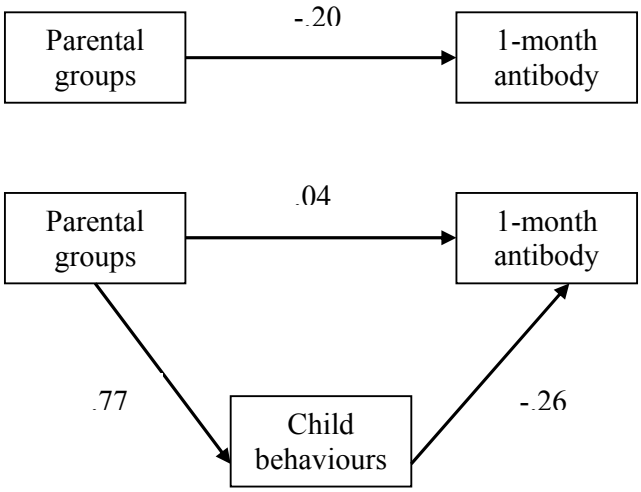
Figure 2. Mediation analysis of the association between parental group and 1-month antibody titre for child problem behaviour; statistics are standardized regression coefficients adjusted for baseline antibody titre.

Figure 3. Mean (SE) antibody titre at 1-month follow-up, adjusted for baseline antibody titre, for parents of children with developmental disabilities with high and low reported conduct behaviour problems.

Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity*, 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006. http://dx.doi.org/10.1016/j.bbi.2008.05.006



Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity,* 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006



Post-print, not final published version. Cite this article as: Gallagher, S., Phillips, A.C., Drayson, M., & Carroll., D. (2009, invited article). Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. *Brain, Behavior & Immunity,* 23, 338-346. DOI: 10.1016/j.bbi.2008.05.006.
http://dx.doi.org/10.1016/j.bbi.2008.05.006