A case-control study of measles vaccination and inflammatory bowel disease

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Summary

Background The cause of inflammatory bowel disease (IBD) remains to be established. Evidence has linked measles infection in early childhood with the subsequent risk of developing IBD, particularly Crohn’s disease. A cohort study raised the possibility that immunisation with live attenuated measles vaccine, which induces active immunity to measles infection, might also predispose to the later development of IBD, provoking concerns about the safety of the vaccine.

Method We report a case-control study of 140 patients with IBD (including 83 with Crohn’s disease) born in or after 1968, and 280 controls matched for age, sex and general practitioner (GP) area, designed to assess the influence of measles vaccination on later development of IBD. Documentary evidence of childhood vaccination history was sought from GP and community health records.

Findings Crude measles vaccination rates were 56-4% in patients with IBD and 57.1% among controls. Matched odds ratios for measles vaccination were 1.08 (95% CI 0.62–1.88) in patients with Crohn’s disease, 0.84 (0.44–1.58) in patients with ulcerative colitis, and 0.97 (0.64–1.47) in all patients with IBD.

Interpretation These findings provide no support for the hypothesis that measles vaccination in childhood predisposes to the later development of either IBD overall or Crohn’s disease in particular.


Introduction

The possibility that the inflammatory bowel diseases (IBDs)—ulcerative colitis and Crohn’s disease—are caused by a transmissible agent such as a virus is an attractive hypothesis.1 Wakefield and colleagues have suggested that Crohn’s disease might be the late result of measles virus infection at a critical time during early childhood. This “measles hypothesis” is based on a series of pathological and epidemiological studies.2

Wild-type measles infection is associated with substantial morbidity and mortality. In the developed world, complications occur in about one in 15 infections, and most deaths result from the development of pneumonia, acute encephalitis, or the rare but relentlessly progressive subacute sclerosing panencephalitis.3,4 Live attenuated measles vaccine was introduced in the UK in 1968, and as a result of the vaccination campaign the incidence of measles infection and complications has fallen strikingly.5,6

The measles hypothesis has been embellished with evidence from a cohort study suggesting an increased risk of IBD in individuals given live attenuated measles vaccine in early childhood.7 This report has led to concern about the safety of measles vaccination and resulted in some parents declining an effective vaccine. Counselling has been particularly difficult because the evidence on which to base reassurance on this issue is very limited.8

The present investigation was devised to assess the risk of IBD associated with vaccination against measles in early childhood. A case-control design was used because of the relative rarity of the disease and the frequency of vaccine exposure in the population.9,10 The study focuses on the period between 1968 and 1991, during which measles vaccination was routinely offered and immunisation status documented in the UK by general practitioners (GPs) and community health services within the National Health Service. National uptake rates for measles vaccination ranged from 34% in 1968 to 90% in 1991.11

Method

This case-control study was done in East Dorset, UK, with the approval of the local research ethics committee. 164 patients with a definite diagnosis of IBD on the basis of standard clinical
Table 1: Summary of patient details

<table>
<thead>
<tr>
<th>IBD group</th>
<th>Crone's disease</th>
<th>Ulcerative colitis</th>
<th>IBD overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>83</td>
<td>57</td>
<td>140</td>
</tr>
<tr>
<td>Year of birth</td>
<td>16-22</td>
<td>16-24</td>
<td>19-24</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>19 (15-22)</td>
<td>20 (16-24)</td>
<td>19 (15-24)</td>
</tr>
</tbody>
</table>

Table 2: Crude vaccination rates and age (median and interquartile range) at first vaccination (under 5 years)

<table>
<thead>
<tr>
<th>IBD group</th>
<th>Pertussis</th>
<th>Diphtheria/tetanus</th>
<th>Measles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (%)</td>
<td>70.7</td>
<td>92.9</td>
<td>56.4</td>
</tr>
<tr>
<td>Age (months)</td>
<td>5 (4-7)</td>
<td>6 (4-8)</td>
<td>16 (14-20)</td>
</tr>
<tr>
<td>Controls</td>
<td>70.7</td>
<td>93.2</td>
<td>57.1</td>
</tr>
<tr>
<td>Rate (%)</td>
<td>6 (4-8)</td>
<td>9 (4-8)</td>
<td>17 (15-21)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>6 (4-8)</td>
<td>9 (4-8)</td>
<td>17 (15-21)</td>
</tr>
</tbody>
</table>

Table 3: Odds ratios (95% CI) for IBD in vaccine recipients

<table>
<thead>
<tr>
<th>IBD group</th>
<th>Crone's disease</th>
<th>Ulcerative colitis</th>
<th>IBD overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>1.08 (0.62-1.88)</td>
<td>0.84 (0.44-1.58)</td>
<td>0.97 (0.64-1.47)</td>
</tr>
<tr>
<td>Pertussis</td>
<td>-</td>
<td>-</td>
<td>1.00 (0.62-1.62)</td>
</tr>
<tr>
<td>Diphtheria/tetanus</td>
<td>-</td>
<td>-</td>
<td>0.84 (0.39-2.26)</td>
</tr>
</tbody>
</table>

Discussion

The concept that IBD might be caused by a chronic viral infection is attractive, and fits with the observation that some viruses may produce a chronic and sometimes relapsing tissue-specific disease. The theory could also account for the apparent link between markers of childhood hygiene and the subsequent risk of developing IBD, in particular Crohn’s disease.9 However, the evidence implicating wild-type measles infection as the cause of IBD is very controversial.7,21

A cohort study that suggested that live attenuated measles vaccine given in early childhood increases the risk of later developing IBD takes the measles hypothesis a step further. Odds ratios derived for the risk of ulcerative colitis and Crohn’s disease in recipients of live attenuated measles vaccine were similar to 2.53 and 3.01, respectively. Despite concerns regarding design and interpretation, this study provoked considerable media interest. This media attention has tended to undermine public confidence about the safety of the highly effective measles vaccine, particularly among parents with IBD who have infants of vaccination age. There was sufficient concern to provoke a circular to all GPs from the Chief Medical Officer stressing that the study was unsubstantiated. The history of pertussis vaccination in the UK illustrates the major influence that public uncertainty about vaccine safety may exert on vaccination uptake rate.4

There are few published data on the relation between vaccination history and the development of IBD. One large international case-control study reported no association between measles vaccination and IBD risk, although detailed figures were not provided, and it is likely that many of the study participants were from the pre-live-vaccine era. The need for a definitive contemporary case-control study has been stressed.1 Contrary to the suggestion that immunisation records in the UK are inadequate, we found that the records in Dorset going back to 1968 were sufficiently comprehensive to support a large case-control study.

During the period 1968–1991, 11 measles vaccines were available all containing attenuated virus closely related or identical to the Schwartz strain used in the original Medical Research Council trial. The particular vaccine used was only documented for a minority of the participants in our study; but from the limited information available we deduce that most of our vaccinated participants were given Schwartz strain virus.

The validity of our study clearly hinges on the accuracy of the data concerning childhood vaccinations. It seems inherently reasonable to assume that written evidence specifying that a vaccine has or has not been given is likely to be accurate. A more questionable assumption is that the absence of documentation that a vaccine was given, when...
other contemporary health records are documented, is confirmation that no vaccination actually occurred. However, there is no reason to believe that this assumption would introduce bias, since case and control data are likely to be affected similarly. We have reason to believe that the reliability of our data is within acceptable limits. Firstly, there was the 87% concordance between the official vaccination records and personal records in a small subgroup of ten patients who had kept vaccination documents since childhood. Secondly, the overall measles vaccination rate in this study—56.4% in the IBD group and 57.1% in the control group—is close to the figure of 54.2% predicted from national vaccination data11 given the age distribution of the study population.

The definitive study to determine whether live measles vaccination in early childhood causes IBD would be a large, randomised, placebo-controlled trial. This is not a practical option, however, since deliberately leaving large, randomised, placebo-controlled trials. This is not a plausible confounding factor that could account for our negative result being a spurious one.

In conclusion, our results show no evidence of a link between live attenuated measles vaccination in early childhood and the subsequent risk of developing either Crohn’s disease or ulcerative colitis. Considering specifically Crohn’s disease, for which the evidence implicating measles is perhaps stronger, our study has a power of over 99% for detecting an odds ratio of 3 at the p less than 0.05 level,12 and so is incompatible with the results of the cohort study.7 The findings of our study do not directly disprove the possibility that Crohn’s disease is a late consequence of wild-type measles infection in predisposed individuals. If this were the case, however, a major fall in the incidence of Crohn’s disease in young people over the last 20 years might have been expected following the striking reduction in the incidence of wild-type infection resulting from the vaccination programme.26

In reality, the incidence of Crohn’s disease has risen substantially over this time.22-28

Acknowledgments
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References
8 Calman KC. Measles virus and inflammatory bowel disease. Letter to GPs from the Chief Medical Officer, April 28, 1995.
11 Korner Data (vaccination and immunisation). Department of Health (Statistics Division), England.

Contributions
All authors were responsible for protocol design and writing the paper. Mark Fenney and Paul Winwood were responsible for data collection. Andrew Clegg and Jonathan Snook were responsible for statistical analysis.