ENCYCLOPEDIA
on Early Childhood
Development

[Archived] Autism and Immunization

Eric Fombonne, MD, FRCPsych

McGill University and The Montreal Children's Hospital, Canada

January 2006

Introduction

Over the last seven years, a controversy has developed about the possible etiological role of immunization with respect to autism. The controversy has involved two separate hypotheses. The first hypothesis posited a link between the Measles-Mumps-Rubella (MMR) immunization and autism, and more specifically between the measles component of the MMR vaccine and autism. The second hypothesis involved the exposure of young children through the immunization schedule to excessive amounts of thimerosal, a mercury-based chemical used since the 1930s to stabilize vaccine preparation. These two hypotheses are different, since there is no thimerosal in the MMR vaccine (and never was). Accordingly, each of these hypotheses has given rise to two separate research endeavours, which are summarized below.

Recent Research Results

The MMR hypothesis

In 1998, the publication by a prestigious medical journal of a small case series of 12 children presenting in a gastroenterology department in a London hospital raised the possibility of a new

©2006-2026 ABILIO | IMMUNIZATION

syndrome associating intestinal symptoms, loss of acquired skills and regression in the course of the development, and autism.[1] These children were presumably normal before the regression, which occurred within 14 days of the MMR immunization according to retrospective parental reports. However, no attempts were made to corroborate these retrospective accounts. Neurological investigations showed no signs of brain inflammation or disorder associated with this clinical picture. Endoscopies found lymphoid nodular hyperplasia and chronic colitis, both non-specific inflammatory lesions from the intestine. In the years following this initial report, Wakefield changed his hypothesis and postulated that atypical patterns of exposure to measles virus were a risk for chronic intestinal inflammation and for autistic enterocolitis, a presumably new syndrome. Persistent measles virus infection was thought to increase gut permeability and allow intake of neurotoxins in the body. In susceptible children, MMR would therefore increase the risk of intestinal infection and developmental regression.[2] Wakefield further hypothesized that the widespread use of MMR since the 1970s had been responsible for the epidemic of autism in the world.[3] Several of these predictions have been tested, using a range of different epidemiological designs.

First, to address the issue of a possible epidemic of autism, several reviews of the existing literature on this topic indicated that it was not possible to conclude that the incidence of autism had truly increased over time. Several reports using referral statistics to educational services were shown to be methodologically flawed[4] and inappropriate for testing the hypothesis of a secular increase in the incidence. Evidence was provided by several authors[5,6,7,8] that a substantial proportion of the increase in prevalence of autism and related conditions was due to diagnostic switching, changes in diagnostic criteria, improved detection of autism in populations and increased awareness of the disorder in the professional and lay audience.

Second, several investigators examined the relationship between changes in immunization practices and rates of diagnosed autism. If there was an association between MMR and autism, rates of autism should have increased when MMR immunization uptake was going up, and conversely. Taylor et al[9] investigated this possibility in a London study where they found no evidence that the massive introduction of MMR in the U.K. in 1988 was associated with a step-up in the rates of autism, a finding subsequently replicated in the same country by Chen et al.[10] In addition, a case series analysis conducted by these researchers failed to document a clustering of onset of autism following MMR immunization. Other ecological studies were conducted by Kaye et al[11] who showed that rates of autism in the U.K. increased between 1988 and 1993, at a time

©2006-2026 ABILIO | IMMUNIZATION

when there was no change in the uptake of MMR in the population. The same approach, used by Dales et al[12] in California, also indicated that the number of children diagnosed with autism rose between 1979 and 1995, at a time where MMR coverage in two-year-old children in that population remained stable. In Sweden, Gillberg and Heijbel[13] compared two birth cohorts born in 1975-1980 and 1980-1984 that had respectively low and high MMR coverage. In these two cohorts, there were no differences in the rate of autism and in fact, the rate of autism was slightly lower in the high MMR coverage cohort.

Third, systematic reviews of adverse events following the introduction of MMR were carried out in several countries. In Finland, Patja et al[14] followed 1.8 million individuals after the introduction of MMR immunization in that country in 1982. The incidence of serious events was low (173 serious events; 3.2 per 10,000 vaccine doses), involving a neurological reaction in 77 children, with no mention of autism ever.

Fourth, since Wakefield had postulated earlier that exposure to the measles virus was also explaining increasing rates of Crohn's disease and other inflammatory bowel disorders, some investigators examined whether or not there was an increase in the rate of inflammatory bowel disorders in autism. If such an association was found, that could have given support to Wakefield's hypothesis. Fombonne[15] examined two large series of 1987 subjects with PDD referred in a London hospital and 174 children with autism included in a large epidemiological survey of educational and psychiatric handicaps in France. In both datasets, controlled data were available and no cases of Crohn's disease or ulcerative colitis were found in any of the autism series, whereas a few cases were found among the controls, consistent with a low incidence of these disorders in children. Black et al,[16] relying on an electronic database used in general practice in the U.K., also failed to document an increased incidence in children with autism compared to controls of celiac disease, ulcerative colitis, malabsorption, food intolerance and chronic gastroenteritis.

Fifth, systematic reviews of vaccine safety are regularly performed with monitoring systems such as the Vaccine Adverse Event Reporting System maintained by the Centers for Disease Control and Prevention (CDC) in the United States. The CDC also uses the Vaccine Safety Datalink to perform case control and cohort studies to examine negative outcomes following exposure to specific vaccines. Before Wakefield's paper, there had been no report of autism as a possible adverse event following measles vaccine or MMR vaccine. Indeed, a systematic review of all the literature performed by the Institute of Medicine in 1994 reviewed in detail the safety of the

©2006-2026 ABILIO | IMMUNIZATION

triple MMR vaccine, and no mention of autism can be found in this report.[17]

Sixth, investigations were performed to validate the new autistic enterocolitis syndrome postulated by Wakefield. Fombonne and Chakrabarti[18] used an epidemiological representative sample of 96 children with PDD, all but one of whom had received MMR immunization at the age of 13.5 months. In this epidemiological study, there was no evidence for an increased incidence of childhood disintegrative disorder, a particular form of PDD associated with massive regression in development. Compared to another sample that was not exposed to MMR, no difference was found for the mean age at which parents first became concerned with their child's development. In addition, the rates of regressive autism in exposed and unexposed-to-MMR children were not different, suggesting that there had been no increase over time in the rates of regressive autism. Further analyses showed that the children who regressed did not differ from those without regression for the mean age of parental recognition of symptoms and for their levels of autistic symptoms. Furthermore, in that study, there was no association between regression in the developmental course of autistic children and the incidence of gastrointestinal symptoms. This investigation gave no support for the validation of the so-called new syndrome of autistic enterocolitis. Another group also showed that regressive autism had not increased after the introduction of MMR in the U.K.,[19] although in this study, children with regression tended to report more gastrointestinal symptoms. In a similar vein, DeWilde et al[20] used an electronic general practitioner English database and showed that compared to matched controls, children with PDD were no more likely to consult their general practitioner in the month following MMR immunization.

Finally, two large epidemiological studies have focused specifically on the role of individual exposure to MMR and the subsequent onset of autism. In the first study, Danish children born from 1991 to 1998 were followed from the end of their first year for several years (n = over 537,000). MMR had been introduced in Denmark in 1987 and was usually given at the age of 15 months. The study relied on linkages between national registries to establish diagnostic status and measure exposure. In that large sample, 82% of children were vaccinated at an average age of 17 months, and 738 children were diagnosed with autism or PDD at the end of the follow-up period. No association was found between autism and MMR exposure and between MRR and PDD. The adjusted risk ratios were below one in a study that was extremely well powered.[21] A more recent study adopted a case-control design and recruited 1,294 PDD cases matched to 4,469 controls, all selected from the general practitioner research database in the U.K. The

validity of the diagnosis was confirmed on a sub-sample[22] and MMR vaccination was not associated with an increased risk of PDD in that study (adjusted odds ratio .86).[23] These authors also conducted a quantitative analysis of published studies that indicated a combined odds ratio across studies of 0.87 (95% confidence interval, .76 to 1.001), again strongly suggestive of no association between MMR exposure and autism. The latter two studies could not perform separate analyses for the regressive subtype of autism but, as shown in previous studies attempting to validate the autistic enterocolitis phenotype, there is little evidence of its distinctiveness. To date, therefore, all epidemiological studies have failed to document an association between autism and MMR,[24] and recent reviews of this hypothesis by the Institute of Medicine concluded that the evidence was in favour of rejecting the hypothesis.[25]

The biological mechanisms that may underlie this association are as yet ill defined. Uhlmann et al[26] have reported an identification of the measles virus genome in the gut of 75 of 91 children with developmental problems, compared to five out of 70 normal controls. This work has not been replicated in independent laboratories. Concerns have been raised about the techniques used, the possibility of contamination, and uncertainties about the identification of the measles virus genome as coming from a vaccine strain. Even if these findings were replicated, it cannot be inferred that the measles virus is a cause of autism (rather than a consequence) in a context where all human studies that have assessed the risk of autism following MMR exposures are negative.

The thimerosal hypothesis

Thimerosal is a form of organic ethyl mercury that has been used since 1930 as a preservative for stabilization of vaccines. In 1998, the Food and Drug Administration reviewed the immunization schedule of infants in the U.S. and concluded that exposure to mercury of infants up to age 18 months exceeded the limits set by various agencies. In July 1999, a joint statement by the American Academy of Pediatrics and the Public Health Service called for the removal of thimerosal from all U.S. licensed vaccines. Most vaccinations now exist in a thimerosal-free format. High-dose exposure to mercury can produce kidney and neurological damage. Most of the mercury intoxications described in the literature concern methyl mercury; much less is known about ethyl mercury. Massive intoxications occurred in industrial disasters, such as in Minamata Bay, Japan, or in Iraq in the early 1970s. Children exposed to high doses of methyl mercury were followed and again, no increased incidence of autism has ever been documented. Similarly, two ongoing cohort studies in the Faroe Islands and the Seychelles are studying the

©2006-2026 ABILIO | IMMUNIZATION

long-term cognitive and neurological outcomes of prenatal and postnatal exposure to methyl mercury. In these fish-eating populations, it is well documented that mercury levels are many times higher than in other populations. The findings from these two cohorts have so far been inconsistent with subtle psychological deficits (in the areas of attention, memory and language) reported in the Faroe Islands study,[27] whereas the study in the Seychelles[28] has failed to replicate these findings.

Following the 1999 thimerosal scare, a controlled observational study was conducted in Denmark by Hviid et al,[29] who compared Danish children who had received thimerosal-containing vaccine or thimerosal-free vaccines following a 1992 change in the nationwide production of pertussis vaccine. The study included over 540,000 children, 407 of whom were diagnosed with autism and 751 with other PDDs during the study. The adjusted rate ratios were non-significant both for autism (0.85) and for other PDDs (1.12). Furthermore, there was no dose-response relationship between increasing levels of methyl mercury exposure and risk of autism. Another controlled observational study was conducted in the Vaccine Safety Datalink by Verstratten et al.[30] The study was conducted in two phases and autism was examined as a potential neurodevelopmental outcome associated with exposure to mercury in the first phase of that study. A sample of 124,000 children were followed in two health maintenance organizations up to the date of an autism diagnosis or the end of the follow-up period. In the health maintenance organization where sufficient numbers were detected, 202 children with autism were identified. Analysis of mercury exposure, treated either as a continuous or a categorical variable, showed no association with the risk of autism.

Madsen et al[31] examined trends in autism rates in Denmark before and after the use of thimerosal-containing vaccines was discontinued in 1992. Incidence rates were calculated for the period 1971-2000. The rates remained level up to 1990, when they started to increase, with a peak in 1999. As autism rates continued to go up after the discontinuation of thimerosal in the vaccines, the study concluded that there was no support for an association between thimerosal and autism. A comparable study was conducted in Denmark by Stehr-Green et al,[32] who also showed that rates of autism increased while thimerosal was progressively eliminated from vaccines in Denmark. The same authors also included data from Sweden, which showed that the incidence of autism increased in the mid to late 1980s up to 1993. As for Denmark, rates of autism continued to go up when thimerosal was practically completely eliminated from the immunization schedule.

Some attempts have been made to reanalyze the CDC data[33,34] but methodological flaws in their analyses have precluded an interpretation of their findings.[25] Andrews et al[35] have analyzed the U.K. general practice database between 1988 and 1999. A total of 104 children were diagnosed with autism in this sample of 100,572 children. Hazard ratios for autism, after receiving increasing doses of thimerosal, were all non-significant.

Conclusion

Thus, there appears to be no epidemiological study that has confirmed a possible increase in the risk of autism or PDD in children as a function of exposure to the ethyl mercury used in some vaccine preparations. A review of this hypothesis by the Institute of Medicine Ad Hoc Committee concluded that the evidence was in favour of rejecting the hypothesis.[25]

References

1. 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(9103):637-641.
2. Wakefield AJ, Anthony A, Murch SH, Thomson M, Montgomery SM, Davies S, O'Leary JJ, Berelowitz M, Walker-Smith JA. Enterocolitis in children with developmental disorders. *American Journal of Gastroenterology* 2000;95(9):2285-2295.
3. Wakefield AJ. MMR vaccination and autism. *Lancet* 1999;354(9182):949-950.
4. Fombonne E. Is there an epidemic of autism? *Pediatrics* 2001;107(2):411-413.
5. Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: An update. *Journal of Autism and Developmental Disorders* 2003;33(4):365-382.
6. Gurney JG, Fritz MS, Ness KK, Sievers P, Newschaffer CJ, Shapiro EG. Analysis of prevalence trends of autism spectrum disorder in Minnesota [comment]. *Archives of Pediatrics and Adolescent Medicine* 2003;157(7):622-627.
7. Croen LA, Grether JK, Hoogstrate J, Selvin S: The changing prevalence of autism in California. *Journal of Autism and Developmental Disorders* 2002;32(3):207-215.
8. Jick H, Kaye JA. Epidemiology and possible causes of autism. *Pharmacotherapy* 2003;23(12):1524-1530.
9. Taylor B, Miller E, Farrington CP, Petropoulos MC, Favot-Mayaud I, Li J, Waight PA. Autism and measles, mumps, and rubella vaccine: no epidemological evidence for a causal association. *Lancet* 1999;353(9169):2026-2029.
10. Chen W, Landau S, Sham P, Fombonne E. No evidence for links between autism, MMR and measles virus. *Psychological Medicine* 2004;34(3):543-553.
11. Kaye JA, Melero-Montes MD, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ - British Medical Journal* 2001;322(7284):460-463.
12. Dales L, Hammer SJ, Smith NJ. Time trends in autism and MMR immunization coverage in California. *JAMA - Journal of the American Medical Association* 2001;285(9):1183-1185.

©2006-2026 ABILIO | IMMUNIZATION

13. Whiteley P, Rodgers J, Shattock P. MMR and autism. *Autism* 2000;4(2):207-211.

14. 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. *Pediatric Infectious Disease Journal* 2000;19(12):1127-1134.

15. Fombonne E. Inflammatory bowel disease and autism. *Lancet* 1998;351(9107):955.

16. 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 - British Medical Journal* 2002;325(7361):419-421.

17. Institute of Medicine (IOM). *Adverse events associated with childhood vaccines: Evidence bearing on causality*. Washington, DC: National Academies Press; 1994.

18. Fombonne E, Chakrabarti S. No evidence for a new variant of measles-mumps-rubella-induced autism. *Pediatrics* 2001;108(4):E58.

19. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: Population study. *BMJ - British Medical Journal* 2002;324(7334):393-396.

20. DeWilde S, Carey IM, Richards N, Hilton SR, Cook DG. Do children who become autistic consult more often after MMR vaccination? *British Journal of General Practice* 2001;51(464):226-227.

21. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M. A population-based study of measles, mumps, and rubella vaccination and autism. *New England Journal of Medicine* 2002;347(19):1477-1482.

22. Fombonne E, Heavey L, Smeeth L, Rodrigues LC, Cook C, Smith PG, Meng L, Hall A. Validation of the diagnosis of autism in general practitioner records. *BMC Public Health* 2004;4:5.

23. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, Hall AJ. MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* 2004;364(9438):963-969.

24. Fombonne E, Cook EH. MMR and autistic enterocolitis: consistent epidemiological failure to find an association. *Molecular Psychiatry* 2003;8(2):133-134.

25. Institute of Medicine (IOM). *Immunization safety review: Vaccines and autism*. Washington, DC: National Academies Press; 2004.

26. 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. *Journal of Clinical Pathology-Molecular Pathology* 2002;55(2):84-90.

27. Davidson PW, Myers GJ, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, Cernichiari E, Needham L, Choi A, Wang Y, Berlin M, Clarkson TW. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. *JAMA – Journal of the American Medical Association* 1998;280(8):701-707.

28. Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R, Jorgensen PJ. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicology and Teratology* 1997;19(6):417-428.

29. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. *JAMA - Journal of the American Medical Association* 2003;290(13):1763-1766.

30. Verstraeten T, Davis RL, DeStefano F, Lieu TA, Rhodes PH, Black SB, Shinefield H, Chen RT; Vaccine Safety Datalink Team. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization

databases. *Pediatrics* 2003;112(5):1039-1048.

31. Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB. Thimerosal and the occurrence of autism: Negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112(3):604-606.

32. Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D. Autism and thimerosal-containing vaccines: Lack of consistent evidence for an association. *American Journal of Preventive Medicine* 2003;25(2):101-106.

33. Geier DA, Geier MR. An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. *Pediatric Rehabilitation* 2003;6(2):97-102.

34. Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. *Medical Science Monitor* 2004;10(3):PI33-PI39.

35. Andrews N, Miller E, Grant A, Stowe J, Osborne V, Taylor B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association. Pediatrics 2004;114(3):584-591.

©2006-2026 ABILIO | IMMUNIZATION