CORRESPONDENCE

Measles vaccination and inflammatory bowel disease

SIR—Mark Feeney and colleagues (Sept 13, p 764)[1] are to be commended on their efforts to investigate a possible link between measles vaccine and inflammatory bowel disease (IBD). However, as they themselves acknowledge, the potential difficulty of poor ascertainment of vaccination status could blur any relation between vaccination and the risk of IBD. Thompson and co-workers,[2] who used the Royal College of General Practitioners (RCGP) database covering a nationally representative 1% of the UK population, found that, at a time when national vaccine uptake rates exceeded 55%, general practitioners recorded having given measles vaccine in only 8% of patients in the appropriate age-group. According to the RCGP, recording was only improved when general practitioners were remunerated for achieving vaccination targets. On the basis of Thompson's study,[2] ascertainment of vaccination status from general-practitioner records covering the relevant period[1] could have underestimated measles vaccination rates by as much as 47% among either cases or controls. Absence of a record of measles vaccination cannot be taken as absence of vaccination.

Poor ascertainment of measles vaccination status is likely to reduce the statistical significance of any relation between vaccination and subsequent disease, so that a small systematic bias is more likely to obliterate any such relation. There is a risk that by replacing controls, but not patients with IBD who had inadequate vaccination records, systematic bias may have been introduced into this study. Feeney and colleagues have attempted to address the issue of unobserved heterogeneity by looking at the uptake rates for vaccination against pertussis and diphtheria/tetanus. Although examination of vaccinations other than against measles provides more evidence about reliability of these data, it cannot provide conclusive evidence of homogeneity among cases and controls. The significantly higher uptake rates for pertussis and diphtheria/tetanus indicate that there could be a less significant relation between socioeconomic circumstances and vaccine uptake when compared with vaccination against measles. When this is coupled with the uncertainty of vaccination records, it renders them inadequate as indicators of childhood circumstances and characteristics. It is important that trials such as this are conducted and reported, but they cannot be a substitute for adequate safety trials of procedure that might cause severe iatrogenic damage, even if only in a few cases.

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1 Feeney M, Clegg A, Winwood P, Snook J. A case control study of measles vaccination and inflammatory bowel disease. *Lancet* 1997; **350:** 764–66.

2 Thompson NP, Flemming DM, Pounder RE, Wakefield AJ. Crohn's disease, measles, and measles vaccination: a case control failure. *Lancet* 1996; **347:** 263.

Authors' reply

SIR—Scott Montgomery and colleagues raise important questions about the accuracy of the data on which our study is based, and suggest some possible sources of bias. In our discussion we set out the reasons why we feel that the data are sufficiently reliable to justify the conclusions drawn.

On the basis of national vaccination figures and the age distribution of our study population, we would have expected a measles vaccination prevalence of 54·2% in the control group—in fact the observed figure was 57·1%. It therefore seems most unlikely that we failed to identify vaccine recipients in appreciable numbers.

It remains unclear why this apparently did happen in the study of Thompson et al,[1] although the numbers concerned were small. Unfortunately, this study is difficult to interpret because it was published in brief letter format. In particular, it is not clear how rigorously health-care records were searched for the relevant information, a key determinant of successful data retrieval.

Subgroup analysis does not support the suggestion that replacing controls with reserves when records were inadequate introduced bias into our study. Of 45 reserve controls, 25 (56%) had received measles vaccine, compared with 24 (53%) of matched cases.

Finally, the suggestion that there is a "less significant relation between socioeconomic circumstances and vaccine uptake" for pertussis or diphtheria/tetanus than for measles is unsubstantiated. Evidence does not support this view.[2]

We share Montgomery and colleagues' sentiments about the importance of adequate safety trials. However, in the case of measles vaccine a trial with an unvaccinated limb would now be ethically questionable because the vaccine has proved so effective. In the absence of this type of trial, our finding of no link between measles vaccination and the later development of inflammatory bowel disease is reassuring,[3] especially since this conclusion has recently been supported by a smaller case-control study.[4]

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1 Thompson NP, Fleming DM, Pounder RE, Wakefield AJ. Crohn's disease, measles and measles vaccination: a case-control failure. *Lancet* 1996; **347:** 263.

2 Clegg AJ. Childhood immunisation uptake: geographical perspectives. PhD Thesis, Portsmouth University, 1993.

3 Baxter T, Radford J. Measles vaccination as a risk factor for inflammatory bowel disease. *Lancet* 1995; **345:** 1363.

4 Morris DL, Montgomery SM, Ebrahim S, Pounder RE, Wakefield AJ. Measles vaccination and inflammatory bowel disease in the 1970 British cohort study. *Gut* 1997; **41** (suppl 3): A37.

SIR—The case-control study by Mark Feeney and colleagues[1] is an important contribution in the search for possible links between measles and Crohn's disease. The study shows that for individuals born in the 1970s and vaccinated during their second year of life, no increased risk of developing Crohn's disease could be demonstrated during over 20 years of follow-up.

The purported basis for an association between measles and Crohn's disease is persistent measles virus or measles vaccine virus infection. Explaining Crohn's disease through association with measles vaccination requires a mechanism for the development of such persistent infection. We have proposed such a mechanism on the basis of an immunological tolerance window (unpublished data). We postulate that in the absence of maternal antibodies against measles, and before the maturation of the child's immune system, during the immunological tolerance window, exposure to measles virus (be it wild virus or vaccine virus) could result in tolerance to measles antigen and therefore persistent infection. Individuals with tolerance to measles antigen would consequently be at high risk of Crohn's disease.

A large immunological tolerance window is most obviously present in the few children born to mothers without measles antibodies; from the in-utero period until immunological maturity at, say, 6 months of age. A shorter window is also present in some children in whom maternal antibodies wane early, before maturation of their immune system. Several studies[2,3] back up the existence of such a mechanism. Of particular interest are non-boostable primary non-responders to live attenuated measles vaccine. This non-response is much more frequent in the case of vaccination at very young age (6–9 months), and may indicate such induced tolerance.

The study by Feeney does not invalidate the measles tolerance hypothesis, since the individuals studied were vaccinated during their second year of life, when maturation of most children's immune system is reached. According to the measles tolerance hypothesis, an association between measles vaccination and Crohn's disease would only be expected in case of vaccination of a child who is (a) not protected by maternal antibodies anymore, and (b) not yet immunological mature. The discussion thus remains open.

If the measles tolerance hypothesis were to prove correct, it could contribute to the explanation of the increase in Crohn's disease in western countries. More important though, are the potential consequences for developing countries. A combination of vaccination as young as 6 months of age (the practice in Kinshasa, Congo, for the past 10 years), and reduced protection by maternal antibodies of children born to mothers who derive their immunity from vaccine, would multiply the opportunities for developing immune tolerance. The prospect of an epidemic of Crohn's disease in African countries 20 years from now, induced by vaccination at too young an age today, would be gloomy indeed.

To clarify the possible link between measles and Crohn's disease, two research tracks should be explored. First we need to demonstrate, or refute, the existence of immunotolerance to measles virus. The non-boostable primary non-responders to measles vaccine identified in several studies could be a good starting point.[4] Second, we should test the link between immunotolerance to measles virus and Crohn's disease. Studies of links between measles vaccination and Crohn's disease should then focus on vaccination at very young ages. In view of the potential high stakes, this would constitute a worthwhile contribution to the debate.

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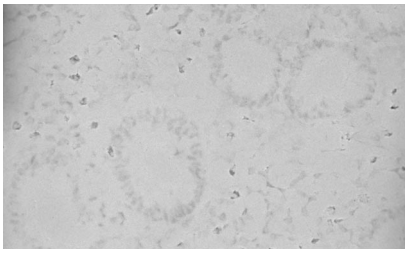
1 Feeney M, Clegg A, Winwood P, Snook J. A case-control study of measles vaccination and inflammatory bowel disease. *Lancet* 1997; **350:** 764–66.
2 Thompson NP, Montgomery SM, Pounder RE, Wakefield AJ. Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet* 1995; **345:** 1071–74.
3 Ekbom A, Daszak P, Kraaz W, Wakefield AJ. Crohn's disease after in-utero measles virus exposure. *Lancet* 1996; **348:** 515–17.
4 Mendelson E, Duvdevani P, Varsano N, et al. Measles immunity and response to revaccination of a young adult population in Israel. *J Med Virol* 1996; **50:** 249–53.

SIR—Persistent measles virus infections is implicated in Crohn's disease.[1,2] This measles hypothesis is based mainly on immunohistochemical[1] and epidemiological findings.[2] However, Mark Feeney and colleagues' case-control study[3] has provided evidence against this hypothesis.

Immunohistochemical evidence derives essentially from the observation that both a monoclonal antibody and polyclonal hyperimmune serum specific for measles-virus-stained measles antigen are present in the intestine of Crohn's disease. We confirmed this observation with the same monoclonal antibody (MAS 182r: Harlan Sera-lab, Crawley Down, UK) that Wakefield and colleagues[1] used (figure). However, we failed to identify measles virus genome, even with a highly sensitive reverse-transcriptase (rt)-PCR.[4]



Intestinal tissue of Crohn's disease immunohistochemically stained with measles monoclonal antibody

Measles-specific monoclonal antibody MAS 182r was used to screen 1·5 million clones in a λgt11-expression library constructed from the intestinal tissue surgically excised from a 38-year-old patient with typical Crohn's disease. We thus identified and sequenced one positive clone to find that it was not a part of any measles virus genome but that it was 99% homologous with an undefined human gene deposited in the DNA data bases (AA449055). A Southern blot analysis further confirmed the host origin of this protein. This unexpected result led us to produce a monoclonal antibody (4F12) against this protein. When the intestinal tissues from the patients with Crohn's disease were doubly-stained with the monoclonal antibodies MAS 182r and 4F12, virtually all MAS 182r-positive cells were stained with 4F12. Although the possibility still remains that the antigen recognised by MAS 182r was a measles virus antigen, we assume that such a possibility is slight since none of measles-virus related clones were identified in the cDNA library.

Thus, our findings, together with earlier rt-PCR results,[4] are not in accord with the hypothesis that persistent measles virus infection is the cause of Crohn's disease. Previous immunohistochemical observations can be accounted for by antigen mimicry between measles virus and an undefined host protein found in the intestine of Crohn's disease.

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1 Wakefield AJ, Pittilo RM, Sim R, et al. Evidence of persistent measles virus infection in Crohn's disease. *J Med Virol* 1993; **39:** 345–53.
2 Ekbom A, Daszak P, Kraaz W, et al. Crohn's disease after in-utero measles virus exposure. *Lancet* 1996; **348:** 515–17.
3 Feeney M, Clegg A, Winwood P, et al. A case-control study of measles vaccination and inflammatory bowel disease. *Lancet* 1997; **350:** 764–66.
4 Iizuka M, Nakagomi O, Chiba M, et al. Absence of measles virus in Crohn's disease. *Lancet* 1995; **345:** 199.