Is measles vaccination a risk factor for inflammatory bowel disease?

N P Thompson, S M Montgomery, R E Pounder, A J Wakefield

Summary

Measles virus may persist in intestinal tissue, particularly that affected by Crohn's disease, and early exposure to measles may be a risk factor for the development of Crohn's disease. Crohn's disease and ulcerative colitis occur in the same families and may share a common aetiology. In view of the rising incidence of inflammatory bowel disease (Crohn's disease and ulcerative colitis), we examined the impact of measles vaccination upon these conditions.

Prevalences of Crohn's disease, ulcerative colitis, coeliac disease, and peptic ulceration were determined in 3545 people who had received live measles vaccine in 1964 as part of a measles vaccine trial. A longitudinal birth cohort of 11 407 subjects was one unvaccinated comparison cohort, and 2541 partners of those vaccinated was another. Compared with the birth cohort, the relative risk of developing Crohn's disease in the vaccinated group was 3·01 (95% CI 1·45–6·23) and of developing ulcerative colitis was 2·53 (1·15–5·58). There was no significant difference between these two groups in coeliac disease prevalence. Increased prevalence of inflammatory bowel disease, but not coeliac disease or peptic ulceration, was found in the vaccinated cohort compared with their partners.

These findings suggest that measles virus may play a part in the development not only of Crohn's disease but also of ulcerative colitis.

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Inflammatory Bowel Disease Study Group, Royal Free Hospital School of Medicine, London, UK (N P Thompson MRCP, Prof R E Pounder DSc, A J Wakefield FRCS); **and Social Statistics Research Unit, City University** (S M Montgomery BSc), **London**

Correspondence to: Mr A J Wakefield, Department of Medicine, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF, UK

Introduction

Persistent measles virus infection has been identified in intestinal tissue by immunohistochemistry for measles nucleocapsid protein, in-situ hybridisation for measles genomic RNA, and electron microscopy.[1] The persistence of measles in Crohn's-disease-affected bowel has been confirmed by the more specific technique of immunogold electron microscopy.[2] In Sweden, a positive association was reported between perinatal exposure to measles and the development of Crohn's disease, but not ulcerative colitis.[3] However, a similar association was not detected in the UK.[4] The incidence of inflammatory bowel disease has increased over the past few decades, during which the use of live measles vaccines has become routine. We therefore tested the hypothesis that measles vaccination is a risk factor for the development of inflammatory bowel disease (Crohn's disease and ulcerative colitis).

Methods

In 1964 the UK Medical Research Council (MRC) Measles Vaccines Committee did a randomised trial of measles vaccine.[5] Children aged 10–24 months were allocated to receive live vaccine (9577) or inactivated followed by live vaccine (10 625), or to be unvaccinated controls (16 328). The live vaccine used was the Schwarz strain derived from the Enders-Edmonston B strain. Postal follow-up to assess long-term vaccine efficacy has been carried out annually and was last reported in 1994.[6] The end-point of the follow-up is a report of measles. Owing to the withdrawal of five local authorities, about 2000 children were lost from each group after 9 months.[5] Children whose parents failed to respond to the annual follow-up for 3 successive years were withdrawn from the study, as were those who emigrated. In May, 1994, there were 3967 recipients (mean age 31 years) of live measles vaccine who were still involved in long-term follow-up.

We could not use the children who did not receive vaccine in the MRC trial as controls because many either developed measles or were offered vaccine as part of the national vaccination scheme (introduced in 1968); by 1990 only 274 were still included in follow-up.[6] We identified a surrogate control cohort, members of which were of a similar age to those in the vaccine trial. The National Child Development Study (NCDS) is a national longitudinal study of 17 414 people born in Great Britain (UK except Northern Ireland) between March 3 and 9, 1958,[7] representing 98% of births occurring during this week. There have been five subsequent data collections, the most recent (NCDS-5) in 1991, when subjects were aged 33 years. By 1991 the target population had fallen, because of death or emigration, to 15 666 of whom 13 444 were traced. Subjects were too old to have been involved either in the measles vaccine trial or in the national measles vaccination programme. A further control group was partners of those who had measles vaccine. Although their vaccination history was not known, most are likely to have had measles or to have been vaccinated at an older age (greater than 5 years).

Recipients of live vaccine in the MRC trial and their partners were asked whether they "had, or had ever been told, by a doctor, that they had" Crohn's disease, ulcerative colitis, coeliac

	MRC measles vaccine follow-up	NCDS 5th survey	RR (95% CI)
Number of respondents	3545	11 407	.
Crohn's disease	14	15	3·01 (1·45–6·23)
Ulcerative colitis	11	14	2·53 (1·15–5·58)
Coeliac disease	2	4	1·62 (0·30–8·83)
Rate of inflammatory bowel disease per 1000	7·09	2·54	. .

Table 1: **Rates of gastrointestinal disease in vaccine and longitudinal cohorts**

	MRC measles vaccine follow-up	Partners of measles vaccinee	RR (95% CI)
Number of respondents	3545	2541	. .
Crohn's disease	14	5	2·01 (0·72–5·57)
Ulcerative colitis	11	5	1·58 (0·55–4·54)
Coeliac disease	2	4	0·36 (0·07–1·96)
Peptic ulcer disease	44	49	0·64 (0·43–0·96)
Rate of inflammatory bowel disease per 1000	7 09	3·94	. .

Table 2: **Rates of gastrointestinal disease in vaccine cohort and partners**

disease, or peptic ulcer disease. Coeliac disease was chosen as a rare condition that was unlikely to elicit false-positive replies, and peptic ulceration to prevent an excessive emphasis on inflammatory bowel disease. The rates of peptic ulcer were compared between the vaccine cohort and their partners but not with subjects in NCDS. Experience from NCDS suggests that individuals reporting peptic ulcer at 25 years of age (NCDS-4) do not report the condition when 31 years old (NCDS-5) and therefore life-long prevalence rates are unreliable. In addition, this diagnosis tends not to be made with the same rigour as inflammatory bowel disease or coeliac disease. The ages at vaccination of those who later developed either Crohn's disease or ulcerative colitis were compared with those of the group as a whole (data from Dr Mary Ramsay, CDSC).

The NCDS group were asked about any condition that required regular medical supervision, the presence of "any long-standing illness, disability, or infirmity" and details of all out-patient appointments and hospital admissions. Replies were coded according to the 9th revision of the International Classification of Diseases (ICD), for Crohn's disease (ICD 555), ulcerative colitis (ICD 556), and coeliac disease (ICD 559).

Subjects in the MRC trial follow-up who reported having inflammatory bowel disease were contacted again by letter, requesting permission for their physician to be approached to confirm the diagnosis. For members of NCDS reporting inflammatory bowel disease, permission to approach the relevant physician had usually been obtained already. When permission was given, the individual's diagnosis was confirmed with standard criteria.[8] A reported diagnosis of coeliac disease was not validated on the basis that self-reported coeliac disease could be assumed to be a reliable diagnosis. MRC trial subjects were sent a further questionnaire if they did not respond initially. If their physicians did not reply to one letter, a second was sent, followed, if necessary, by a telephone request.

The differences in observed rates of ulcerative colitis and Crohn's disease in the two cohorts were compared by means of a two-by-two table. The relative risk (RR) of either disease developing, with 95% CI, was calculated, and a Yates' corrected p value derived. Fisher's exact test was used to compare rates of coeliac disease because the numbers involved were small. A Normal test was used to compare age at vaccination between those with and without inflammatory bowel disease. The study was approved by the ethical practices subcommittee of the Royal Free Hampstead NHS Trust.

Results

Replies to questions about gastrointestinal disease were obtained from 3545 (89%) of 3967 members of the MRC measles vaccine trial cohort who had received the live vaccine. 50·5% of those sent questionnaires were men. 14 reported Crohn's disease, 14 ulcerative colitis, 2 coeliac disease, and 44 peptic ulcer disease. 26 of 28 (93%) reporting inflammatory bowel disease gave permission for their doctor to be approached for clinical details and replies were obtained from the doctors of 24 (86%). In 19 cases the diagnosis was confirmed (12 with Crohn's disease and 7 with ulcerative colitis), in 2 cases records were unavailable, in 3 cases the diagnosis of ulcerative colitis was refuted or uncertain.

Completed questionnaires were obtained from 11 407 (85%) of 13 444 NCDS cohort members traced in 1991. 89% had reported measles by the age of 11 years. 16 reported Crohn's disease, 15 ulcerative colitis, and 4 coeliac disease. 26 of 31 (84%) reporting inflammatory bowel disease gave permission for their doctor to be approached. Replies were obtained from doctors of 25 (81%) cohort members. In 23 cases the diagnosis of inflammatory bowel disease was confirmed (12 cases of Crohn's disease and 11 of ulcerative colitis), and in 2 cases the diagnosis was refuted (1 case of Crohn's disease) or was uncertain (1 case of ulcerative colitis).

Crohn's disease and ulcerative colitis were reported significantly more often among the measles vaccine cohort (RR 3·01, p=0·004; 2·53, p=0·03, respectively) (table 1). When only confirmed cases were analysed, RR for Crohn's disease was 2·95 (p=0·01) and for ulcerative colitis was 2·05 (p=0·21). There was no significant difference in the rates of coeliac disease between the vaccine and NCDS cohorts (p=0·63). Since the number who reported inflammatory bowel disease but had the diagnosis refuted by their physician is low (5 of 46 cases), we have assumed for statistical analysis that those who report inflammatory bowel disease, and in whom we were unable to refute the diagnosis, have the disease. The mean ages at vaccination in those who developed Crohn's disease (497 [SD 119] days) and ulcerative colitis (469 [119] days) were not significantly different from the age for all those vaccinated (526 [116] days). There was no significant difference between vaccine and NCDS cohorts in the age of presentation with inflammatory bowel disease.

Answers were obtained from 2541 partners of those in the vaccine cohort. Crohn's disease was reported by 5 (RR 2·01, p=0·27), ulcerative colitis by 5 (1·73, p=0·55), coeliac disease by 4 (0·36, p=0·24), and peptic ulcer by 49 (0·64, p=0·04) (table 2).

Discussion

This study shows an association between measles vaccination and inflammatory bowel disease. It does not show a causal relation. Considerable efforts were made in both NCDS and the MRC measles vaccine trial to keep to a minimum the number of cohort members lost to follow-up. In the NCDS, 76% of those initially enrolled in the study were traced for the fifth survey (NCDS-5). Of those who received live measles vaccine in the MRC measles vaccine trial, 41% were still involved in follow-up. Response rates to enquiries were excellent in both cohorts (over 85%). It is, therefore, unlikely that the difference observed in rates of inflammatory bowel disease in the two cohorts is due to the difference in rates of follow-up.

The NCDS cohort was born in one week whereas the children in the MRC group were born throughout the

year. This difference would be important only if there is a seasonal variation of dates of birth in those with inflammatory bowel disease, which there was not in a study of 1506 patients with Crohn's disease and 798 patients with ulcerative colitis.[4] The overall prevalence of inflammatory bowel disease of 2·54/1000 in the NCDS cohort is higher than found in most previous studies; prevalence rates for Crohn's disease of 0·12–0·95/1000 and for ulcerative colitis of 0·37–2·10/1000[9–10] have been described. Therefore the increased risk of inflammatory bowel disease in the vaccine cohort is not due to an abnormally low prevalence in the NCDS cohort.

Subjects in the vaccine cohort were younger, with a mean age of 31 compared with 33 in the control group. Since the prevalence of inflammatory bowel disease increases with age, more cohort members in NCDS would be expected to have developed Crohn's disease or ulcerative colitis. The sex distribution in the vaccine recipients was the same as the general population. Could selection bias in the vaccine cohort explain the observed difference in the prevalence of inflammatory bowel disease? Children were allocated to receive live vaccine if they were born from the 11th to the 20th day of the month and were excluded from the trial if they had a history of fits, eczema, sensitivity to eggs, treatment with chemotherapeutic agents or steroids, other current immunisations, or illness at the time they were called for vaccination;[5] none of these factors in infants has been shown to be risk factors for inflammatory bowel disease. In the NCDS cohort there was no social class effect, in adulthood, in the distribution of patients with inflammatory bowel disease (unpublished data), and so social class seems not to be a potential confounder. There are no social class data for the measles vaccine trial cohort. There are no other obvious confounding factors, although children in the MRC trial, whose parents volunteered to take part in a research project, might differ from the general population with respect to unknown factors associated with inflammatory bowel disease. Of the children involved in the MRC measles vaccine trial, only those who had received live vaccine were studied since this is the routine vaccine regimen in the UK. The end-point of the annual follow-up is the development of measles; by 1994 13% of the cohort had been withdrawn from the study because they had had measles.[6]

There may have been biases in case ascertainment. The measles cohort were asked about specific diseases whereas the NCDS cohort were asked about any long-standing illness and details of hospital visits. That no significant difference was observed in the rates of coeliac disease suggests that these differences in case ascertainment were not materially important, although the numbers are small. Inflammatory bowel disease and coeliac disease are diagnoses that are only made after the patient has attended hospital and had investigations, so patients are unlikely to under-report these illnesses when completing health questionnaires.

For the partners of the vaccine cohort there was undefined matching, an age range of subjects, and no documentation of measles infection or vaccination (some of the partners will have been vaccinated). However, a similar pattern of disease was seen—increased prevalence of inflammatory bowel disease but not coeliac disease or peptic ulceration in the vaccine cohort. Reports of inflammatory bowel disease in partners were not validated because we wished to trouble them as little as possible.

Rates of inflammatory bowel disease have been increasing in the UK over the past 40 years,[10] certainly before measles vaccination was introduced in 1968. Since 1968, the rate of Crohn's disease, but not of ulcerative colitis, in children has risen rapidly with a three-fold increase in cases in Scotland over a 10-year period.[11] There is evidence from subacute sclerosing panencephalitis associated with measles infection[12] and from other potentially persistent viral infections[13] that age of exposure may be of importance in determining viral persistence. Ekbom et al[3] have shown that exposure to measles at the time of birth appears to be risk factor for Crohn's disease but not for ulcerative colitis. The mean age at vaccination was 15 months whereas the peak incidence rate for measles is at 4–5 years.[14] Whether the vaccine strain of measles virus is more likely than wild strains to persist is not known.

People with inflammatory bowel disease are more likely than controls to have had certain childhood illnesses[15,16] which may reflect altered immunity. Measles virus infection can cause prolonged disruption of immune function, particularly in helper T-cell response.[17] Measles vaccine has been associated with other unexpected adverse findings in long-term studies. In developing countries, the use of high-titre vaccine at 4–6 months of age was associated with an unexpectedly high mortality in girls by the age of 2 years from infectious childhood illnesses.[18]

Our findings of significant differences in the rates of Crohn's disease and ulcerative colitis, but not coeliac disease, between people receiving active immunisation with measles vaccine and those having measles provides further evidence that measles virus has a role in the aetiology of inflammatory bowel disease.

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Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph?

Paul Wilkinson, David M Hansell, Judy Janssens, Michael Rubens, Robin M Rudd, Anthony Newman Taylor, Corbett McDonald

Summary

This study was designed to test the hypothesis that the risk of lung cancer from asbestos exposure is confined to persons with radiographic evidence of pulmonary fibrosis.

Occupational and smoking histories were obtained from 271 patients with a confirmed diagnosis of primary lung cancer and 678 referents (279 with other respiratory disease and 399 with cardiac disease). Histories were reviewed blind to assess the timing, duration, and probability of exposure to asbestos. To allow for a lag between asbestos exposure and the development of lung cancer, subjects were classified by the time they had spent in an occupation entailing definite or probable exposure more than 15 years before diagnosis. The presence and extent of fibrosis was assessed blindly from chest radiographs by three readers and scored for small opacities with the ILO 1989 International Classification of Radiographs of the Pneumoconioses. 93 (34·3%) cases had worked in an occupation with definite or probable asbestos exposure compared with 176 (25·8%) referents (crude odds ratio for lung cancer 1·49, 95% CI 1·09–2·04). After adjustment for age, sex, smoking history, and area of referral, the odds ratio (95% CI) was 2·03 (1·00–4·13) in the subgroup of 211 with a median ILO score for small parenchymal opacities of 1/0 or more, and 1·56 (1·02–2·39) in the 738 with a score of 0/1 or less (ie, those without radiological evidence of pulmonary fibrosis).

These results suggest that asbestos is associated with lung cancer even in the absence of radiologically apparent pulmonary fibrosis.

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London Chest Hospital, London (P Wilkinson MRCP, J Janssens SEN, M Rubens FRCR, R M Rudd FRCP); **and Royal Brompton Hospital and National Heart and Lung Institute, London SW3 6LY, UK** (D M Hansell FRCR, Prof A Newman Taylor FRCP, Prof C McDonald FRCP)

Correspondence to: Prof Corbett McDonald

Introduction

Asbestos exposure increases the risk of lung cancer, but it is unclear whether such exposure does so in the absence of radiological evidence of pulmonary fibrosis. In the UK and several other countries, compensation for asbestos-related disease recognises lung cancer as asbestos related only if there is radiological or pathological evidence of lung fibrosis or diffuse pleural thickening. In other countries, compensation is based on duration of exposure in relevant occupations.

Cohort studies show that the excess of lung cancer in asbestos-exposed workers is at least as great as the number of cases of mesothelioma.[1] De Vos Irvine and colleagues estimated that 5·7% of lung cancers in Glasgow and the west of Scotland were asbestos related.[2] This is in line with estimates from the USA.[3] There are around 35 000 new lung cancers each year in England and Wales,[4] of which 2000 or so may be asbestos related. Data from the SWORD surveillance scheme[5] suggest that comparatively few such cases are recognised, possibly because once the patient is identified as a tobacco smoker, the physician does not inquire into asbestos exposure. But another factor may be the prevailing view that pulmonary fibrosis is a necessary prerequisite.

Small opacities on the chest radiograph are a useful, if imperfect, marker of pulmonary fibrosis. They can be objectively assessed with the ILO 1989 International Classification of Radiographs of Pneumoconioses.[6] With this system, a score of 1/0 or more for small, characteristically irregular opacities is usually considered evidence of fibrosis, whereas a score of 0/1 or less indicates no radiological evidence of fibrosis. We used this score in a hospital-based case-referent study to examine whether pulmonary fibrosis is a prerequisite of asbestos-related lung cancer.

Patients and methods

Subjects were selected from routine adult admissions to the London Chest Hospital between September, 1992, and March, 1993. Cases were consecutive patients with a histologically or cytologically confirmed diagnosis of primary bronchial carcinoma; referents were consecutive patients with respiratory diseases other than lung cancer and a random sample (averaging one in three) of admissions with cardiac disease (table 1). A patient was excluded if he or she had first been admitted with the