CURRENT OPINION

Drug Safety 2001; 24 (13): 939-946
0114-5916/01/0013-0939/$22.00/0

Measles Vaccination and Inflammatory Bowel Disease

Controversy Laid to Rest?

Robert L. Davis[1,2] and *Kari Bohlke*[2]

1 Departments of Paediatrics & Epidemiology, University of Washington Schools of Medicine and Public Health, Seattle, Washington, USA
2 Center for Health Studies, Group Health Cooperative, Seattle, Washington, USA

Abstract

The increasing incidence of Crohn's disease has lead to speculation about changes in exposures to environmental or infectious agents. Considerable attention has focused on the role of measles infection and/or vaccination in the pathogenesis of Crohn's disease and ulcerative colitis.

Current evidence regarding the association between measles vaccination and inflammatory bowel disease (IBD) comprises analytic epidemiological studies, a case-series report and ecological studies. The first of these, a 1995 cohort study, found an association between measles vaccination and Crohn's disease and ulcerative colitis, but was widely questioned on methodological grounds. This was followed by a 1997 case-control study showing no association between measles vaccination and IBD. In 1998, public concern was rekindled by a report of 12 children with nonspecific colitis, ileal-lymphoid-nodular hyperplasia, and developmental disorders largely attributed to measles-mumps-rubella vaccine, but the nature of the report limited its scientific conclusions. Two additional studies, one case-control and one cohort, then followed and neither found an association with measles vaccination. Of the several ecological studies of measles vaccine coverage or measles schedule changes, none found an association with rates of IBD.

The role of measles infection in IBD has been examined more extensively with studies of *in utero* measles exposure, measles infection early in life, and laboratory based investigations. An initial report of high rates of Crohn's disease among pregnancies affected by measles infection was followed by negative studies. Numerous case-control and ecological studies of children with measles infections early in life have also had discordant findings. Of three recent cohort studies, two showed no relationship between infection with early measles exposure and risk for IBD, while one found an approximate 3-fold elevation in risk. Laboratory investigations into persistent measles infection and IBD have been contentious. While some investigators have claimed to find persistent measles infection among patients with IBD, others, using highly sensitive polymerase chain reaction techniques, have not been able to replicate the findings. Recent controversy has centred on whether there is any evidence for molecular mimicry in the pathogenesis of IBD.

In summary, available evidence does not support an association between measles-containing vaccines and risk of IBD, nor between measles infection and IBD.

While further research is necessary into the causal factors underlying Crohn's disease and ulcerative colitis, continued public education efforts are needed to reassure the public about vaccine safety and to prevent declines in vaccine coverage.

There has been considerable recent interest in the potential role of measles infection and/or measles vaccination in the pathogenesis of Crohn's disease and ulcerative colitis. Part of this interest stems from the findings, by a number of reports, that the incidence of Crohn's disease has markedly increased within industrialised countries since the 1940s.[1-5] While this increase suggests that some pattern of exposure has changed, including perhaps the pattern of exposure to measles virus, the cause of inflammatory bowel disease (IBD) remains unknown in spite of active research.

Studies from Sweden in the early 1990s suggested that infectious agents, or measles infection specifically – either *in utero* or in early life – might increase the risk for IBD.[6,7] The possibility that early life measles infection might be linked to IBD led researchers to question whether IBD might be the result of a chronic infection, and similar in this regard to subacute sclerosing panencephalitis, a degenerative CNS disorder and a sequelae of chronic measles infection. Molecular evidence supporting this theory was presented, and then, subsequently, other studies suggested that measles vaccination itself might also increase the risk for IBD.[8-10] These theories generated considerable media attention and public discussion, with one result being that vaccination coverage for measles-containing vaccine declined in many parts of the UK.[11-13]

We recently published data showing that neither Crohn's disease nor ulcerative colitis is related to vaccination with the monovalent measles vaccine or with the combination measles-mumps-rubella (MMR) vaccine.[14] This study was performed as part of the Vaccine Safety Datalink (VSD) Project – a large collaborative project between four health maintenance organisations (HMOs) and the Centers for Disease Control and Prevention (CDC) specifically created and designed to address questions of vaccine safety. We looked at the vaccine histories of 142 persons with IBD born between 1958 and 1989 and compared them with up to five controls, matched by gender, health maintenance organisations and birth year. Even with such a large project, however, our ability to exclude a very small increase in risk due to vaccination was limited. At the same time, other researchers have continued to publish findings potentially implicating vaccines in the pathogenesis of Crohn's disease and IBD.[15]

Because these theories are highly controversial, the safety of routine childhood vaccination against measles has been increasingly scrutinised by the lay public, scientists, lawyers, and legislators. The purpose of our paper is to summarise for the practising physician available data about the alleged association between measles containing vaccines and IBD. In addition, we believed it would be useful to review past studies that have looked at measles infection itself – as opposed to vaccination – and its possible relationship to Crohn's disease or ulcerative colitis.

1. Vaccination and Risk of Inflammatory Bowel Disease (IBD)

An association between measles vaccination and IBD was first proposed in 1995 in a cohort study by Thompson et al.[8] This study assessed a cohort of vaccinated children enrolled in a 1964 UK Medical Research Council trial of the Schwarz strain of measles vaccine, and followed until 1994. The incidence of IBD in this cohort was compared with that in a group of presumably unvaccinated children enrolled in the National Child Development Study (NCDS), a longitudinal study of persons born in Great Britain during 1 week in 1958. Thompson et al.[8] found that children in the vaccinated cohort had a 3-fold increased risk of Crohn's disease and a 2.5-fold increased risk of ulcerative colitis compared with the children in the NCDS.

A number of important methodological con-

cerns were raised about this study.[16,17] There was differential loss-to-follow-up between the two cohorts, differential ascertainment of outcome by exposure category (vaccinated individuals were asked specifically about Crohn's disease and ulcerative colitis, while unvaccinated individuals were asked about 'any longstanding illness, disability, or infirmity'), and vaccinated and unvaccinated individuals were selected from different populations. All of these factors led to questions about the validity of the study findings or whether there might be other reasons why the study findings were positive.

Given the potential public health impact of the Thompson et al.[8] findings, several additional studies of measles vaccine were initiated. In 1997, Feeney et al.,[18] in a study from East Dorset, UK, compared 140 individuals with IBD born in or after 1968 with 280 controls matched for age, gender, and general practitioner area. There was no association between measles vaccination and Crohn's disease [odds ratio (OR) = 1.08, 95% confidence interval (CI) 0.62 to 1.88], ulcerative colitis (OR = 0.84, 95% CI 0.44 to 1.58), or all IBD combined (OR = 0.97, 95% CI 0.64 to 1.47).

Following this report, public concern was rekindled in 1998 with a report by Wakefield et al.[9] of 12 children with nonspecific colitis, ileal-lymphoid-nodular hyperplasia, and developmental disorders.[9] In 8 of these 12 children, onset of behavioural symptoms was attributed by the parent or provider to MMR vaccination. Chen and DeStefano[19] pointed out a number of potential biases and difficulties in interpreting these findings, including selection bias (patients were all referred to a centre known for its interest in MMR and IBD), recall bias, and lack of a clear case definition.[19] Furthermore, as there was no comparison group (as might be found in either cohort or case/control studies), the rate of disease following vaccination could not be calculated or compared with an expected value.[20-22]

In response, the CDC-funded VSD initiated a case-control study to assess measles vaccine in relation to risk of IBD. Cases were identified from the computerised medical databases of four large HMOs.[14] Following chart review to confirm the diagnosis, 142 individuals with IBD, born between 1958 and 1989, were compared with 432 control individuals matched by birth year, gender, and HMO. There was no evidence for an increased risk for ulcerative colitis or Crohn's disease related to either the monovalent measles vaccine or the combination MMR vaccine, nor was there evidence that timing of vaccination (with either the monovalent or combination measles vaccine) influenced the risk of IBD. In addition, there was no evidence that vaccination 'triggered' the acute onset of symptoms that were eventually diagnosed as IBD.

A lack of association between measles vaccination and IBD was also seen in a 1970 British Cohort Study.[23] Subjects consisted of all individuals born in Great Britain during a single week during 1970. Vaccination history was based on a survey conducted when the children were 5 years of age, and IBD history was collected when they were 25 to 26 years of age. Complete data regarding vaccination history and potential confounding variables were available for 20 individuals with Crohn's disease and 15 individuals with ulcerative colitis. There was no significant association between monovalent measles vaccination and either Crohn's disease (OR 0.67, 95% CI 0.3 to 1.6) or ulcerative colitis (OR 0.57, 95% CI 0.2 to 1.6). There was a significant trend in risk of Crohn's disease with increasing age at vaccination, but this was based on only 3 children vaccinated at age 2 years or older.

Several ecological studies have also looked at how IBD rates over time coincided with changes in the measles vaccination schedule or with changes in coverage. Herman-Taylor et al.[24] plotted trends in Crohn's disease reports from 3 centres in the UK (South Wales, Derby, and northeast Scotland) during 1940 to 1990. While the incidence of Crohn's disease showed an increase over time since the 1940s, this trend began some 20 years prior to introduction of the measles vaccine, suggesting reasons other than vaccination for the increase.

Miller and Waight[25] looked at hospital admissions in England from January 1992 to March 1996, to determine if a 1994 national measles-rubella vaccine campaign targeted at school-aged

children led to an increase in hospital admissions for Crohn's disease. In the 16 months following the campaign, there was no increase apparent among children 5 to 16 years of age. Finally, Pebody et al.[26] used Finnish data to compare the rate of Crohn's disease during 1986 to 1992 with the proportion of the population receiving measles vaccine. While the proportion of the population receiving at least one dose of measles vaccine increased over time, the rate of Crohn's disease remained stable among children, adolescents, and adults aged 0 to 14 and 15 to 24 years.

Taken as a whole, then, the available studies do not support an association between receipt of measles-containing vaccines and IBD. Of the two cohort studies conducted to date, one reported a positive association but was widely questioned on methodological grounds, and one reported no association. Neither of two case-control studies found an association. The 1998 report by Wakefield[9] received a great deal of publicity, but few inferences can be derived from this study due to the methodological limitations discussed earlier. Only one analytic epidemiological study has addressed exposure to MMR, and no association was found in this study.[14]

2. Measles Infection and IBD

In developing countries, mortality rates associated with measles infection can range from 5 to 15%, with pneumonia being a frequent cause of death. Gastrointestinal manifestations such as stomatitis and diarrhoea result from mucosal inflammation, and can be particularly deadly among malnourished children.[27]

The question of whether measles infection increases the risk of either Crohn's disease or ulcerative colitis has been looked at more extensively than that of vaccination and IBD, and has concentrated mainly on three avenues of evidence. These include: (i) studies of IBD and *in utero* exposure to measles; (ii) studies of IBD and measles infection early in life; and (iii) laboratory based investigations looking for evidence of past or persistent measles infection among people with IBD.

2.1 *In utero* Exposure to Measles

The concept that *in utero* exposure to measles virus might increase the risk of IBD was addressed by Ekbom[28] in a Swedish study of 25 000 deliveries between 1940 and 1949. Four of these pregnancies had maternal measles infection, and three of the offspring developed Crohn's disease – a rate far higher than expected. However, this study was stimulated (at least in part) by the discovery (in a prior study) of two of these cases of Crohn's disease among the measles-exposed pregnancies.[6] Nevertheless, the findings in the subsequent study of an additional case of Crohn's disease in the remaining two pregnancies was striking. A subsequent study in Denmark identified 33 women with measles during pregnancy from 1915 to 1966.[29] Of 26 offspring, 25 were available for follow up (one died in infancy); none developed Crohn's disease. Another study, using data from the UK Office of National Statistics study MR10, compared over 3000 individuals exposed *in utero* to viral diseases (including measles) to a matched set of unexposed individuals with follow up through ages 16 to 53 years.[30] Among the non-exposed individuals there was one case of ulcerative colitis and one of Crohn's disease, while among those exposed to measles *in utero* there were no cases of IBD. In both these studies, the rate of IBD was appreciably less than would be expected had the original findings by Ekbom been replicated.

2.2 Perinatal Exposure or Infection

Some of the earliest evidence that early life measles infection might increase the risk for ulcerative colitis or Crohn's disease again came from Sweden.[6] Ekbom looked at the birth records of 257 individuals with IBD from 1924 through to 1957, and compared them with 514 control individuals, matched by birth date, gender and maternal age or parity. While a history of post-natal infections increased the risk of IBD over 5-fold (OR 5.5; 95% CI 2.6, 11.8), the study did not specifically address whether it was measles infection that accounted for the increased risk. A US study of IBD in North

Carolina compared 322 individuals with IBD with neighbourhood controls or acquaintances, and found that childhood infections (not just measles infection) increased the risk of Crohn's disease but not of ulcerative colitis.[31] For measles infection specifically, there was an increased risk of Crohn's disease and ulcerative colitis, but in neither case was the risk statistically significant (OR 1.32; 95% CI 0.77 to 2.26 and 2.14; 95% CI 0.97 to 4.75, respectively).

Ekbom then looked at Crohn's disease among persons born during or shortly following a measles epidemic.[7] Individuals in whom IBD occurred before age 30 were identified from children born in four Swedish counties from 1945 through 1954. During this time span, in these counties, there were five measles epidemics, and the observed number of individuals with Crohn's disease was compared with the expected number for children born during the 3 months after the measles epidemic peaks. Among children born after the epidemic peaks, the rate of Crohn's disease was elevated [standardised incidence rate (SIR) of 1.46; 95% CI 1.11 to 1.89], while that of ulcerative colitis was not (SIR 0.94; 95% CI 0.63 to 1.36). Since measles exposure might have occurred in the latter trimester of pregnancy or in the first few months of life, this study could not differentiate between *in utero* and early infancy exposure to measles.

A study by Haslam et al.[32] of births in the UK that analysed patients with Crohn's disease diagnosed between 1972 and 1989 came to different conclusions. While measles incidence fluctuated biennially, there was no increased risk for Crohn's among children born in years with high measles incidence rates compared with children born in other years.

Finally, three recently published studies – one from the British Cohort Study in the UK,[15] one from the Mayo Clinic in the US,[33] and one that combined cohorts from the Medical Research Council National Survey of Health and Development of 1946 and the 1958 NCDS[34] – have looked at the role of early life measles infection (as opposed to perinatal infection) and the risk for IBD. In the 1970 British Cohort Study,[15] measles infection at <2, 2 to 5 and 6 to 10 years of age was not associated with an increased risk for Crohn's disease. Out of 20 total individuals with Crohn's disease, none were infected with measles before age 2; five were infected between 2 and 5 years of age (OR 1.06; 95% CI 0.37 to 3.06) and four were infected between 6 and 10 years of age (OR 1.33; 95% CI 0.42 to 4.19). The risk of ulcerative colitis also was not significantly associated with early life measles infection.

Interestingly, the combination of mumps and measles infection in the same year of life was associated with a statistically significant increase of both Crohn's disease and ulcerative colitis. However, this combination of infection was very rare (three of the individuals with Crohn's disease and four of the individuals with ulcerative colitis had this pattern of exposure). Furthermore, the authors did not state whether this relationship (the combination of measles and mumps infection within a single year period) was an *a priori* hypothesis, or whether it was discovered during the analysis phase of the study. In either situation, however, the role of concomitant viral infection as a risk for IBD deserves further investigation. This study was widely interpreted in the media as suggesting that MMR may also increase risk of IBD, although the authors were quick to reject such an interpretation.[35]

In the Mayo clinic study,[33] 662 patients with measles prior to age 5 during the period 1950 to 1966 were followed for 10 to 48 years. As with the British Cohort Study, the number of individuals observed to have Crohn's disease or ulcerative colitis were compared with the number expected based on age and gender-specific population incidence rates. A total of six individuals with Crohn's disease and six with ulcerative colitis were found (compared with 1.9 and 2.0 expected cases, respectively), giving a standardised incidence rate of 3.1 for Crohn's disease (95% CI 1.1 to 6.8) and 3.0 for ulcerative colitis (95% CI 1.1 to 6.5). No information was presented on the risk of concomitant infection, so the findings from the British Cohort Study could not be replicated here.

In a study that looked at two longitudinal UK birth cohorts, 26 patients with Crohn's disease and 29 patients with ulcerative colitis were identified through a series of surveys repeated over time, along with validation of diagnoses by medical record review.[34] Neither measles nor mumps infection by 7 years of age were associated with an increased risk for Crohn's disease (OR 1.1; 95% CI 0.4 to 3.5 for measles; OR 0.9; 95% CI 0.3 to 2.4 for mumps) or for ulcerative colitis (1.5; 95% CI 0.5 to 5.5 for measles; OR 1.0; 95% 0.4 to 2.4 for mumps).

In summary, the evidence to date is conflicting, and does not consistently support an association between *in utero* exposure to measles virus and subsequent risk for developing IBD. While the original case reports suggested such a risk for persons exposed during pregnancy, follow-up studies failed to replicate these findings. In terms of future risk for IBD among children infected with measles early in life, there have been numerous case-control, cohort, and ecological studies, also with discordant findings.

2.3 Laboratory Evidence of Measles Infection in IBD

Wakefield et al.[10] presented evidence of persistent measles virus infection in patients with Crohn's disease, demonstrating that hybridisation for measles virus RNA and immunohistochemical staining for measles virus nucleocapsid protein was more common in patients with Crohn's disease than in patients without Crohn's disease. Two other studies used immunogold electron microscopy and found antibody labelled measles virus nucleocapsid to be more common in Crohn's disease patients than in patients without Crohn's disease.[36,37] Other laboratory evidence in support of the role of measles virus in IBD was presented by Miyamoto et al.[38] who, using tissue from a patient with Crohn's disease, detected a reaction to a monoclonal antibody derived from measles virus infected cells, and by Kawashima et al.,[39] who detected measles virus RNA in peripheral mononuclear cells in some patients with Crohn's disease and ulcerative colitis.

Other investigators failed to replicate these findings. Using highly sensitive polymerase chain reaction (PCR) techniques, studies by Iizuka et al.[40] and Haga et al.[41] did not detect measles virus genome in intestinal specimens of patients with Crohn's disease or ulcerative colitis, and Afzal et al.[42] and Chadwick et al.[43] also failed to detect measles virus genome in peripheral blood mononuclear cells and intestinal samples of patients with IBD. Most recently Iizuka and colleagues[44,45] demonstrated that the measles related antigen found by the Wakefield group in patients with Crohn's disease was a human protein and was not unique to Crohn's disease. These data, combined with the negative results from the PCR, are incompatible with the hypothesis that persistent measles infection is related to IBD. However, Wakefield and Montgomery[46] noted that the specimens of Iizuka et al.[44,45] excluded the granuloma regions found to be most important in his own studies. They further postulated that the human protein identified by Iizuka et al.[44,45] might represent an inappropriate host immune response and that a form of molecular mimicry may play a fundamental role in the inflammation of IBD. In a recent letter, Iizuka et al.[47] reported no evidence of such an antibody or molecular mimicry in 15 patients with Crohn's disease or in 15 patients with ulcerative colitis.

While clearly the findings to date are conflicting and unresolved, the accumulated evidence is not convincing that persistent measles infection, or an abnormal host immune response to past infection, plays an important role in the aetiology of IBD.

3. Conclusion

Since vaccination against measles was introduced, measles incidence has decreased by over 99% in the US and is no longer an endemic disease.[48] However, measles infection still affects 30 million people annually, and accounts for close to 1 million deaths worldwide.[49] If measles infection early in life carried a significant risk for IBD, then it would logically follow that IBD rates would have fallen as vaccination coverage increased. However, this is not the case; IBD has risen since the 1940s in

industrialised nations. One hypothesis proposed to explain this apparent contradiction is that the improved survival from measles infection preferentially affected children at increased risk for developing IBD. Another suggestion has been that vaccination against measles has imposed a risk for IBD similar to that of wild type infection. As demonstrated above, studies to date have not borne out such a relationship between vaccination and either short-term or long-term risk for IBD.

One of the challenges of using observational epidemiological studies (e.g. case-control and cohort studies) to assess the relationship between measles vaccine and IBD is the high vaccine coverage in many populations. In many developed countries where vaccine coverage is high, unvaccinated individuals may differ from vaccinated individuals in ways that are related to their risk of disease or their propensity to seek medical care for mild or moderate disease. In these situations, such unvaccinated children may not be an appropriate comparison group in studies of vaccine safety. Even here, however, the risk of disease dependent upon age at vaccination may be assessed among vaccinated individuals, as can the question of whether vaccination acutely triggers the onset of symptoms diagnosed as IBD. Large scale vaccine trials might offer a study population with less bias for the study of vaccination and later onset of chronic diseases, but the challenges in collecting high quality follow data are daunting, as demonstrated by the Thompson et al. study.[8] While observational epidemiological studies may be the best available option to address the question of the association between vaccination and IBD, these limitations underscore the importance of considering the entire body of evidence, including laboratory evidence and biological plausibility, when making causal inferences.

Discussion of these issues in the medical literature and the popular press has frequently been heated, due in some part to the fact that an increasing number of vaccinations are being administered to healthy children, in the face of an increasingly sceptical public. In the case of measles vaccination and IBD, the totality of evidence at this point does not support an association. The link between measles infection is similarly obscure, with the most recent evidence suggesting a lack of association.

Vaccine safety concerns are taken seriously by scientists and policy makers, but negative studies typically do not receive the same attention or coverage as positive ones. As Gellin and Schaffner[50] recently pointed out, it is often difficult to persuade the public about the absence of harm, especially when scientific studies follow highly publicised case reports or publicised controversy. While further research is necessary to understand the causal factors that underlie IBD, it is important that efforts also are made to educate the public and to prevent unnecessary declines in vaccine coverage and the resultant increases in vaccine preventable disease.

Acknowledgements

This work was supported in part by Contract 200-95-0957 from the Centers for Disease Control and Prevention's Comprehensive Linked Data Collection of Medical Events and Immunization.

References

1. Gollop JH, Phillips SF, Melton LJ, et al. Epidemiologic aspects of Crohn's disease: a population based study in Olmstead County, Minnesota, 1943-1982. Gut 1988; 29: 49-56
2. Barton, JR, Gillon S, Ferguson A. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983: marginal fall in ulcerative colitis, three-fold rise in Crohn's disease. Gut 1989; 20: 618-22
3. Calkins BM, Whittaker DJ, Rider AA, et al. Trends in incidence rates of ulcerative colitis and Crohn's disease. Dig Dis Sci 1984; 29: 10: 913-20
4. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there any difference between north and south? Results of the European Study on Inflammatory Bowel Disease. Gut 1996; 39: 690-7
5. Loftus Jr EV, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted County , Minnesota, 1940-1993: incidence, prevalence, and survival. Gastroenterology 1998; 114: 1161-8
6. Ekbom A, Adami HO, Helmick CG, et al. Perinatal risk factors for inflammatory bowel disease: a case-control study. Am J Epidemiol 1990; 132: 1111-10
7. Ekbom A, Wakefield AJ, Zack M, et al. Perinatal measles infection and subsequent Crohn's disease. Lancet 1994; 344: 508-10
8. Thompson NP, Montgomery SM, Pounder RE, et al. Is measles vaccination a risk factor for inflammatory bowel disease? Lancet 1995; 345: 1071-74
9. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998; 351: 637-41

10. 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
11. MMR vaccine coverage falls after adverse publicity. Commun Dis Rep CDR Wkly 1998; 8: 43-44
12. Begg N, Ramsey M, White J, et al. Media dents confidence in MMT vaccine. BMJ 1998; 316: 561
13. Thomas D Rh, Salmon RL, King J. Rates of first measles-mumps-rubella immunization in Wales (UK) [letter]. Lancet 1998; 351: 1927
14. Davis RL, Kramarz P, Bohlke K, et al. MMR and other measles-containing vaccines do not increase risk for inflammatory bowel disease: a case-control study from the Vaccine Safety Datalink Project. Arch Pediatr Adolesc Med 2001; 155: 354-9
15. Montgomery SM, Morris DL, Pounder RE, et al. Paramyxovirus infections in childhood and subsequent inflammatory bowel disease. Gastroenterology 1999; 116: 796-803
16. Patriarca PA, Beeler JA. Measles vaccination and inflammatory bowel disease. Lancet 1995; 345: 1062-3
17. Farrington P, Miller E. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. Lancet 1995; 345: 1362
18. Feeney M, Ciegg A, Winwood P, et al. A case-control study of measles vaccination and inflammatory bowel disease. The East Dorset Gastroenterology Group. Lancet 1997; 350: 764-6
19. Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? Lancet 1998; 351: 611-2
20. Lee JW, Melgaard B, Clements CJ, et al. Autism, inflammatory bowel disease, and MMR vaccine [letter]. Lancet 1998; 351: 905
21. Payne C, Mason B. Autism, inflammatory bowel disease, and MMR vaccine [letter]. Lancet 1998; 351: 907
22. Lindley KJ, Milla PJ. Autism, inflammatory bowel disease, and MMR vaccine [letter]. Lancet 1998; 351: 907
23. Morris DL, Montgomery SM, Thompson NP, et al. Measles vaccination and inflammatory bowel disease: a national British Cohort Study. Am J Gastroenterol 2000; 95: 3507-12
24. Hermon-Taylor J, Ford J, Sumar N, et al. Measles virus and Crohn's disease. Lancet 1995; 345: 922-3
25. Miller E, Waight P. Measles, measles vaccination, and Crohn's disease: second immunisation has not affected incidence in England [letter]. BMJ 1998; 316: 1745
26. Pebody RG, Paunio M, Ruutu P. Measles, measles vaccination and Crohn's disease: Crohn's disease has not increased in Finland. BMJ 1998; 316: 1745-6
27. Markowitz LE, Katz SL. Measles Vaccine. In: Plotkin SA, Mortimer EA, editors. Vaccines. 2nd ed. Philadelphia: WR Saunders, 1994: 229-76
28. Ekbom A, Daszak P, Kraaz W, et al. Crohn's disease after in-utero measles virus exposure. Lancet 1996; 348: 515-7
29. Nielsen LLW, Nielsen NM, Melbye M, et al. Exposure to measles in utero and Crohn's disease: Danish register study. BMJ 1998; 316: 196-7
30. Jones P, Fine P, Piracha S. Crohn's disease and measles. Lancet 1997; 349: 473-4
31. Wurzelman JI, Lyles CM, Sandler RS. Childhood infections and the risk of inflammatory bowel disease. Dig Dis Sci 1994; 39: 555-60
32. Haslam N, Mayberry JF, Hawthorne AB, et al. Measles, month of birth, and Crohn's disease. Gut 2000; 47: 801-3
33. Pardi DS, Tremaine WJ, Sandborn WJ, et al. Early measles virus infection is associated with the development of inflammatory bowel disease. Am J Gastroenterol 2000 Jun; 95: 1480-5
34. Thompson NP, Montgomery SM, Wadsworth MEJ, et al. Early determinants of inflammatory bowel disease: use of two national longitudinal birth cohorts. Eur J Gastroenterol Hepatol 2000; 12: 25-30
35. Anderson P. Another media scare about MMR vaccine hits Britain. BMJ 1999; 318: 1578
36. Lewin J, Dhillon AP, Sim R, et al. Persistent measles virus infection of the intestine: confirmation by immunogold electron microscopy. Gut 1995; 36: 5654-9
37. Daszak P, Purcell M, Lewin J, et al. Detection and comparative analysis of persistent measles virus infection in Crohn's disease by immunogold electron microscopy. J Clin Pathol 1997; 50: 299-304
38. Miyamoto H, Tanaka T, Kitamoto N, et al. Detection of immunoreactive antigen, with a monoclonal antibody to measles virus, in tissue from a patient with Crohn's disease. J Gastroenterol 1995; 30: 28-33
39. Kawashima H, Mori T, Kashiwagi Y, et al. Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism. Dig Dis Sci 45; 2000: 723-9
40. Iizuka M, Nakagomi O, Chiba M, et al. Absence of measles virus in Crohns disease [letter]. Lancet 1995; 345: 199
41. Haga Y, Funakoshi O, Kuroe K, et al. Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction. Gut 1996; 38: 211-5
42. Afzal MA, Armitage E, Begley J, et al. Absence of detectable measles virus genome sequence in inflammatory bowel disease tissues and peripheral blood lymphocytes. J Med Virol 1998; 55: 243-9
43. Chadwick N, Bruce IJ, Schepelmann S, et al. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcription followed by the polymerase chain reaction. J Med Virol 1998; 55: 305-11
44. Iizuka M, Masamune O. Measles vaccination and inflammatory bowel disease [letter]. Lancet 1997: 350: 1775
45. Iizuka M, Chiba M, Yukawa M, et al. Immunohistochemical analysis of the distribution of measles related antigen in the intestinal mucosa in inflammatory bowel disease. Gut 2000; 46: 163-9
46. Wakefield AJ, Montgomery SM. Immunohistochemical analysis of measles related antigen in IBD [letter]. Gut 2001; 48: 136
47. Iizuka M, Itou H, Chiba M, et al. The MMR question [letter]. Lancet; 2000: 356: 160
48. Measles: United States, 1999. MMWR Morb Mortal Wkly Rep 2000 Jun 30; 49 (25): 557-60
49. Measles, MMR and autism: the confusion continues. Lancet 2000; 355: 1379
50. Gellin BG, Schaffner W. The risk of vaccination: the importance of negative studies. N Engl J Med 2001; 344: 372-3

Correspondence and offprints: Dr *Robert L. Davis*, Child Health Institute, University of Washington, Department of Pediatrics, Box 358853, 146 North Canal Street, Suite 300, Seattle, WA 98103, USA.
E-mail: rdavis@u.washington.edu