

A shot in the arm for research

Anna C. Phillips and Victoria E. Burns on why vaccinations are so interesting to psychologists

Next time you get flu or a cold after a particularly difficult week, don't dismiss it as coincidence. Interdisciplinary work between psychologists and immunologists has shown that factors like stress could be the trigger. By studying the response to vaccination, we can examine immune function in a clinically meaningful way. This technique has demonstrated relationships between factors such as stress, social support, and personality and vaccination-induced protection against disease. The types of stress and social support that influence our immune response also change as we age, emphasising the importance of a life course approach to study.

questions

Why is the vaccination response a good model of immune function?
Why are different psychosocial factors related to vaccination response in younger and older adults?
By which pathways might psychosocial factors influence immunity, and why do they affect the response to some vaccines but not others?

resources

Vedhara, K. & Irwin, M.R. (2005). *Human psychoneuroimmunology*. Oxford: OUP.
www.pnirs.org
www.psychosomatic.org

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. Now some new tools of the trade – vaccines and blood samples – are providing a unique insight into how psychological processes affect the ability of the body to defend itself against infection.

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 physiological pathways through which our thoughts and feelings could feasibly 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. Antibodies are proteins produced by white blood cells. Their task is to

circulate in the body and tag, destroy, or neutralise bacteria, viruses or other harmful or foreign materials (antigens). The antibody level is the culmination of a series of immunological events, starting with 'foreign body' antigen recognition and resulting in the production of highly specific antibodies by B cells. 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.

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 caregiving 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, 2000; Vedhara et al., 1999).

However, caregiving 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 or greater perceived stress are characterised by poorer antibody status following a range of vaccinations including hepatitis B (Burns, Carroll et al., 2002; Glaser et al., 1992), meningococcal C (Burns, Drayson et al., 2002), and influenza (Burns, Carroll et al., 2003; Miller et al., 2004; Phillips, Burns et al., 2000).

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

references

- Boyce, W.T., Adams, S., Tschann, J.M. et al. (1995). Adrenocortical and behavioral predictors of immune response to starting school. *Pediatric Research*, 38, 1009–1017.
- Burns, V.E., Carroll, D., Drayson, M. et al. (2003). Life events, perceived stress and antibody response to influenza vaccination in young healthy adults. *Journal of Psychosomatic Research*, 55, 569–572.
- Burns, V.E., Carroll, D., Ring, C. & Drayson, M. (2003). Antibody response to vaccination and psychosocial stress in humans: Relationship and mechanisms. *Vaccine*, 21, 2523–2534.
- Burns, V.E., Carroll, D., Ring, C. et al. (2002a). Stress, coping and hepatitis b antibody status. *Psychosomatic Medicine*, 64, 287–293.
- Burns, V.E., Drayson, M., Ring, C. & Carroll, D. (2002). Perceived stress and psychological well-being are associated with antibody status following meningitis c conjugate vaccination. *Psychosomatic Medicine*, 64, 963–970.
- Carroll, D., Phillips, A.C., Ring, C. et al. (2005). Life events and hemodynamic stress reactivity in the middle-aged and elderly. *Psychophysiology*, 42, 269–276.
- Cohen, S., Miller, G.E. & Rabin, B.S. (2001). Psychological stress and antibody response to immunization. *Psychosomatic Medicine*, 63, 7–18.
- Dhabhar, F.S. (2003). Stress, leukocyte trafficking, and the augmentation of skin immune function. *Annals of the New York Academy of Sciences*, 992, 205–217.
- Edwards, K.M., Burns, V.E., Reynolds, T. et al. (2006). Acute stress exposure

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 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, Carroll, Ring et al., 2003; 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 response are influenced by psychological factors:

- I Thymus-dependent vaccines: Most vaccinations consist of inactivated or dead viruses like influenza, and they induce a

response in which the B cells (the antibody 'factories') require the help of T cells, in order to produce antibody.

- I Thymus-independent vaccines: Protect against bacterial infections or toxins like meningococcal A or tetanus respectively, and the immune response does not require T-cell help in order to produce antibodies.

- I Conjugate vaccines: Substances that elicit a T-cell response are joined 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. 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 the thymus-independent meningococcal A vaccination (Phillips, Burns et al., 2005). Similarly, no association was found between stress and antibody

response to a thymus-independent pneumonia vaccination in pre-school

children (Boyce et al., 1995). However, as poorer maintenance of antibody levels in the longer term following pneumonia vaccination has been shown in older caregivers in comparison with 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 caregivers are likely to differ from the general population in ways other than the stress of caregiving, 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 increased infectious disease susceptibility due to immune ageing (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

"stress is related to pervasive immune effects throughout the life course"

No association was found between stress and antibody response to a thymus-independent pneumonia vaccination in pre-school children

prior to influenza vaccination enhances antibody response in women. *Brain, Behavior and Immunity*, 20, 159–168.

Ginaldi, L., Loreto, M.F., Corsi, M.P. et al. (2001). Immunosenesescence and infectious diseases. *Microbes Infect*, 3, 851–857.

Glaser, R., Kiecolt-Glaser, J.K., Bonneau, R.H. et al. (1992). Stress-induced modulation of the immune response

to recombinant hepatitis b vaccine. *Psychosomatic Medicine*, 54, 22–29.

Glaser, R., Sheridan, J.F., Malarkey, W. et al. (2000). Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosomatic Medicine*, 62, 804–807.

Kohut, M.L., Cooper, M.M., Nickolaus, M.S. et al. (2002). Exercise and psychosocial factors modulate immunity to influenza vaccine in

elderly individuals. *Journal of Gerontology*, 57, 557–562.

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 Psychology*, 20, 4–11.

Miller, G.E., Cohen, S., Pressman, S. et al. (2004). Psychological stress and

antibody response to influenza vaccination. *Psychosomatic Medicine*, 66, 215–223.

Morag, M., Morag, A., Reichenberg, M.A. et al. (1999). Psychological variables as predictors of rubella antibody titers and fatigue. *Journal of Psychiatric Research*, 33, 389–395.

Petrie, K.J., Booth, R.J., Pennebaker, J.W. et al. (1995). Disclosure of trauma and immune response to a

stressor of importance may change with the age of the sample studied.

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, Burns et al., 2005). 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 are married, and particularly those who are happily married, show a better antibody response to the influenza vaccination than those who are 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.

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, Carroll et al., 2005) 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

Older adults who are married, and particularly those who are happily married, show a better antibody response to the influenza vaccination

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 (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 caregivers.

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.



I Anna C. Phillips
is in the School of Sport
and Exercise Sciences,
University of Birmingham
A.C.Phillips@bham.ac.uk



I Victoria E. Burns
is in the School of Sport
and Exercise Sciences,
University of Birmingham
V.E.Burns@bham.ac.uk

hepatitis b vaccination program. *Journal of Consulting and Clinical Psychology*, 63, 787–792.

Phillips, A.C., Burns, V.E., Carroll, D. et al. (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*, 19, 325–333.

Phillips, A.C., Carroll, D., Burns, V.E. & Drayson, M. (2005). Neuroticism, cortisol reactivity, and antibody response to vaccination. *Psychophysiology*, 42, 232–238.

Phillips, A.C., Carroll, D., Burns, V.E. et al. (2006). Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. *Brain, Behavior and Immunity*, 20, 279–289.

Pressman, S.D., Cohen, S., Miller, G.E. et al. (2005). Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychology*, 24, 297–306.

Vedhara, K., Bennett, P.D., Clark, S. et al. (2003). Enhancement of antibody responses to influenza vaccination in the elderly following a cognitive-behavioural stress management

intervention. *Psychotherapy and Psychosomatics*, 72, 245–252.

Vedhara, K., Cox, N.K.M., Wilcock, G.K. et al. (1999). Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *The Lancet*, 20, 627–631.

Vedhara, K., McDermott, M.P., Evans, T.G. et al. (2002). Chronic stress in non-elderly caregivers. *Journal of Psychosomatic Research*, 53, 1153–1161.