The MMR vaccine and autism

Abstract
In February 1998, the Lancet published a study by Dr Andrew Wakefield, a British gastroenterologist, which suggested a link between the measles, mumps and rubella (MMR) vaccine as an environmental trigger, and a novel bowel disorder that led to a regressive form of autism. Despite repeated assurances from health professionals and extensive epidemiological studies, which categorically refuted such a link, the controversy sparked a huge public health scare in the United Kingdom. After a decade of controversy and investigation, Dr Wakefield was found guilty of ethical, medical and scientific misconduct in carrying out the study and publishing fraudulent data. It is important for healthcare professionals to be aware of the specifics of the controversy in this multifaceted scandal and the ongoing implications, which have led to a resurgence in cases of measles, mumps and rubella. It is also imperative to question how effectively science is being communicated to the general public to allow them to make better health decisions for their children and themselves.

Introduction
The measles, mumps and rubella (MMR) triple vaccine, consisting of a live, attenuated measles virus as the immunogen, is given by injection in two doses. The first is given to toddlers aged 12-15 months, with a second ‘booster’ injection given to school children to safeguard the 5-10% who do not develop full immunity. The first public suggestion of a link between the MMR vaccine and autism was made by the mother of an autistic child in 1993 on a Danish television programme. This prompted an investigation in 1994 by the Danish Department of Epidemiology at the National Statens Serum Institut looking for a change in trend in incidence or age at diagnosis associated with the introduction of the vaccine. Although no link, either epidemiological or biological, was found at the time, fear of an association between the two inspired parents and lawyers to form anti-MMR groups. The possibility of such a link entered public discourse in 1998 when the Lancet published a paper suggesting a link between the MMR vaccine and the onset of autism, which has led to repercussions in healthcare and the sociopolitical arena that are still being experienced to this day.

This review will look at the extensive studies undertaken by the scientific community, which have categorically refuted any relationship between the MMR vaccine and autism.

The Lancet study by Andrew Wakefield
On February 28, 1998, together with 12 co-authors, Andrew Wakefield published a study in the Lancet suggesting that the MMR vaccine could be an environmental trigger that led to the onset of developmental regression in infants. The study involved 12 children referred to the Royal Free Hospital with a history of gastrointestinal disease, in particular inflammatory bowel disease. Nine of these children were diagnosed with a regressive form of autism in which they had seemingly normal infant development before a gradual deterioration in communication and other acquired skills. The other three children had suspected encephalitis, also presenting with developmental problems. Histological examinations found abnormalities in the colonoscopy samples showing ileal lymphoid nodular hyperplasia (LNH) present in nine of the 12 children. Eight of these nine had mucosal...
abnormalities and a distinct non-specific mild-to-moderate colitis, not classified as either Crohn’s disease or ulcerative colitis. The paper suggested that the damaged intestine triggered the regression in the children through the previously proposed “opioid-excess" hypothesis for autism. The hypothesis states that incomplete digestion of certain foods resulting from a dysfunctional gut leads to undigested ‘toxic’ peptides, which are absorbed into the bloodstream. These peptides are thought to be bound to peptidase enzymes, normally responsible for breaking down the naturally occurring opioid peptides in the central nervous system (CNS). The hypothesis suggests that the toxic peptides consequently lead to CNS disruption, which adversely affects brain development. The paper also reported that eight of the children’s parents or physicians said that the onset of behavioural problems was within two weeks of the vaccine administration. The authors conceded that due to a small sample size and inadequate published evidence, they could not fully substantiate a causative link. However, at a press conference following publication, Andrew Wakefield suggested that the MMR vaccine could lead to what he termed “autistic enterocolitis” and suggested that the immunisation programme be changed, with the three vaccines given separately as single injections. Within five years of the publication of Wakefield’s study, the rates of MMR inoculation in the UK fell from 92% to under 80%, well below the 95% rate recommended by the World Health Organisation for a population to acquire herd immunity and protect that population from an endemic.

**Reaction by the government and scientific community**
In response to the Wakefield paper, the Medical Research Council assembled 37 experts to thoroughly review published (and unpublished) evidence at the time, and concluded that there was no link between autism and the MMR vaccine. Despite this, Wakefield’s claim, together with widespread media coverage of the debate, meant that the controversy remained alive, especially for parents concerned with making inoculation decisions for their children. In 2004, an apology was issued by Richard Horton, the *Lancet*’s editor, where he described the paper as “flawed”. In addition, 10 of the 12 co-authors of the study retracted the interpretation of an MMR-autism link. The major remaining issue was that the paper had shown that eight out of 12 children were “previously normal” and had developed “behavioural symptoms” after receiving the vaccine. The first set of symptoms was observed to be on average 6.3 days post inoculation. Assessment of the medical reports showed several inconsistencies with the paper’s reporting of patient data regarding autism onset dates. The children’s parents, general practitioners and other specialists reported that some of the behavioural symptoms associated with autism were observed prior to vaccine administration and, in some cases, months after. Indeed, some of the children had been hospitalised with developmental concerns prior to inoculation. The suggestion of “autistic enterocolitis” as a distinct disease process of intestinal dysfunction has been refuted by the consultants at the Royal Free Hospital who took the biopsies of the children’s colons. They concluded in pathology reports that the samples, rather than “non-specific colitis”, were not uniform but varied, and nothing out of the ordinary.

**Investigations by the press, as well as allegations of conflicts of interest, manipulation of data and ethics violations as reported by the General Medical Council led to the *Lancet* announcing a full retraction of Wakefield’s paper in February 2010.**

On May 24, 2010, Andrew Wakefield was removed from the medical register by the General Medical Council of the UK. He was found guilty of professional misconduct and having “breached fundamental principles of research medicine”, including carrying out unnecessarily invasive tests on children without the required ethical approval or paediatric qualifications, and not disclosing that he was paid to conduct the study by solicitors representing parents who believed that their children had been harmed by the MMR vaccine.

**The evidence, or lack thereof**
In 2005, the Cochrane Collaboration systematically reviewed 31 studies and found no credible evidence to support a relationship between MMR and autism. A case-control study in 2008 replicated Wakefield’s study designs to test for the presence of the measles vaccine RNA in the GI tract. The study included ileal and caecal tissue samples from 25 children with autism spectrum disorders (ASD) who had GI disturbances, and 13 children with GI disturbances with no neurological deficits as control. All children had received at least one MMR injection. The study, repeated three times in different laboratory sites, also examined the order of onset of GI disturbances and autism symptoms relative to the timing of vaccine administration. The study consistently demonstrated strong evidence against the autism association. Persistent measles RNA presence in the bowel after MMR inoculation was found in only five of the 25 autistic children having received the vaccine prior to GI tract disturbances. Only in those five children did the disturbances precede the autistic behavioural symptoms. The vast majority of evidence against the MMR-autism hypothesis, however, lies in the number of epidemiological studies carried out: more than 20, with large sample sizes and substantial follow-up time.

**Epidemiological studies**
In the immediate aftermath of the Wakefield study, the Department of Health in the UK commissioned the Committee on Safety of Vaccines (CSM) of the Medicines Control Agency (MCA), working with groups internationally, to carry out epidemiological studies and review the existing ones. In April 2001, the MCA and CSM endorsed the safety of the vaccine. One of the studies conducted involved a team of Professor Brent Taylor, community paediatrician at the Royal Free Hospital, with a vaccine specialist and a statistician. The team studied the vaccine profile and medical records of 498 children, all with ASD, who were born between 1979 and 1998 in eight North Thames district hospitals.
The study noted a steady increase in the incidence of ASD from 1979 but attributed that increase to the introduction of computerised disability registers, increased recognition of the disorders, earlier and wider acceptance of diagnosis, and significant changes to the diagnostic criteria.

The incidence trend of ASD did not show any sudden change with the introduction of the MMR vaccine in 1988, nor was there any data clustering of developmental regression in the immediate timeframe after MMR inoculation. The study also commented that no significant differences were found in the reporting of rates and onset of bowel problems between those vaccinated and those not. Bowel problems are common in ASD children pertaining to an unusual diet.17

A 14-year prospective study in Finland monitored 31 MMR-vaccinated children who reported mild GI symptoms or signs such as diarrhoea, vomiting and abdominal pains that lasted for 24 hours or more immediately after inoculation. Follow-ups of those 31 children lasted, on average, up to nine years. None of the children developed ASD.18

Furthermore, a population study published in 2005, of over 30,000 children in the city of Yokohama in Japan disproved the association (Figure 1).19 The study showed a rise in incidence of regressive autism (the type suggested by Wakefield as being linked to MMR), despite the discontinuation of MMR in Japan from 1993 onwards.

Long-term consequences of the study
In April 2006, the death of a 13-year-old was the first reported mortality from measles in the UK in 14 years. By 2008, approximately 85% of all two-year-olds were reported to have received the first injection, with the second injection for children around the age of five having an inoculation rate of only 78%.20

Figure 2 (with data from the Health Protection Agency, UK) shows a rising incidence of measles infections with fluctuating rates of MMR inoculation.21

Incidences of rubella in 2012 are at a nine-year high (Table 1).

![Figure 1: The records of 31,426 children in a Yokohama district were looked at.](image1)

![Figure 2: Data from the Health Protection Agency, UK, shows a rising incidence of measles infections with fluctuating rates of MMR inoculation.](image2)

Table 1: The number of confirmed cases of measles, mumps and rubella in the UK from 1996 to 2012.22

<table>
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<th>Year</th>
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<th>Mumps</th>
<th>Rubella</th>
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</table>

Data from the Health Protection Agency (UK), August 2012.
*Andrew Wakefield’s study is published in February 1998.
**Provisional data from the HPA from 01/01/2012 – 31/06/2012.

However, the HPA is now reporting more encouraging news regarding vaccine uptake (93% and 87% for first and second dose, respectively, in England). The reported cases are attributed to older children who may not have received vaccination.

Conclusion
In February 2002, the polling company Independent Communications and Marketing (ICM) surveyed 1,000 adults over
the age of 18, and found that 75% of parents agreed that single vaccines should be made available by the NHS.\textsuperscript{24} Some 20% said they would be prepared to pay for single vaccines. Worryingly, 4% said they would not inoculate their children at all against any of the three diseases. However, 43% said they would agree with the scientific opinion on the controversy. A total of 63% said that they agreed with what their doctors said about the MMR. A decade later, the continuing rise in measles incidence year after year suggests that it is incorrect of emphasising the risks of measles, mumps and rubella, and counteract what has been described as possibly the most damaging medical hoax of the last 100 years.\textsuperscript{25}

This may indicate a failure to effectively communicate and provide reliable information for the public to base decisions on. The media, in reporting there to be a “controversy”, possibly led parents to believe that there is equal weight of evidence on either side of the argument, which is as disingenuous as it is factually inaccurate. With developments in recent years lowering the credibility of Andrew Wakefield’s work even further, it is critical for primary physicians and all health professionals to find a more effective way of emphasising the risks of measles, mumps and rubella, and counteract what has been described as possibly the most damaging medical hoax of the last 100 years.\textsuperscript{25}

References

10. Deer B. How the case against the MMR vaccine was fixed. BMJ. 2011;342:c5347.