April 3, 2008

Autism and Vaccination: The Real Story

Richard B. Philp, *University of Western Ontario*

AUTISM AND VACCINATION: THE REAL STORY

R.B. Philp, Ph.D., Emeritus Professor of Pharmacology and Toxicology, The University of Western Ontario

There is a persistent belief amongst some parents of autistic children that childhood immunizations, especially with measles-mumps-rubella vaccine (MMR), contributed to the development of autism in their child. MMR vaccination is performed commonly between the ages of 15 months and three years. The onset of observable signs of ASD usually occurs slightly later, from three to five years of age although very observant parents may notice something amiss earlier. Thus there is a temporal association between the two events that has led parents to suspect a causal connection and this began to emerge by the mid- '80s.

Credence was lent to this belief by a 1998 paper by Wakefield *et al* (1) in which they reported on 12 children (mean age 6 years, range 3-10 years) with chronic enterocolitis and regressive developmental disorder. Their report stated that the onset of behavioral symptoms was associated *by the parents* (my italics) with MMR vaccination in 8 of the 12, measles infection in one and otitis media in another. All 12 had intestinal disorders. Nine were autistic, one had disintegrative psychosis and two had possible post viral or post vaccinal encephalitis. This report received widespread media coverage resulting in massive community outrage that spread around the world. The level of community protection in Great Britain with MMR fell from 92% in 1995 to 80% in 2003 (2). 90% is considered the minimum for "herd" protection (a term borrowed from veterinary medicine and referring to that level of immunization necessary to avoid an outbreak) (2). The level did not begin to recover until after 2004, largely as a result of several outbreaks of measles in the UK that changed parental attitudes about immunization. The media also reported about this time that Wakefield had a vested financial interest in promoting single vaccines and that he had not fully disclosed his source of funding (2). Little noted by the media, famous for its short attention span, was a retraction published in 2004 by 10 of the 12 authors of the original paper. (The other two could not be contacted.) It is worth quoting.

"We wish to make it clear that in this paper no causal link was established between MMR vaccine and autism as the data were insufficient. However the possibility of such a link was raised and consequent events had major implications for public health. In view of this, we consider now is the appropriate time that we should together formally retract the interpretation placed upon these findings in the paper, according to precedent" (3). Wakefield's name was absent from the retraction.

Despite the retraction, the damage was done and repercussions continue to this day. Recently the US dept. of Health and Human Services determined that a child named Hannah Poling given MMR vaccine at 18 months of age became ill as a result and that the vaccine aggravated an underlying disorder leading to signs and symptoms of autism. There are currently 4900 cases pending in "vaccine court" in the US.

There have now been numerous studies that have failed to show any association between MMR immunization and the onset or course of ASD. The first of these was published in 2004 (4). These authors reviewed papers listing key terms that included measles, mumps, rubella and autism. They identified 10 papers meeting their selection criteria and that looked for a link between MMR vaccination and autism and failed to find any evidence of such. Papers specifically examining a link between gastrointestinal systems in autistic children and MMR vaccine were excluded from the study. Cochrane Database Systematic Reviews, an independent publication that compiles and analyzes data from various journals, published a comprehensive review in 2005 (5). They found 139 papers that met their selection criteria and found no evidence of an association between MMR and autism but did find higher incidences of other medical problems irrespective of the occurrence of ASD. In 2006 Richler *et al.* (6) Studied 351 children with ASD and 31 typically developing children and found no evidence that the onset of autistic symptoms or of regression was related to MMR vaccine. For ASD children who experienced regression (loss of acquired skills) their pre-loss development was clearly atypical.

One of the most extensive studies of the question of a link between MMR vaccination and developmental disorders was conducted in Montreal by Forbonne *et al.* (7). They examined 27,749 children from the largest Anglophone school board, born from 1987 to 1998. A special needs team identified children with pervasive developmental disorders (PDD). The cumulative exposure to thimerosal (ethylmercury, the most frequently cited suspect agent) ranged from 100-185 mcg from 1987-1991 to 200-225 mcg from 1992-1995 to nil from 1996, when the use of thimerosal was discontinued in Canada, and thereafter. (Thmerosal use as a preservative was discontinued in the US in 2004.) The MMR immunization schedule was a single dose at 12 months of age up to 1995 and a second dose at 18 months of age after 1996. A diagnosis of PDD was found in 180 children of whom 82.8% were males. The incidence was thus 64.9/10,000. The incidences of specific sub-types (per 10,000) were autistic disorder 21.6, PDD not otherwise specified 32.8, Asperger syndrome10.1. The combined incidence of Asperger syndrome and autistic disorder was 2.7/500 which is higher than the oft-quoted figure of 1/300-1/500 but in keeping with recent estimates.. There was a statistically-significant, linear increase in PDD incidence throughout the study period. The prevalence of PDD in the thimerosal-free birth cohorts was significantly higher than that in the thimerosal-exposed birth cohorts (82.7 vs. 59.5 per 10,000). When thimerosal exposure was used either as a continuous or a categorical variable, no significant effect on PDD incidence could be demonstrated. MMR immunization coverage in the study group declined from 96.1% in the older cohorts (1988-89) to 92.4% in the younger ones (1996-98). The rise in the rate of PDD did not change after the introduction of a second dose of MMR vaccine and continued to increase even in the face of declining MMR immunization coverage or the discontinuation of thimerosal.

These authors note that the incidence of PDD has been increasing in recent birth cohorts in most countries as found in their study. Reasons for this could include broader diagnostic criteria and increased public awareness. Their findings ruled out any association between ethylmercury exposure (comparable to that experienced in the USA in the 1990s) or one vs. two doses of MMR vaccine. This study would seem to answer

criticisms from some quarters that some other contaminant such as aluminum, could be the toxic agent in MMR vaccine causing an increased risk of ASD.

Other studies could not identify any difference in the immune response to measles or MMR vaccine between ASD children and typically developing children (8), nor did fecal calprotectin measurements (an indicator of bowel inflammation) indicate that vaccination with either MMR vaccine or Pentavac* caused an intestinal inflammatory response (9). Nonetheless, a report on the demographics and clinical characteristics of children reported to the (US) Vaccine Adverse Event reporting System (VAERS) as having a PDD emerge after vaccination, found that 27 of 31 (87%) had autism/ASD and 19 (61.3%) had evidence of developmental regression (loss of social, language or motor skills) (10). These were higher incidences than in the reported in the general population and the authors speculate that this may reflect preferential reporting of autism with regression. These authors leave the door ajar, however, by stating that "Further research might determine whether the pathogenesis of autism with developmental regression differs from that of autism without regression".

A survey in 2005 of vaccine-critical websites identified some common characteristics including statements linking vaccination with idiopathic chronic diseases such as multiple sclerosis, autism and diabetes, and charges that vaccines contained contaminants like mercury. Other allegations were that "hot lots" caused adverse reactions. There were claims that vaccinations provide only temporary protection or none at all. Charges of conspiracies and cover-ups also were made (11). Nothing much has changed. Similar claims and charges are levied on a blog devoted to Jenny McCarthy's appearance on Oprah (12). Predictably, quacks are now hawking "chelation" remedies purporting to remove heavy metals from children's bodies with clay applied to the skin or oral treatments that are supposed to remove them through the urine.

Celebrities have immense power to do good when they exploit their fame in a worthy cause. They also have the power to cause harm, especially when they enter the arena of science and medicine without appropriate qualifications. Jenny McCarthy has an autistic son and to her credit has done much to raise awareness of the nature and extent of the problem of Autism Spectrum Disorders (ASD). She is the spokesperson for TACA (Talking About Curing Autism). In her Sept. 19/'07 appearance on the Oprah TV show, however, she reinforced the common belief that vaccination with MMR vaccine was a causal agent for ASD.

Medicine and science strive to promote decision-making based on the best available evidence (evidence-based medicine). These efforts are undermined by unsubstantiated claims made on the internet and by the actions of fringe groups like anti-vaccination fringes and conspiracy theorists as well as those seeking to line their pockets by exploiting desperate parents. Celebrities, regardless of how well meaning they may be, must seek to obtain the best available information before using their fame for a cause. It is understandable but unfortunate that judgement is often clouded by emotion. Finally, any problems associated with vaccines should not be viewed in the absence of

consideration of their protective value. The risk-benefit analysis should always be conducted.

Footnote: There is one area in which a non-active ingredient of vaccines has been associated with an adverse reaction. Bergfors *et al.* (13) noted that during vaccine trials in the '90s a high incidence of pruritic (itching) nodules was seen in 645 cases of 76,000 recipients of a multi-agent vaccine. 77% of these were associated with an allergy to aluminum. The authors report on 19 cases of pruritic nodules at the injection site after vaccination with Pentavac or Infanrix. These signs and symptoms persisted for up to seven years. The authors note that sensitization to aluminum following vaccination with aluminum-adsorbed vaccines is a low risk but one that should stimulate research for alternative adjuvants.

*diphtheria, tetanus, polio, whooping cough and Haemophilus influenzae type B.

References

1. Wakefield AJ, Murch SH, Anthony A, *et al*. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder. Lancet 351: 637-641, 1998.
2. Burgess DC, Burgess MA, Leask J. The MMR vaccination and autism controversy in United Kingdom1998-2005: inevitable community outrage or failure of risk communication? Vaccine 24: 3921-3928, 2006.
3. Murch SH, Anthony A, Cason DH *et al*. Retraction of an interpretation. Lancet 363: 750, 2004.
4. Klein KC, Diehl EB. Relationship between MMR vaccine and autism. Ann Pharmacother 38: 1297-1300, 2004.
5. Demicheli V, Jefferson T, Riveti A, Price D. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev Oct 19;(4): CD004407.2005
6. Richler J, Luyster R, Risi S, *et al.* Is there a 'regressive phenotype' of Autism Spectrum Disorder associated with the measles-mumps-rubella vaccine? A CPEA study. J Autism Dev Disord 36: 299-316, 2006.
7. Fombonne E, Zakarian R, Bennett A, Meng L, McClean-Haywood D. Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunization. Pediatrics 118: e139-150, 2006.
8. Baird G, Pickles A, Simonoff E. *et al.* Measles vaccination and antibody response in autism spectrum children. Arch Dis Child Feb 5, 2008 (epub ahead of publication.)
9. Thornjorrleifsson B, Daviosdotter K, Agnarsson U, *et al.* Effect of Pentavac and MMR vaccination on the intestine. Gut 51: 816-817, 2002.
10. Woo EJ, Ball R, Landa R, *et al.* Developmental regression and autism reported to the Vaccine Adverse Event Reporting System. Autism 11: 301-310, 2007.
11. Zimmerman RK, Wolfe RM, Fox DE, *et al.* Vaccine criticism on the world wide web. J Med Internet Res 7: e17, 2005.
12. http://adventuresinautism.blogspot.com/2007/09/jenny-mccarthy-on-oprah-vaccine-injury

13. Bergfors E, Bjorklund C, Trollfors B. Nineteen cases of persistent pruritic nodules and contact allergy to aluminium after injection of commonly used aluminium-adsorbed vaccines. Eur J Pediatr 164; 691-697, 2005.