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Shots in the desert and Gulf war syndrome

Evidence that multiple vaccinations during deployment are to blame is inconclusive

Papers p 1363

Vaccinations could have long term, non-specific effects on immune responses in children and adults, some undesirable, others beneficial. For example, there has been speculation that vaccines could influence the development of atopy. We have known for years that the pertussis vaccine is an adjuvant for IgE production, and conjecture that vaccinations might have contributed to the rise in atopic disease in children was an inevitable corollary of the "hygiene hypothesis."[1] This hypothesis proposes that the prevalence of atopy has increased because infections in early life protect against atopy and children have been less exposed to infections over time. The discovery of polarised T helper cell responses, Th1 and Th2, fuelled the debate.[2] It led to a theoretical model whereby the development of atopy characterised by Th2-type cytokine responses to allergens and production of IgE might be promoted by vaccines that induce Th2 cytokines or inhibited by those that induce Th1 cytokines.

However, evidence from observational studies that vaccinations increase the risk of atopy is contradictory, and early follow up of a cohort from a trial of pertussis vaccine suggests that this vaccine, at least, is unlikely to be an important cause of atopic disease.[3] On the other hand, it is possible that mycobacterial vaccines that induce Th1 cytokines might prevent atopy in children, and trials are under way to see whether they can reduce atopic symptoms in adults.

Three years ago Rook and Zumla proposed that the multiple vaccines given to service personnel might have contributed to the symptoms of Gulf war syndrome by causing a long term systemic shift in cytokine balance from Th1 to Th2.[4] They suggested that such an effect was most likely to have occurred if the vaccines included pertussis, if they were given during the stress of deployment, and if pesticides were used concurrently.[4] Aetiological studies of Gulf war syndrome have presented a major challenge to epidemiologists, not least because of the lack of exposure records and reliance on recall many years later.[5] A recent cross sectional study of British Gulf war veterans, done six years after the conflict, found that veterans who reported having been given multiple vaccinations were more likely to report illnesses with multiple symptoms.[6]

In this issue of the *BMJ*, Hotopf et al report further analyses of the effects of multiple vaccinations. They show that multiple vaccinations given during deployment, but not before, were associated with five out of six main health outcomes—namely, multisymptom illness, fatigue, psychological distress, health perception, and physical functioning (p 1363).[7] These findings seem to support the hypothesis of Rook and Zumla, although a puzzling observation is that post-traumatic stress disorder was related to multiple vaccinations given before, but not during, deployment.

These findings demand cautious interpretation. Firstly, the possibility of confounding by exposure to other agents cannot be ruled out. More than 20 types of exposure were implicated in the original paper but were not controlled for in these analyses.[6] Secondly, the apparent interaction between multiple vaccinations and deployment was seen in a subset of 923 out of 3284 respondents who had kept vaccination records but not in the whole cohort, suggesting that the findings in the restricted sample might in some way be biased. Thirdly, the information obtained from participants about their vaccination records might not have been reliable. For example, there was no evidence of "catch-up" vaccination occurring during deployment among those who had had the fewest vaccinations before deployment. Also, anthrax vaccination was reported much more frequently than pertussis vaccination, even though they were always given together. Since the reporting of pertussis vaccination is thought to be reasonably accurate, this suggests that anthrax vaccination was substantially overreported, a problem confirmed in US veterans of the Gulf war.[8] Fourthly, an overriding concern is that symptomatic veterans who had kept their vaccination records might have been aware of the hypothesis being tested and hence overreported the vaccinations that they had received during deployment. The paper by Rook and Zumla was published a few months before the British survey, and it was suggested in the UK media that veterans could get compensation if the hypothesis was confirmed.[9]

Hotopf et al could not confirm that the effects of multiple vaccinations were stronger when pertussis vaccine was included or that they were potentiated by stress and pesticide use, as proposed by Rook and Zumla. Because there were no immunological data, Hotopf et al used reported atopic disease as an indicator of skewing towards a Th2 response. However, they could not determine whether atopic symptoms were present before deployment or had developed subsequently. Having had multiple vaccinations during deployment was unrelated to "eczema and psoriasis," which is not surprising since eczema in adults includes non-atopic contact dermatitis and this, like psoriasis, is Th1 mediated. While there was

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some evidence for a link with "asthma," wheezing in adults may not be atopic. There was also no association between having had multiple vaccinations and hay fever. In fact there is little support for Gulf war syndrome being associated with a shift towards a Th2 profile, and a study of US veterans of the Gulf war who had chronic fatigue syndrome found evidence of a cytokine shift in the opposite direction.[10]

Similar poorly defined illnesses have been seen after other conflicts in which soldiers were not given multiple vaccinations.[11] Whether or not the hypothesis is correct, the authors propose a sensible solution, namely for the armed forces to keep the routine vaccinations of their personnel up to date during peacetime, thus reducing the number of vaccines given during deployment. Improved systems of health surveillance and record keeping in the military should facilitate rapid retrieval of data on exposures and health outcomes that are more complete and less biased.[12] This will allow more rigorous aetiological studies of illnesses occurring after conflicts to be undertaken in future.

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Screening for breast and cervical cancer as a common cause for litigation

A false negative result may be one of an irreducible minimum of errors

A delay in the diagnosis of cancer is now one of the commonest reasons for medical litigation. Increasingly women in whom breast or cervical cancers are diagnosed after a "normal" screening test are alleging negligence through a delay in diagnosis and are seeking compensation through the legal system. Medical staff involved in providing screening are highly concerned about this situation.[1] How has it arisen?

The enthusiasm of the health service to promote screening has perhaps given women unrealistic expectations. Women may falsely believe that screening prevents cancer rather than detects it earlier. There is also a perception that cancers arising after a normal screening examination must have been "missed" and that the delays in diagnosis have prognostic significance.

Population screening is different from health care, which manages individuals with symptoms; most people who are screened are free from disease, and an acceptable balance between the sensitivity and specificity of the screening test must take this into account.[2] The legal position here seems to differ from that of the health providers. In the case of a number of patients who were given false negative results on cervical screening in east Kent in England, the courts awarded the patients compensation. An appeal by the health authority was dismissed by the appeal court, which ruled that sensitivity in screening is paramount—"a false negative result could have very adverse consequences. A false positive would have nothing like this disadvantage to the patient … the patient could be caused anxiety, but this is a small price to pay for the protection against the adverse consequences."[3] False positive screening tests, however, cause serious morbidity and anxiety to women several months after a screening recall despite reassurance.[4 5] In screening for breast cancer, specificity is no more than 15% with about 5% of women recalled for further tests to diagnose 5-6 cancers per 1000 women screened. Reducing specificity further to improve sensitivity would be unlikely to increase appreciably the detection of early cancers or reduce mortality. It would also be to the detriment of the considerably larger number of women subjected to the anxiety of a recall for a false positive result.[6 7]

At best, screening mammography has a sensitivity for cancer of around 90%, and in the three year cycle of the NHS breast screening programme around 40% of breast cancers present symptomatically (interval cancers). A small proportion of these interval cancers (around 10%) are so called "false negative" screens in which, in retrospect, the previous mammogram shows abnormalities. An independent expert opinion may well conclude that in these individual cases a detectable abnormality was not identified and that this

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