Medical Research on MMR, autism and bowel disease, and other safety issues

The papers that are listed below were chosen because they report original research, or are authoritative reviews. This list does not include the many expert opinions on the subject which are to be found in the editorial columns and letters in medical journals. The first group of papers are those that suggested that MMR vaccine may cause autism and bowel disease, have been put first because they started the debate. These are followed by papers that give evidence that MMR vaccine does not cause autism or bowel disease, then those that cover other safety issues, and finally by reviews made by national and international bodies. Our conclusions are at the end.

Research suggesting a link between MMR vaccine, autism and bowel disease

The theory that MMR vaccine might be linked to bowel disease started in 1995 with a paper in the Lancet from the Inflammatory Bowel Disease Study Group at the Royal Free Hospital in London. This research group included Andrew Wakefield, who has been the leading proponent for this theory. The reasoning behind the theory was that infection. The Inflammatory Bowel Disease Study Group had found traces of measles virus in patients with Crohn's disease. To see if measles vaccination in childhood (an event in which one could be sure that the child did get measles virus) was followed by bowel disease in adulthood, the research group followed up 3,545 people who had taken part in the measles vaccine trials in the UK when they were children in the 1960's. They found that the prevalence of Crohn's disease was three times higher than in a group of 11,407 people of the same age who were not vaccinated in the early trials. A point that is worth remembering is that the children who were vaccinated in the 1960's had single measles vaccine, not MMR.
Thompson et al. Is measles vaccination a risk factor for inflammatory bowel disease? Lancet 1995; 345:1071 -74.

The key paper that increased the interest appeared three years later, again in the Lancet. The theory of a link between vaccination and bowel disease had been developed by Inflammatory Bowel Disease Study Group to include autism. This paper published in February 1998 described a study of 12 children with a new type of autism, pervasive developmental disorder, which was combined with inflammation of the bowel. The parents of 8 children said that the symptoms started after measles or MMR vaccine. The paper was cautious in its conclusions and said 'We did not prove an association between MMR and the syndrome described'.
Wakefield A J et al. Ileallymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998; 351: 637-41.

The possible impact of this paper on the confidence in vaccination was recognised by the Lancet. A commentary in the same issue of the Lancet said that it was important that the suspected link between bowel disease, autism and MMR vaccine should be examined critically and with an open mind, because vaccine-safety concerns "may snowball into societal tragedies when the media and the public confuse association with causality and shun immunisation."
Chen RT and De Stefano F. Vaccine adverse events: causal or coincidental? Lancet 1998; 351: 611-12.

The paper by Wakefield et al attracted considerable interest in newspapers as well as in letters to the Lancet. Much of the medical correspondence was sceptical that there a was a link between MMR vaccine and autism, and pointed out the consequences of any loss in confidence in the safety in the vaccine. The first batch of letters were published in the Lancet on 21 March 1998 (vol. 351, 905 – 909). Some of the criticism was aimed at the method used in the paper to link the autistic syndrome with MMR vaccination. In reply, Wakefield reported that his research group now had 48 cases of

autism with bowel symptoms after MMR vaccination, and asserting that the possible link should be taken seriously and investigated (*Wakefield AJ. Autism, inflammatory bowel disease and MMR vaccine. Lancet 1998; 351: 908*). Letters with some support for Wakefield's arguments appeared in the Lancet on 2 May 1998 (vol 351: 1355 –1558), and some offered ideas of why inflammatory bowel disease and autism might be related.

The link between MMR vaccination, bowel disease and autism was discussed a greater length in two reviews published in1999 and 2000 by Wakefield and Montgomery. The conclusion was that the link was biologically plausible and supported by the increasing prevalence of autism. *Wakefield J and Montgomery S M. Autism, Viral Infection and Measles-Mumps-Rubella Vaccination, Israel Medical Association Journal 1999,1:183-187 and Wakefield AJ & Montgomery SM. Mumps measles rubella vaccine: through a glass darkly. Adverse Drug Reactions and Toxicological Reviews 2000; 19:265-83.*

Although Wakefield and his colleagues had described evidence of measles virus persisting in the intestinal wall of patients with Crohn's disease (Journal of Medical Virology 1993; 39:345-53, 1993 and 1997; 51:90-100), his Study Group at the Royal Free Hospital had some difficulty in confirming this finding using sensitive RNA tests (RNA tests are like DNA tests used in forensic science). *Chadwick N et al. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcription followed by the polymerase chain reaction. Journal of Medical Virology 1998; 55:305-311.*

However there was more success in a later study with a research group in Dublin, finding RNA evidence of measles virus in biopsy samples from 75 out of 91 children with the form of bowel inflammation, ileal hyperplasis, that the Royal Free group associated with autism. *Uhlmann V et al. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. Journal of Clinical Pathology (Molecular pathology) 2002; 55: 84-90.*

These results have not been replicated by others, using similar sensitive techniques to look for measles virus in patients with inflammatory bowel disease. *Afzal M A et al. Absence of measles-virus genome in inflammatory bowel disease. Lancet, 1998; 351: 646-7 and Afzal A et al. Further evidence of the absence of measles virus genome sequence in full thickness intestinal specimens from patients with Crohn's disease. Journal of Medical Virology 2000; 62: 377-82.*

One American study claimed a link between autism and MMR vaccine, from data collected by the Vaccine Adverse Events Reporting System. There were 37 reports of autism occurring after MMR vaccination, on average after an interval of 5 – 10 days. To try to see what this meant, the authors compared the rate with side-effects after DTP vaccine, not appreciating at DTP vaccination is given to children in the USA before they are 7 months old, an age when autism does not appear. This paper does not contribute much to the evidence, but it is the only paper apart from those from the Inflammatory Bowel Disease Study Group to support their theory. *Geier M, Geier D. Pediatric MMR Vaccination Safety. International Pediatrics 2003, Vol 18: 203-208.*

Research not finding a link between MMR vaccination, autism and bowel disease

Following the controversial papers and correspondence in the Spring of 1998, the Lancet published two studies which gave evidence against the theory developed by Wakefield and his colleagues. Two large sets of medical records on young people with behavioural disorders, including autism, were described by Fombonne in 1998, also in the Lancet. At the Maudsley Hospital in London, there were two cases of Crohn's disease in 8,889 psychiatric patients, seen between 1973 and 1991. In France, there were two cases of inflammatory bowel disease (IBD) in 6,100 people who had behavioural problems in childhood. None of the patients with IBD had autism, and the incidence of IBD was the

same as the rest of the population. The conclusion was that IBD was not associated with autism. *Frombonne E. Inflammatory Bowel Disease and Autism. Lancet 1998; 351: 955.*

In May 1998, the Lancet reported a study in Finland where MMR vaccination was started in 1982 and over 1.8 million children had been vaccinated and followed up. Only 31 children had gastro-intestinal illness after MMR vaccinations, and the illness was short-lived in most cases. No children had developed autism soon after vaccination. *Peltola H et al. No evidence for measles, mumps, and rubella vaccine associated in inflammatory bowel disease or autism in a 14 –year prospective study. Lancet 1998; 351: 1327 – 8.*

This Finnish study was reported in more detail in 2000. The authors said that simply because an event occurred after a vaccination was not a reason to claim cause and effect. They concluded that serious events caused related to MMR vaccine are rare and greatly outweighed by the risks of natural MMR diseases. *Patja A et a.l Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. Pediatric Infectious Diseases Journal 2000; 19:1127 – 34.*

Another Finnish study assessed whether there was an association between MMR vaccination and encephalitis, aseptic meningitis, and autism. This retrospective record linkage study in Finland looked at over 500,000 children aged between 1 and 7 years of age vaccinated during November 1982 and June 1986.This study did not identify any association between MMR vaccination and encephalitis, aseptic meningitis or autism. *Mäkëla et al. Neurologic disorders after measles-mumps-rubella vaccination. Pediatrics 2002; 110:957-63.*

The next year, the Lancet published a paper which assessed 498 cases of autism that had occurred in North London since 1979. There had been an upward trend in the numbers of children diagnosed with autism, but there had not been a step up in the trend after MMR vaccination was started in 1988. Nor was there any tendency for the age of onset of these 389 cases born after 1987 to fall within a few weeks of MMR vaccination, or for the children to have had MMR vaccination than the rest of the population. *Taylor B et al. Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999; 353: 2026-9.* This study by Taylor and colleagues was criticised by Wakefield, on the grounds that the onset of autism might not follow soon after MMR vaccination. So the data was reanalysed two years later using an extended timescale. The results provided further evidence against a causal association between the MMR vaccine and autism. *Farrington P et al. MMR and autism: Further evidence against a causal association Vaccine 2001; 19:3632-5.*

Taylor's group, some of whom work at the same hospital as the Inflammatory Bowel Disease Study Group have published two more papers on the subject. In the first, they concluded that there is not a new syndrome of autism and bowel disease linked with MMR vaccine *Taylor B et al. Measles, mumps and rubella vaccination and bowel problems or developmental regression in children with autism: a population study. BMJ 2002; 324:393-6.* In the second they argued that better recognition and diagnosis at an earlier age were two reasons why autism appeared to be more common. *Taylor et al. Prevalence of autism and parentally reported triggers in a north east London population. Archives of Disease in Childhood 2003:88: 666-670.*

A study in four large American health maintenance organisations compared the vaccination records of 155 people with inflammatory bowel disease (IBD) with matched controls of the same age and health-care provider. This found no association between MMR vaccination and IBD. This study looked at the age when MMR vaccination was given and showed that vaccination before the age of 18 months had no risk of IBD. *Davis RL et al. Measles-mumps-rubella and other measles-containing*

vaccines do not increase the risk for inflammatory bowel disease: a case-control study from the Vaccine Safety Datalink project. Archives of Pediatric and Adolescent Medicine 2001; 155: 354 – 359.

The GP Research Database (a large sample of records from British GPs) was used to compare MMR vaccine coverage over time with reported rates of autism. The authors concluded that there was no correlation exists between the rate of MMR vaccination and the rapid increase in the rise of autism over time.' *Kaye J, del Mare Melero-Montes M & Jick H. Mumps, measles and rubella vaccine and the incidence of autism recorded by general practitioners: A time trend analysis. British Medical Journal 2001; 322:460-3.*

Another study, using the same database, looked at whether children with autism are more likely to have a history of gastrointestinal disorders than children without autism. There were 96 children born between 1 January 1988 and 31 December 1999 with autism of whom 9 had bowel disorders, exactly the same proportion (9%) as in a control sample of children without autism. *Black C, Kaye JA & Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. British Medical Journal 2002; 325:419-21.*

A third study using the UK General Practice Research Database looked at patients diagnosed to "pervasive developmental disorder" (autism) while registered with a contributing general practice between 1987 and 2001. Controls were matched on age, sex, and general practice. Findings 1,294 cases and 4,469 controls were included. 1,010 cases (78·1%) had MMR vaccination recorded before diagnosis, compared with 3,671 controls (82·1%) before the age at which their matched case was diagnosed. This showed that MMR vaccination is not associated with an increased risk of pervasive developmental disorders in these patients. *Smeeth L et al. MMR vaccination and pervasive developmental disorders: a case-control study. Lancet 2004; 364: 963-69.*

A study of general practice consultations, examined whether 79 children who were later diagnosed as autistic had consulted their GPs more frequently in the 6 months after their MMR vaccination than a control group of 284 children without autism. It found that there was no difference in the number of consultations after MMR vaccination, which was evidence that vaccination did not lead to an early change in behaviour. However the autistic children did have more consultations before their diagnosis was made, showing that consultation rates could reflect changes in children's behaviour. *DeWilde S et al. Do children who become autistic consult more often after MMR vaccination? British Journal of General Practice 2001; 51:226-7.*

In California where the same type of MMR vaccine was used continuously from 1979, a sample of children in nurseries were studied each year from 1980 to 1994. The sample size varied between 600 and 1,900 per year. The percentage of children vaccinated with MMR by their second birth increased modestly from 72% to 82% between 1980 and 1988 and then stayed stable. The prevalence of autism rose at a greater rate, from 44/100,000 in 1980 to 208/100,000 by 1994. However, most of the increase in autism occurred in children born in 1988 or later, after MMR vaccination rates were stable. So it was concluded that there was not association between MMR vaccine and autism. *Dales L, Hammer S & Smith N. Time trends in autism and in MMR immunisation coverage in California. Journal of the American Medical Association 2001; 285:1183-5.*

A group of 96 children born between 1992 and 1995 and diagnosed to have regressive autism were compared with 98 autistic children born before 1988. The study concluded that there was not a distinct syndrome of regressive autism associated with bowel disease and MMR vaccination. *Fombonne E & Chakrabarti S. No evidence for a new variant of measles-mumps-rubella-induced autism. Pediatrics 2001; 108: 58.*

A study of 537,303 children born in Denmark between 1991 and 1998 looked at the occurrence of autism recorded in the Danish Psychiatric Central Registry and MMR vaccination recorded by the Danish National Board of Health. This large and powerful study was possible because of the methods of civil registration used in Denmark. MMR vaccination rates were 82%, 316 children with autism and 422 with autism-related behaviour disorders were identified. The risk of autism or related disorders was very slightly lower, but not significantly different, in the vaccinated children than in the unvaccinated children. There was no association between the age of vaccination, date of vaccination or time since vaccination, with autism. *Madsen KM et al. A population-based study of measles, mumps and rubella vaccination and autism. New England Journal of Medicine 2002; 347: 1477-82.*

A study in Iceland investigated whether MMR vaccination caused inflammation of the intestines by measuring a chemical calprotectin associated with IBD. 109 children took part in the study. It was found that there was no significant increase in calprotectin in the stools after DTP/Hib/polio vaccine or MMR vaccine, and there was no difference between the two vaccines in the 4 weeks following vaccination. *Thjodleifsson B et al. (2002) Inflammation and inflammatory bowel disease. Effect of Pentavac and measles-mumps-rubella (MMR) vaccination on the intestine. Gut 2002; 51:816-17.*

Parents of autistic children with regressive symptoms were asked when they remembered the symptoms starting. The parents of children whose autism was diagnosed after the publicity alleging a link to MMR vaccine tended to recall the onset as shortly after MMR more often than parents of similar children who were diagnosed prior to the publicity. This is consistent with the recall bias expected under such circumstances. *Andrews N et al. Recall bias, MMR and autism. Archives of Diseases in Children 2002; 87:493-4.*

A review of the 12 studies (from 5 countries) examining the theory proposed by the Inflammatory Bowel Disease Study Group was published in 2003. None of the studies examined provided evidence of a link from MMR vaccine to autism and related disorders. The review did not find any evidence of an epidemic of autism related to MMR vaccine, nor evidence of an association between a variant form of autism and the MMR vaccine. *Wilson K et al. Association of Autistic Spectrum Disorder and the Measles, Mumps and Rubella Vaccine. Arch Pediatr Adolesc Med. 2003; 157: 628-34*

A study looked at whether there was a change in the incidence of autism in people under 21 years in Olmsted County, Minnesota, between 1976 and 1997, and found that there was an 8-fold increase in the rate of autism. This was seen only in children less than 10 years of age. This increase occurred following the introduction of a new classification and diagnostic system for developmental disorders, which was broader and more precise, an increased availability of services for children with autism and other developmental disorders, and an increased awareness of autism. These factors may have led to identification of previously unrecognised young children with autism accounting for the increase in rate. MMR vaccine was introduced in Minnesota over 20 years before the increase in rate of autism suggesting that MMR vaccine did not contribute to this rise. *Barbaresi et al. The Incidence of Autism in Olmsted County, Minnesota, 1976-1997. Archives of Pediatric and Adolescents Medicine. 2005; 159:37-44.*

In Japan, MMR vaccine was withdrawn in 1988, because of fears related to mumps vaccine and meningitis. Despite the withdrawal of MMR vaccine the annual rate of autism increased progressively from 47.6 per 10,000 for children born in 1988 to 117.2 per 10,000 for those born in 1996. If MMR vaccine had been a cause of autism, the rate of autism should have fallen. *Honda Hideo, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. Journal of Child Psychology and Psychiatry (2005).*

Other conditions that might be linked to MMR vaccine

The risk of developing viral (aseptic) meningitis following MMR vaccination was studied in South Korea in 1998. All 677 children aged 8 to 36 months admitted to hospital with viral meningitis were investigated, and 67 were found to have had MMR vaccine in the preceding year. The importance of this study was that four types of MMR vaccines were used in Korea at this time: those with Jeryl Lynn mumps vaccine(as used in the UK), and those with Rubini, Urabe or Hoshino strains of mumps vaccine. The last two strains were found to be associated with viral meningitis, occurring within 6 weeks of MMR vaccination. This was similar to the Japanese experience, which reluted in MMR vaccination being stopped in Japan (see above). However the MMR vaccines with Jeryl Lynn and Rubini strains had been given to only 3 children out of the whole group of 677 in the 6 weeks before the aseptic meningitis, a number that was less than expected by chance. *Ki M. et al. Risk analysis of aseptic meningitis after measles-mumps-rubella vaccination in Korean children by using a case-crossover design. American Journal of Epidemiology 2003; 157: 158-65.*

A study by the Public Health Laboratory Service and Royal Free Hospital found that 1 in every 22,300 children immunised are at risk of developing the blood disorder Idiopathic Thrombocytopenic Purpura (ITP). The study concluded that children whose illness was caused by MMR tended to have milder symptoms and spent less time in hospital than when the ITP was unrelated to vaccination. *Miller E et al. Idiopathic thrombocytopenic purpura and MMR vaccine. Archives of Disease in Childhood 2001; 84:227-9.*

A study using the General Practice Research Database was used to estimate the risk of developing idiopathic thrombocytopaenic purpura (ITP) following MMR vaccination. This study confirmed that there is an increased risk of developing ITP within 6 weeks after MMR vaccination, but showed that this risk was low, at 1 in 25,000 vaccinated children. *Black C. et al. MMR vaccine and idiopathic thrombocytopaenic purpura. British Journal of Clinical Pharmacology 2003; 55: 107-11.*

A study of hospital admissions for serious bacterial infections, such as bacterial meningitis and septicaemia, and pneumonia, looked at children in the before and three months after MMR vaccination. 395 children aged between 12-23 months admitted to hospital in selected districts in the Thames region of southern England with a bacterial invasive disease between April 1995 and March 1995. The results of this study showed that MMR did not increase the risk of developing bacterial infections within 90 days following vaccination. This study does not support the theory that MMR causes immunological overload in children. *Miller E, Andrews N, Waight P, Taylor B. Bacterial infections, immune overload, and MMR vaccine. Archives Diseases of Childhood 2003; 88:222–223.*

The same research group examined hospital and GP records to see if there was any association between gait disturbance and MMR vaccination. They found 146 children admitted to hospital and 1,403 seen in general practice for gait disturbance. Looking at the vaccination records, there was no increase in the rate of hospital admission or general practice consultations for gait disturbance after MMR vaccine. *Miller E et al. No evidence of an association between MMR vaccine and gait disturbance Archives of Disease in Childhood 2005;90:292-296.*

Reviews made by regulatory bodies and other authorities

Because if the concern of vaccine safety, the Medicines Control Agency and Department of Health reviewed the paper published by Wakefield & Montgomery in Adverse Drug Reactions and Toxicological Reviews in 2000 (see above). The Medicine Control Agency found that Wakefield and colleagues had not analysed and reported the data correctly, and had not shown all the evidence.

Medicines Control Agency/Department of Health (2001), Combined measles, mumps and rubella vaccines: Response of the Medicines Control Agency and the Department of Health to issues raised in papers published in Adverse Drug Reactions and Toxicological Reviews 19(4): 2000.

The Committee on Safety of Medicines reviewed the Wakefield & Montgomery paper and concluded: 'In those studies where MMR has been compared with the component vaccines there is no suggestion that MMR causes more adverse effects than measles vaccines alone.' *Committee on Safety of Medicines (2001).*

Summary of the Committee on Safety of Medicines meeting held 10 January 2001. The World Health Organisation (WHO) released its view of the evidence regarding the safety of the MMR vaccine. It stated: 'WHO strongly endorses the use of MMR vaccine on the grounds of its convincing record of safety and efficacy. The combination vaccine is recommended rather than the monovalent presentation when available and the disease burden justifies its use. There has been no new scientific evidence that would suggest impaired safety of MMR. On the contrary, all results from vaccine trials published reaffirm the high safety of MMR vaccine.' *World Health Organisation (2001). Statement on the use of MMR vaccine 24 January 2001.*

The US Institute of Medicine Immunisation Safety Review Committee published a report which concluded: 'The evidence favours rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders (ASD).' The chair of the committee warned of possible 'devastating disease outbreaks' if parents refrained from having their children vaccinated due to autism fears. *Institute of Medicine Immunisation Safety Review Committee (2001). Report of measles-mumps-rubella vaccine and autism.*

The American Academy of Pediatrics hosted a multidisciplinary international workshop to review the evidence regarding a possible association between MMR vaccine, inflammatory bowel disease and autism spectrum disorders, specifically autism with regression. It decided a considerable body of evidence did not support a causal relationship between MMR vaccine and autism or inflammatory bowel disease. In addition, it found no data to suggest the separate administration of measles, mumps and rubella vaccines would offer any potential benefit over the MMR vaccine. In fact, it voiced its concern that such an approach would result in many under-immunised children. *American Academy of Pediatrics (2001), Measles-mumps-rubella vaccine and autistic spectrum disorder: A report from the new challenges in childhood immunisation conference.*

The Medical Research Council published a review on autism, which stated that understanding and diagnosis of autism spectrum disorders (ASDs) has improved and called for more research in this area. It also stated that in relation to MMR, current evidence does not support the alleged link of MMR and ASDs.

The Scottish Executive established an expert group in 2001 to inquire into issues surrounding the alleged relationship between the combined measles, mumps and rubella vaccine and autism. The expert group, which reported in 2002, found no scientific link between autism, Crohn's disease and MMR vaccine, and advised against the introduction of single vaccines.

Conclusion

In summary, researchers who have investigated Wakefield's theory, that the MMR vaccine might be linked to bowel disease and autism, have identified important flaws in the theory. Other researchers have not found measles virus in intestinal specimens, which was one of Wakefield's findings, nor found a significant amount of inflammation in the intestine following MMR vaccination. The findings of large epidemiological studies which have investigated adverse reactions to the MMR vaccine have

not identified bowel problems post-vaccination. Further, large-scale studies have not found any evidence of a new form of autism associated with MMR vaccination, or any evidence that trends in the increased incidence of autism are related to MMR or measles vaccines. Taken together, it is unsurprising that the substantial body of medical expert opinion does not support the theory of a link between MMR, bowel disease and autism.

Since these interviews were made, the research that alleged a connection between autism and MMR vaccine has been discredited and the original paper has retracted by the Lancet, on the grounds that several elements of the paper are incorrect and that some of the claims by the authors were proven to be false (*Lancet, 6 Feb 2010, vol 375, issue 9713, page 445. Retraction – Ileal-lymphoidnodularhyperplasia, non-specific colitis and pervasive developmental disorder in children*) The original study by Andrew Wakefield's has since been completely discredited and he has been struck off as a doctor in the UK.

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