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Why are vaccinations interesting to psychologists?

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Vaccines and blood samples are not the usual tools of the trade for psychologists. However, these techniques can provide a unique insight into how psychological processes affect the ability of the body to defend itself against infection. It is a commonly held belief among psychologists, and the general public alike, that our social experiences and emotions can influence our health. Most of us have experienced colds and other infections during stressful times in our lives, but until relatively recently the evidence supporting these observations remained largely anecdotal.

The field of psychoneuroimmunology examines the interplay between psychological and immunological parameters. Although the immune system has historically been thought to operate independently, it is now known that it shares close links with the nervous and endocrine (hormonal) systems. These provide feasible physiological pathways through which our thoughts and feelings can directly impact upon our susceptibility to infection. Psychoneuroimmunology researchers aim to elucidate these pathways and establish their implications for health. However, in order to achieve this, we need models of immune function that are integrated, easy to interpret and clinically relevant.

Assessing the antibody response to vaccination provides one such model. Vaccines act as 'imitation' infections, through which we can measure how well the immune system responds to challenge, in terms of generating an antibody response. The antibody level is the culmination of a series of immunological events, starting with antigen recognition and resulting in the production of highly specific antibodies by B cells. As such, it gives an overall measure of how well the immune system responds to challenge and is both integrated and easy to interpret. It also covers our criteria of being clinically relevant, as variations in antibody levels are likely to reflect disease susceptibility and resistance.

Definition: Antigens

Antigens are antibody generators, any foreign material which is recognised by the body as foreign and causes the production of antibodies.

Definition: Antibodies

Antibodies are proteins produced by white blood cells. Their task is to circulate in the body and tag, destroy, or neutralize bacteria, viruses, or other harmful or foreign materials (antigens).

The most commonly investigated psychological factor in the context of vaccination is psychosocial stress, measured usually as life events exposure, perceived stress, or exposure to a particular chronic stressor, such as care-giving for a spouse with dementia. Studies in older adults have shown that caregivers have poorer antibody responses to vaccination in comparison to matched control participants (Glaser *et al.*, 1992, Glaser *et al.*, 2000, Vedhara *et al.*, 1999). However, care-giving studies in younger populations are less conclusive (Vedhara *et al.*, 2002) and suggest that factors other than chronic stress, such as the disease/condition of the care recipient and the burden of care, may also be important. Studies of student samples, in which stress is usually assessed using a range of life events checklists and perceived stress measures, comprise much of vaccination response literature. Such studies generally confirm that individuals reporting higher numbers of life events and/or greater perceived stress are characterised by poorer antibody status following a range of vaccinations including hepatitis B (Burns *et al.*, 2002a, Glaser *et al.*, 1992), meningococcal C (Burns *et al.*, 2002b), and influenza (Burns *et al.*, 2003a, Miller *et al.*, 2004, Phillips *et al.*, 2005a).

[Insert Figure 1 about here]

An advantage of using the response to vaccination as a model of immune function is that the variation in inoculation schedules for certain vaccinations can be used to examine which particular aspects of the immune response may be vulnerable to psychosocial influence. For example, vaccination with an antigen to which the participant has not been previously exposed induces a primary antibody response. In contrast, vaccination against more common pathogens such as influenza, induce a secondary immune response which is more rapid and effective. By examining the effect of stress on both primary and secondary immune responses, we can begin to determine which aspects of the immune response are most susceptible to stress-induced modulation. Hepatitis B vaccination is useful in this context, as there is a low likelihood of prior naturalistic exposure to this pathogen, and the schedule

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consists of three inoculations over a six month period, thus incorporating an initial primary response and later secondary response to vaccination. The data in this particular area thus far are somewhat mixed, but there appears to be stronger evidence for a negative effect of psychological stress on the secondary response to this pathogen (Burns *et al.*, 2003b, Cohen *et al.*, 2001).

A further advantage to the vaccination model is that there are different types of vaccination, which can be used to help elucidate which cells involved in the vaccination response are influenced by psychological factors. Most vaccinations, which consist of inactivated or dead viruses like influenza, induce what is known as a thymus-dependent antibody response. In this type of response, the B cells, the antibody “factories”, require the help of T cells, in order to produce antibody. A few vaccinations, however, protect against bacterial infections or toxins like meningococcal A or tetanus respectively. The immune response against these pathogens does not require T-cell help in order to produce antibodies, and are thus termed thymus-independent vaccines. A third type of vaccine exists in which substances that elicit a T-cell response are conjugated to a thymus-independent pathogen in order to boost the efficiency of the antibody response against the thymus-independent pathogen. Conjugate vaccines like meningococcal C induce a thymus-dependent response. If psychological factors are consistently associated with the response to thymus-dependent and conjugate vaccinations but not with thymus-independent response, this would imply that it is the T-cells that are particularly liable to psychological influence. Indeed, there is evidence to suggest that psychological factors like stress may exert their effects mainly on T-cells, as in one recent study higher frequency and intensity of stressful life events were associated with a poorer response to influenza and meningococcal C, but not to meningococcal A vaccination (Phillips *et al.*, 2005a). In addition, no association was found between stress and antibody response to a pneumonia vaccination in pre-school children (Boyce *et al.*, 1995). However, as older caregivers have been reported to show poorer maintenance of antibody levels in the longer term following pneumonia vaccination than controls (Glaser *et al.*, 2000), it is possible that other factors such as age and severity of stress may interact to impair antibody-mediated immunity more generally than just the T-cell response.

The vaccination response in older adults has mainly been considered in the context of caregiving for a spouse with dementia. This is a very specific stressor, and care-givers are likely

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to differ from the general population in ways other than the stress of care-giving, for example, in the amount of social support they receive. Research examining the impact of more general psychological stress on antibody levels following vaccination is sparse. However, it is important to study older adults in this context as they are likely to have different stress exposure histories than younger samples (Carroll *et al.*, 2005) and to have less efficient immune systems due to immune ageing or immunosenescence, which contributes to increased infectious disease susceptibility in older adults (Ginaldi *et al.*, 2001). The effects of ageing on immune function may alter individuals' susceptibility to disease in part via a less efficient antibody response. One study found that older adults reporting higher perceived stress had lower antibody levels following influenza vaccination (Kohut *et al.*, 2002). As baseline antibody level prior to vaccination was not known, however, the impact on the actual response to the vaccine could not be assessed. More recently, we observed that the stress of bereavement in the year prior to influenza vaccination was associated with a poorer antibody response (Phillips *et al.*, 2006). Although overall negative life events exposure was not associated with vaccine response in this study, the effect found for bereavement suggests that stress is related to pervasive immune effects throughout the life course, although the particular stressor of importance may change with the age of the sample studied.

[Insert Figure 2 about here]

The support of friends and loved ones may also be an important determinant of immune health. Studies assessing functional social support, a measure of the quantity and quality of social resources available to a person, have found that it is positively related to antibody levels following hepatitis B (Glaser *et al.*, 1992) and influenza vaccinations (Phillips *et al.*, 2005a). Similarly, there is evidence that feelings of loneliness and having a small social network size are associated with poorer influenza vaccination response (Pressman *et al.*, 2005). Further, older adults who were married, and particularly those who were happily married, showed a better antibody response to the influenza vaccination than those who were unmarried or less happily married (Phillips *et al.*, 2006). However, more general functional social support and social network size was not associated with antibody response in this older population (Phillips *et al.*, 2006). These findings perhaps lend weight to the suggestion above that different factors become important, in terms of the influence on immunity, across the life course.

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Certain personality traits have also been found to relate to vaccination response, such as internalisation in adolescents (Morag *et al.*, 1999), and trait negative affect (Marsland *et al.*, 2001) and neuroticism (Phillips *et al.*, 2005b) in students. However, factors such as dispositional optimism were not found to be associated with antibody levels following vaccination in older adults (Kohut *et al.*, 2002). Inconsistencies in results could be attributable to the different populations studied.

The clinical implications arising from a better understanding of the varied relationships between psychological factors and the vaccination response are important, particularly in the context of older adults who already display increased susceptibility to disease. Psychological interventions to improve vaccination response in these populations have included techniques such as stress management (Vedhara *et al.*, 2003) and emotional disclosure (Petrie *et al.*, 1995). At this stage, the results are mixed, and much more work is required to establish what types of intervention are likely to be the most beneficial for psychological, and hence immunological, health. Another potential clinical application of the vaccination model has arisen from recent work in the area of acute stress: animal research has suggested that brief one-off stress exposures may actually be immune-enhancing (see e.g. Dhabhar, 2003). A recent study by our group has shown that the application of acute stress such as a mental arithmetic challenge shortly before vaccination was associated with increased antibody levels following vaccination in those participants who typically display a somewhat lower response (Edwards *et al.*, 2006). Developing a behavioural stress challenge that could be applied in GP settings could be a way forward for improving the vaccination response in groups at risk of infectious disease such as older adults and care-givers.

In conclusion, vaccination programmes have had a substantial impact on public health, but not everyone mounts a satisfactory response to vaccination. This is increasingly the case as we age. Studying antibody responses to vaccination is now contributing to our understanding of how psychosocial exposures can influence immunity and, consequently, resistance to disease. The current challenges are to unravel the underlying mechanisms and to develop and apply feasible behavioural interventions that boost our body's response to vaccination and optimise disease resistance.

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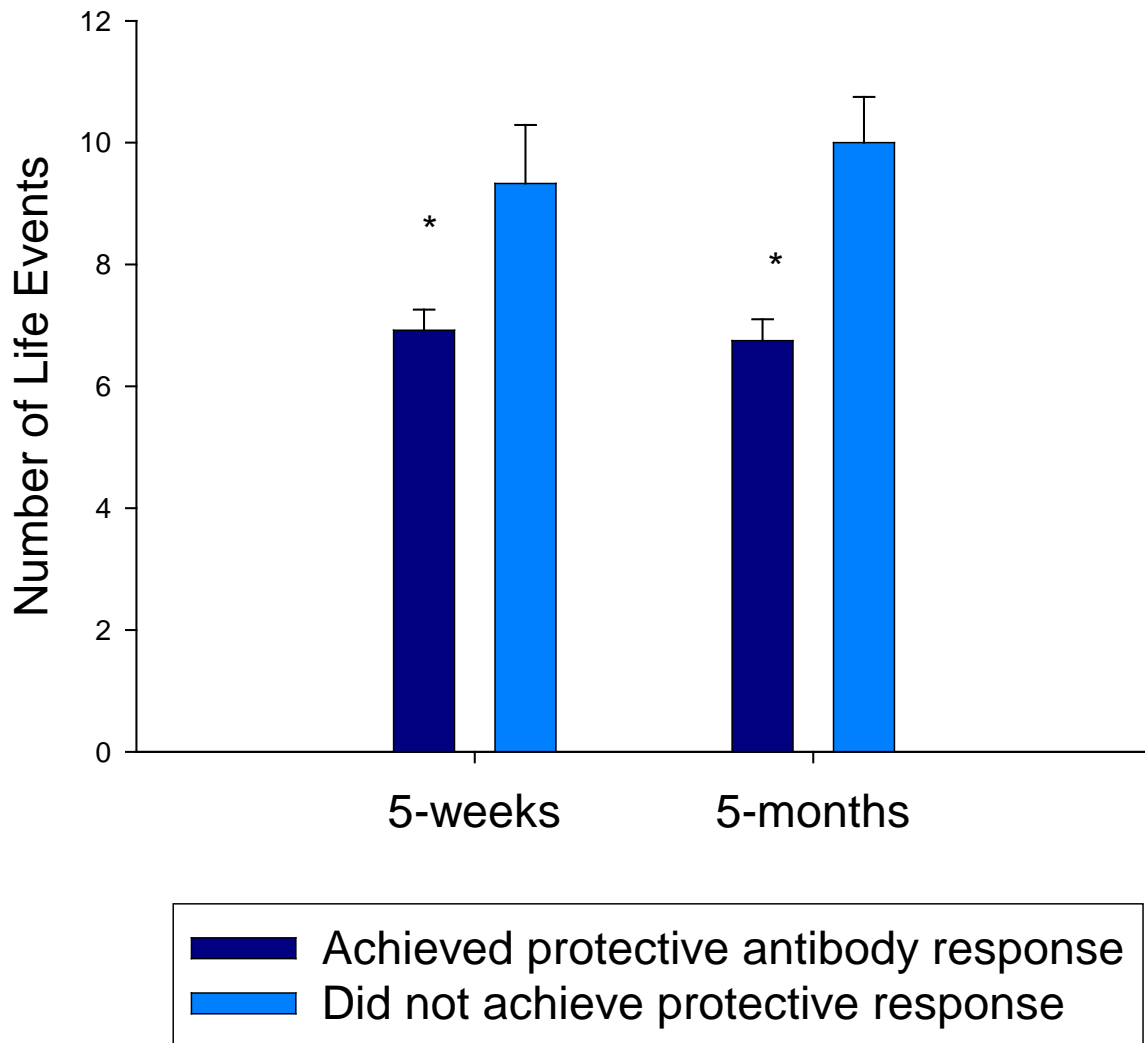
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Figure 1: Life Events Stress and Antibody Response to Influenza Vaccination

Figure 2: Bereavement and Response to Influenza Vaccination in Older Adults



Adapted from Phillips et al., 2005. *Brain, Behaviour and Immunity*, 19, 325-333.

