

Commentary

MMR Vaccination Complications – is it Time to lay the Myth to rest?

Victor Grech

Abstract

Recent, media-hyped controversy has centred on whether there is any link between the combined measles-mumps-rubella (MMR) vaccine and autism or inflammatory bowel disease. The exhaustive available evidence fails to support any such association, yet the known high morbidity and mortality from these conditions has not prevented a small group of concerned parents from failing to vaccinate their children. This paper will outline the reasons and misconceptions behind the current MMR scare. Further efforts are necessary to completely allay the public's unfounded fears.

Introduction

Measles, mumps and rubella are contagious viral illness is that are usually contracted in childhood in non-immunised individuals. The MMR (measles, mumps and rubella) vaccine is a live vaccine designed to protect against measles, mumps and rubella, and was well tolerated and well received by children, parents and doctors alike. 5-10% of children do not develop antibodies to one dose of vaccine, so a pre-school booster is given at 3-5 years, and this two-dose schedule leads to an efficacy of 99%.¹ The measles vaccine was first made available in Malta in 1982 as part of the National Childhood Immunization Schedule, and as the MMR vaccine in 1987, and was introduced into the National Childhood Immunization Schedule in 1990.² MMR vaccination was introduced in the UK in 1988, with the first dose aimed at children aged 12-15 months.

Key words

Vaccines, combined/adverse effects Measles/
complications Measles-Mumps-Rubella Vaccine

Victor Grech PhD MRCP (UK)
Paediatric Department
St. Luke's Hospital, Gwardamangia, Malta
Email: victor.e.grech@gov.mt

The MMR Controversy

On February 28, 1998, Dr. Andrew Wakefield reported in *The Lancet* a possible association between inflammatory bowel disease, autism, and viral infection associated with MMR vaccination.³ This was a descriptive report on twelve children who had been referred to a paediatric gastroenterology clinic with both bowel symptoms and pervasive developmental disorder characterised by loss of skills that had been previously acquired – a form of autism. Testing of these children included blood tests, cerebrospinal fluid tapping and gastrointestinal biopsies obtained endoscopically and the investigators attempted to explore the extent of bowel inflammation and to exclude other diseases. The paper has several flaws which have been criticised objectively by many independent scientists:

- There was no clear stated research hypothesis.
- The study group was highly selected, extremely small, had no blinded investigators, included no controls, had a very short follow-up period and was therefore inherently incapable of proving or excluding a causal link between MMR and autism and/or inflammatory bowel disease.
- The alleged link with MMR vaccination was made solely on the basis of retrospective parental recall, that is, parents who had signed a consent form to take part in a study to determine a causal link between MMR and autism were asked to remember how closely in time the vaccine was with the onset of autism-like behaviour pattern in their child, instantly invoking the spectre of recall bias. This *modus operandi* is unreasonable because autism is known to develop over a period of weeks or months, hence the questionnaire asking for a link of forty-eight hours to two weeks between vaccination and onset of abnormal behaviour is scientifically implausible.
- No test was consistently abnormal in all of the children.
- Eleven had microscopic evidence only of inflammatory reaction in their bowel.
- The study was not approved by any ethics committee despite a battery of invasive tests including endoscopies, and the study contravenes several sections of the Helsinki Declaration,⁸ particularly: 'The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator'.

Wakefield called a press conference to launch the paper, an unusual step for a medical researcher to call a national press conference in order to announce the results of a scientific trial. For a prestigious teaching hospital to do so for a study concerning just twelve children was rather extraordinary. At the briefing, Wakefield discredited the vaccine as posing risks of causing autism and inflammatory bowel disease. He is also on record as saying that he had a 'feeling' that the risk of autism was related to the combined MMR vaccine, rather than the single vaccines. A storm of controversy erupted, fomented by a media frenzy, and the resulting global scare was immediate. MMR

vaccination rates in England fell from 92% of children reaching the age of two in 1996-97 to 82% in 2002-03⁴ and confirmed cases of measles rose from 112 in 1996 to 442 in 2003.

In the interim, it has been alleged that Dr. Wakefield – the paper's lead author and senior investigator – may also have been guilty of professional misconduct for several reasons. Wakefield had not disclosed that he had been commissioned by the Legal Aid Board (for the sum of £55,000) to determine whether there was any evidence to support legal action by parents of children allegedly harmed by the vaccine. Legal Aid is available in the UK to fund eligible individuals in their quest to protect their rights. Legal Aid also funds a network of solicitors, Citizens Advice Bureaux and other advice providers. Help varies from information leaflets and directing people to other services, to specialist advice and taking cases to court where necessary. In effect, Wakefield had been funded through solicitors seeking evidence to use against vaccine manufacturers, and some of these children had been included as subjects in Wakefield's paper. Wakefield did not disclose this conflict of interest either during or after the research to his colleagues, medical authorities or journal editorial board and the facts only came to light during an investigation led by a Sunday Times of London Journalist, Brian Deer.⁵ This led to the partial retraction of the article by eleven of its thirteen authors (not including Wakefield),⁶ and the Lancet's Editor, Richard Horton, partially retracted the article, calling it 'fatally flawed'.⁷

It has also been alleged that Dr. Wakefield failed to reveal that he was developing his own commercial rival product to the conventional accepted vaccine and that he had made a series of applications to patent measles-related products. The first was filed at the Patent Office just nine months before Wakefield's press conference in February 1998, and two more were filed on June 4, 1998. The patent application papers detail products aimed at preventing and even curing diseases allegedly caused by MMR, and included transfer factors, a now largely abandoned fringe conjecture based on a theory that desirable chemicals can be harvested from white blood cells. The proposal included injecting mice with measles, extracting and processing white cells, injecting the result into pregnant goats, milking them after kid-birth and turning the product into capsules for children,⁹ and was to be done with the help of a neurologist.¹⁰

Further doubts have been cast on the original paper as the High Court in London has requested that the Irish courts order Professor John O'Leary, the Dublin pathologist who carried out the study, to hand over all the raw data so that it can be re-examined by independent experts following claims of anomalies in O'Leary's laboratory reports on samples from hundreds of autistic children who are allegedly victims of the MMR vaccine. Unigenetics, O'Leary's private company, found that 80% of the 91 autistic children it had tested had traces of measles in their bodies, presumably as a result of MMR vaccination.¹¹ Two other laboratories, testing samples from the same children, failed to confirm O'Leary's findings. One, at Edinburgh University, had been commissioned by the drug companies, and the other, at

Table 1: Diseases and Complications

Measles - 30% have at least one complication including:

- Diarrhoea (commonest cause of death in developing countries).
- Otitis media with significant risk of deafness.
- 1st viral/2nd bacterial pneumonia in 1:20 cases (commonest cause of death in developed countries).
- Bronchitis, croup, sinusitis.
- Conjunctivitis/corneal ulceration may cause blindness especially in Vit. A deficiency.
- Gangrenous stomatitis.
- Acute glomerulonephritis that may cause acute renal failure.
- Malnutrition, hepatitis, mesenteric adenitis.
- Increased risk of premature labour and fetal loss.
- Myocarditis.
- Thrombocytopaenic purpura.
- Acute encephalitis in 1:1000 cases: 15% mortality & 30% permanent disability.¹⁷
- Subacute sclerosing panencephalitis (SSPE) in 1-4: 100,000 individuals: 100% fatal.^{18,19}
- Mortality rates: 1 in 3,000 in developed countries, up to 1 in 5 in developing countries.

Mumps

- Meningoencephalitis in 1:300 cases: high fatality rate
- Nephritis and myocarditis may also be fatal.
- 1st trimester disease: 25% fetal loss.
- Mumps orchitis in postpubertal males only causes sterility if bilateral.
- Otitis: one of the most frequent causes of unilateral hearing loss.²⁰

Rubella

- Arthropathies of the fingers, wrists, and knees may persist for over a year.
- Thrombocytopenia with purpura and hemorrhage is extremely rare.
- Congenital rubella syndrome: multi-organ system malformations including cardiac, ocular, CNS, and skeletal systems especially in the first trimester.²¹

Queen Mary Medical School, London, by the children's lawyers.¹² The entire issue is currently the subject of a General Medical Council inquiry.

More importantly, studies since have failed to show any links between autism, inflammatory bowel disease and MMR vaccination. For example, a Finnish study prospectively followed 1.8 million children after MMR vaccination for fourteen years and reported a total of 437 vaccine-associated events including allergic reactions and convulsions, but autism could not be linked to the vaccine.¹³ Furthermore, an analysis of 500 cases of autism found no excess in MMR-immunised children.¹⁴ Another large study analysed the incidence of inflammatory bowel disease in individuals who had received the MMR vaccine, other measles-containing vaccines, and no vaccine at all, and showed that the risk of inflammatory bowel disease was the same for vaccinated or unvaccinated individuals, and not related to early age at vaccination.¹⁵ Moreover, the National Autism Society has stated that regressive autism – the type identified by Wakefield – has remained constant since the introduction

of the MMR vaccine.¹⁶ The overall conclusions were that reported adverse reactions established that serious events causally related to MMR vaccine are rare and are greatly outweighed by the risks of wild measles, mumps and rubella.

Known complications of wild viral infection

Measles has been called the greatest killer of children in history and remains the leading cause of vaccine preventable deaths in children worldwide. Because of poverty, with low worldwide availability of vaccine, some 50 million individuals contract the disease annually with over one million deaths per annum. The highest incidence of measles and its associated morbidity and mortality is witnessed in developing countries. Complications of measles, mumps and rubella are briefly listed in Table 1. All of these complications are vaccine preventable and at this time, it is hoped that the MMR scare will fade away like the similar pertussis vaccine scare of the 1970s.²² Table 2 lists some common misconceptions and questions that parents come forward with, and possible replies based on science.

Table 2: *Common parent MMR misgivings and misconceptions*

- **Diseases had already begun to disappear before vaccines were introduced (because of better hygiene and sanitation)**
True but regular peaks due to outbreaks still appeared, and were potentially equally devastating to those affected.
- **The majority of people who still get disease have been vaccinated**
True because of statistics. Since the majority are vaccinated, and vaccines have a know (albeit small) failure rate, then this sort of statistic is inevitable.
- **Thiomersal (a mercury containing compound) is present in MMR**
False, ethylmercury (thiomersal) is not present in MMR and never has been, and anyway, the presence of this compound in other vaccines has not been linked to any adverse effects.
- **There are 'hot lots' of vaccine that have been associated with more adverse events and deaths than others**
Simply untrue.
- **Giving a child multiple vaccinations for different diseases at the same time increases the risk of harmful side effects and can overload the immune system**
Children are exposed to a multitude of foreign antigens on a daily basis, including simply by eating through the introduction of food antigens and bacteria. It is estimated that an upper respiratory viral infection exposes a child to 4-10 antigens, and a case of streptococcal throat infection to 25-50 antigens. There is no proof whatsoever that giving vaccines separately makes any sort of difference whatsoever apart from necessitating multiple doctor visits, increasing the number of jabs exponentially, increasing costs, delaying the vaccination process with risk of disease acquisition and reducing compliance.
- **Vaccines cause many harmful side effects, illnesses, and even death - not to mention possible long-term effects we don't even know about**
Vaccine development typically takes 10 years, post-marketing surveillance by pharmaceutical companies is intensive and taken very seriously. For example, a potential rotavirus vaccine was recently released and rapidly withdrawn after an association was noted with intussusception. With regard to risks of vaccine versus disease, see paper itself!
- **Vaccine-preventable diseases have been virtually eliminated, so there is no need for my child to be vaccinated**
False, uptake rates are not sufficiently high for herd immunity to be sufficient for this statement to be true. Conversely, if uptake rates were to be high enough for this statement to be correct, a very small decline in vaccine uptake would return us to an outbreak potential state.

It is likely that had Dr. Wakefield declared his conflicts of interest, the paper would not have been accepted for publication. Conflict of interest is a crucial principle that has long been enshrined in the organisation of scientific research,²³ and this is especially important when one reviews the growing body of evidence that demonstrates how conflict of interest biases research outcomes. Systematic reviews have unequivocally shown that results of sponsored studies are more likely to favour the sponsor when it is a pharmaceutical company.²⁴ Moreover, industry-sponsored studies are not only associated with pro-industry conclusions, but also lead to restrictions on publication and data sharing.²⁵

Conclusions

It is important to emphasise that the morbidity and mortality related to wild virus infection are not theoretical issues and are eminently vaccine-preventable, and this should be highlighted to misinformed and concerned parents who may be reluctant to vaccinate their children because of conjectural and unproven vaccine side-effects.

References

- Janaszek W, Gay N, Gut W. Measles vaccine efficacy during an epidemic in 1998 in the highly vaccinated population of Poland. *Vaccine* 2003;1: 473-478.
- Muscat M, Sciberras M. Towards Measles Elimination. *Malta Medical Journal* 2003;15:36-38.
- Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637-641.
- Health Protection Agency. Epidemiological data – measles. Available at: www.hpa.org.uk/infections/topics_az/measles/data.htm (accessed December 2004).
- Deer B. Revealed: MMR research scandal. *The Sunday Times* (London) 2004 22 Feb. Available at: www.timesonline.co.uk/article/0,,10009-1012410,00.html (accessed December 2004).
- Murch SH, Anthony A, Casson DH, et al. Retraction of an interpretation. *Lancet* 2004; 363: 750.
- Horton R. A statement by the editors of *The Lancet*. *Lancet* 2004; 363: 820-821.
- World Medical Association. Declaration of Helsinki. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Last amended 41st World Medical Assembly, Hong Kong, September 1989.
- Deer B. Revealed: MMR scare doctor planned rival vaccine. *The Sunday Times* (London) 2004 14 Nov. Available at: <http://www.timesonline.co.uk/article/0,,2087-1358605,00.html> (accessed December 2004).
- Fudenberg HH. Dialysable lymphocyte extract (DLyE) in infantile onset autism: a pilot study. *Biotherapy* 1996; 9: 13-17.
- Uhlmann V, Martin CM, Sheils O, Pilkington L, Silva I, Killalea A, Murch SB, Walker-Smith J, Thomson M, Wakefield AJ, O'Leary JJ. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. *Mol Pathol.* 2002;55:84-90.
- Deer B. Fresh doubts cast on MMR study data. *The Sunday Times* (London) 2004 25 April. Available at: <http://briandeer.com/mmr/oleary-pcr.htm> (accessed December 2004).
- Patja A, Davidkin I, Kurki T, Kallio MJ, Valle M, Peltola H. Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. *Pediatr Infect Dis J.* 2000;19:1127-34.
- Davis RL, Kramarz P, Bohlke K, Benson P, Thompson RS, Mullooly J, Black S, Shinefield H, Lewis E, Ward J, Marcy SM, Eriksen E, Destefano F, Chen R; Vaccine Safety Datalink Team. 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. *Arch Pediatr Adolesc Med.* 2001;155:354-359.
- 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. *BMJ* 2002;325:419-421.
- Committee on the Safety of Medicines. Working Party on MMR vaccine. The safety of MMR vaccine. *Current Problems in Pharmacovigilance* 1999;25:9-10.
- Bloch AB, Orenstein WA, Stetler HC, Wassilak SG, Amler RW, Bart KJ, Kirby CD, Hinman AR. Health impact of measles vaccination in the United States. *Pediatrics* 1985;76:524-532.
- Centers for Disease Control and Prevention. Subacute sclerosing panencephalitis surveillance-United States. *MMWR Morb Mortal Wkly Rep.* 1982;31:585-8.
- Miller C, Andrews N, Rush M, Munro H, Jin L, Miller E. The epidemiology of subacute sclerosing panencephalitis in England and Wales 1990-2002. *Arch Dis Child.* 2004;89:1145-1148.
- Caplan CE. Mumps in the era of vaccines. *CMAJ.* 1999;160:865-866.
- MMWR: Rubella and congenital rubella syndrome-United States, 1994-1997. *MMWR Morb Mortal Wkly Rep* 1997;46:350-354.
- Grech V, Busuttill R. Brain damage following whooping cough vaccination - is it time to lay the myth to rest? *Maltese Med J* 1998;10:15-18
- Institute of Medicine, National Academy of Sciences. *The Responsible Conduct of Research in the Health Sciences.* Washington: Institute Of Medicine, 1989. Available at: <http://books.nap.edu/books/0309062373/html/index.html> (accessed December 2004).
- Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003; 326: 1167-1170.
- Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003; 289: 454-465.