

# **Respondent's Exhibit P**

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**Background and Experience**

1. I am a Professor of Psychiatry and the Head of the Division of Child Psychiatry of McGill University. I am also the Director of the Department of Psychiatry and Director of the Autism Spectrum Program at the Montreal Children's Hospital.
2. I received my medical degree in 1978 from University of Paris V, and won a special distinction for my MD thesis. I received a Masters Certificate in Biostatistic Methods and Human Physiology in 1977. I have a specialization in General Psychiatry and Child and Adolescent Psychiatry.
3. I was a Reader in Epidemiological Child Psychiatry at the University of London (a unique position created in recognition of my epidemiologic expertise in the area of child psychiatry). I have taught epidemiological methodology to physicians and public health workers. Over the course of my career, I have designed, executed, analyzed, and published dozens of epidemiologic studies involving autism and other child psychiatric disorders. All of the studies were funded by either public health organizations or private charitable not-for-profit organizations. None of my research has been funded by private industry.

4. I have had a long-standing professional interest in autism. My research career started in 1984 with the planning of the first population-based epidemiological survey of child psychiatric disorders ever conducted in France. In 1986, I was invited to consult with other professionals (mostly clinicians) to develop an autism research program in France. I subsequently obtained a grant to conduct a large multicenter study of autistic adolescents and developmentally-delayed controls. I also obtained a separate grant with a U.K. group of investigators to examine the neuropsychology of autism. In London, in 1988, I acquired clinical expertise in the assessment and diagnosis of subjects with autism, being one of the first to obtain training on the newly devised diagnostic measure, the Autism Diagnostic Interview (ADI). In 1990, I provided autism expertise in a survey conducted by an Institut National de la Santé et de la Recherche Médicale (INSERM) team, which led to the publication of the first autism survey in France in 1992 (Fombonne & Du Mazaubrun, 1992).

5. In 1993, I accepted an academic position at the Maudsley Hospital and Institute of Psychiatry in London, and worked with the child psychiatric group headed by Professor Michael Rutter. My research activities focused on autism including: an adoption study of children with autism, a family study of autism, the first molecular genetic investigation of autism, epidemiological surveys of autism, and studies of the putative links between autism and the measles-mumps-rubella (MMR) immunization. I served as a consultant to the Department of Health and the Medical Research Council in the U.K. to review the hypothesis of links between measles-mumps-rubella (MMR) immunization and autism.

6. From 1991 to 1994, I was a member of a small study group of international scholars assembled by Professor Rutter on behalf of the Academia Europaea to review the evidence for secular changes in the incidence of psychosocial disorders in young people. This work

culminated in a book that assessed the evidence for increasing rates of problems such as crime, juvenile delinquency, depression, eating disorders, suicide, and alcohol and drug use in young people in various countries in the second half of the twentieth century (Rutter & Smith, 1995). During those years, I gained expertise in reviewing hypotheses on changes over time in the incidence of disorders. In addition to the two chapters authored in the Rutter and Smith book (Fombonne 1995), I published several scientific articles on the topic (i.e., Fombonne, 1995; Fombonne, 1996; Fombonne, 1998). In 1996, I published on the issue of secular changes in the incidence or prevalence of autism in an editorial column (Fombonne, 1996). I was the first investigator in the field of autism to empirically address the issue, using epidemiological data to test whether or not autism was on the rise (Fombonne et al., 1997). At the end of my stay in the U.K., I published two papers that have been regarded as very influential for the epidemiology of autism and for the hypothesis of links between MMR immunization and regressive autism (Chakrabarti & Fombonne, 2001; Fombonne & Chakrabarti, 2001).

7. In 2001, I moved to the Montreal Children's Hospital, McGill University, in Canada. I have been specially appointed to the Canada Research Chair in Child Psychiatry. I have developed an independent research program on autism at McGill. I have been funded recently to conduct several studies of autism including a study of the exposure to environmental neurotoxicants (including mercury), a new molecular genetic study of autism, an epidemiological survey of autism in Montreal, a randomized clinical trial of an intervention to promote language development in young preschoolers with autism, a longitudinal study of autistic preschool children, and a study of the outcome of autism in adult life. I am the Principal Investigator on a large Canadian grant to train and attract to autism research young trainees from all disciplines and, as part of this training program, I have organized the first summer school on autism since 2004 at

McGill University; this program continues and has already funded 32 fellows to boost research capacity on autism in Canada.

8. I have been directly involved in the design, execution, and analysis of 10 different epidemiological surveys of autism (2 in France, 3 in the U.K., 3 in Canada, 1 in South Korea, and 1 in Australia) and I have been providing consultancies on surveys conducted by other research groups, including three in the U.S. – the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, the University of Utah, and the M.I.N.D. Institute in Sacramento, CA.

9. Throughout the years, I have maintained my clinical practice. When I was at the Maudsley Hospital, I was the leading consultant of the autism service, a national team that received referrals from throughout the U.K. for complex cases. My current clinical practice involves assessing, treating, and following up autistic patients of all ages; I also consult about the assessment and management of complex psychiatric cases referred to me by colleagues, especially in the field of affective disorders. Currently, I have ongoing clinical activities and every week assess new patients with suspected pervasive developmental disorders (PDDs) from birth to adult life. I assess over 150 new cases per year and carry a caseload of about 250 autistic children currently.

10. Over the years I have been an advocate for children with autism and their families. I have volunteered my time by attending and lecturing at parent-run advocacy groups for the treatment and the development of services for autistic children.

11. I have trained many professionals and residents in the assessment of patients with autism. I am a teacher for trainees in child psychiatry and other mental health professionals. I spend a considerable amount of time giving seminars for residents, presentations and academic grand rounds at various University hospitals, and providing lectures for the community. I have a

specific training expertise in assessment tools used in the field of autism research. I organize regular training seminars and workshops to train my clinical and research staff and professionals in the community in up-to-date and modern techniques used in the field of PDDs.

12. I am a regular reviewer of research papers on autism for numerous journals and, from 1994 to 2003, I was the associate editor of the *Journal of Autism and Developmental Disorders*, a leading journal in the field of autism.

13. I have served as a consultant to various agencies such as the CDC, the Institute of Medicine (IOM) in Washington, DC, the American Academy of Pediatrics (AAP), the Medical Research Council in the U.K., the M.I.N.D. Institute, and the National Institutes of Health (NIH) in Bethesda, MD. I was a permanent reviewer for one scientific review committee of the National Institute of Mental Health for the period 2002-2006. I am on the Advisory Board of various organizations such as the Canadian Autism Intervention Research Network (CAIRN) and the UC Davis Center for Children's Environmental Health, and I am a member of the Advisory Committee set up by the NIH, NICHD and NIMH to oversee the autism research activities funded in the U.S. as part of the CPEA and STAART Centres (now Autism Centers of Excellence). I was a member of the Planning Committee of a special Neurosciences Seminar on autism and environmental risk factors, organized by the IOM on April 18-19, 2007.

14. I have published over 150 scientific articles in peer-reviewed journals, four books, and 33 chapters.

15. Further information on my background and qualifications is given in my curriculum vitae.

### **Standard for My Opinions**

16. On the basis of my review of the literature and my knowledge, skill, education, experience, research, and training in the fields of Autism and Epidemiology, I have formed the following opinions to a reasonable degree of medical certainty:

17. It is my opinion, to a reasonable degree of scientific and medical certainty, that MMR vaccine or thimerosal-containing vaccines do not cause autism. The claim that there is an autism epidemic caused by vaccinations is unfounded, without reliable scientific support, and is not generally accepted in the autism research community. There is no reliable scientific or medical basis to support a conclusion that there is an association or a causal relationship between MMR or thimerosal-containing vaccines and autism spectrum disorders, and the evidence favors rejection of such a causal relationship.

### **Pervasive Developmental Disorders**

18. Autism Spectrum Disorders (ASDs) are referred to as PDDs in the two current diagnostic classification systems, the *Diagnostic & Statistical Manual, 4<sup>th</sup> Edition, Text Revision (DSM-IV)* of the American Psychiatric Association and the *International Classification of Diseases, 10<sup>th</sup> Edition (ICD-10)* of the World Health Organization. “Autism” is a term that refers to ASDs and PDDs and also is often used as a shorthand reference to one of the specific ASDs, Autistic Disorder.

19. Autism is a disorder that has been recognized, although not named, for hundreds of years. It clearly pre-dates the use of thimerosal in vaccines and other biologicals. Uta Frith, an autism researcher in the U.K., has described the autistic characteristics of Brother Juniper, a 12<sup>th</sup> Century monk, and the Wild Boy of Aveyron, who was found in the wild in France in the 18<sup>th</sup> Century (Frith, 2003). Childhood Disintegrative Disorder, a rare form of severe regressive

autism, was first described in 1908 by Heller as “dementia infantilis” (Heller, 1908). The European medical literature, as early as 1926, contained detailed clinical descriptions of children with symptom patterns typical of those described later as Asperger’s Disorder (Wolff, 1996). The name “autism” was first coined in 1943 by Leo Kanner of Johns Hopkins, who reported on his observations of 11 children who he was seeing with significant social and language deficits and impairment of imaginative play.

20. PDDs are a class of disorders characterized by severe impairments in three developmental domains: communication skills (both language and non-verbal communication); social interaction and reciprocity; and unusual pattern of play, interests, activities, and behaviors. The particular behaviors that index the developmental deficits in the three domains outlined above vary from one individual to the other, within an individual according to age, and according to the overall level of functioning or of intelligence.

21. The DSM-IV provides diagnostic criteria for disorders that are usually first diagnosed during infancy and childhood; it is the standard used to diagnose PDDs in many parts of the world, including in both the U.S. and Canada. It classifies and provides the diagnostic criteria for five Pervasive Developmental Disorders – (1) Autistic Disorder, (2) Rett’s Disorder, (3) Childhood Disintegrative Disorder (CDD), (4) Asperger’s Disorder, and (5) Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS). These PDDs constitute what are referred to as Autism Spectrum Disorders. For consistency and convention, throughout this report I use the term Autism Spectrum Disorder (or ASD) to refer to these PDDs (except for Rett’s Disorder, as discussed below).

22. Rett’s Disorder affects mostly females and is due to a defect on the MECP2 gene localized on the chromosome X (Amir et al., 1999). Because its phenomenology, causes, and

outcome are different from the other PDDs, Rett's Disorder is not included in studies of autistic samples.

23. Childhood disintegrative disorder (CDD) represents a very rare form of ASD (Fombonne, 2002). It is a severe form of autism that differs from Autistic Disorder by its developmental trajectory. In CDD, there is evidence of unambiguous normal development up to at least age 2. After this period of normal development, on average at about 3 years of age, there is a profound regression and loss of skills in at least two domains (language, social skills and adaptive behavior, bowel and bladder control, play, and motor skills) that leads to a clinical picture similar to severe autism.

24. Asperger's Disorder presents the same abnormalities of Autistic Disorder for the social interactive skills and the patterns of abnormal play and interests, but differs insofar as language development proceeds largely within normal limits (i.e., the child uses phrase speech by age 3). In addition, with Asperger's Disorder, there is no mental retardation, whereas approximately 70% of patients with Autistic Disorder are also mentally retarded.

25. The diagnostic criteria for Autistic Disorder consist of a detailed listing of social, communicative, and behavioral symptoms. The diagnosis of Autistic Disorder requires deficits in each of three domains of early development: (1) impairment in social interaction (lack of eye contact, impaired peer relationships, lack of spontaneous seeking of shared experiences, and of social reciprocity); (2) impairment in communication (delay of spoken language, impairment of conversational skills, use of repetitive and idiosyncratic language, lack of imaginative play); and (3) restricted, repetitive, and stereotyped behaviors (restricted patterns of interest, inflexible routines and rituals, stereotypical motor mannerisms, preoccupation with parts of objects). Impairments within these three areas must be evidenced with an onset of symptoms prior to age 3.

If these criteria are met, then the clinician must still rule out Rett's and CDD before a diagnosis of Autistic Disorder can be made.

26. Autistic Disorder is the appropriate diagnosis for children who present with all the typical symptoms of autism. It is used when the child meets full diagnostic criteria as outlined in major nosographies (classifications), such as the DSM-IV or ICD-10. The DSM-IV requires that the child show at least six out of a list of twelve possible symptoms. There must be evidence of two symptoms involving social development, and at least one symptom involving each of the domains of communication malfunction and abnormal pattern of play. The first symptoms must be identified as having existed before the third birthday.

27. The next diagnostic category in the DSM-IV is PDDNOS. PDDNOS is also referred to as atypical autism. This category is used for those children who present the autistic abnormalities but fall short of full diagnostic criteria for autism. For example, the child may have the same symptoms as another child with Autistic Disorder, but the parents may have detected the first developmental abnormality only after age three.

28. The diagnostic assessment of ASD is made by reviewing the current behaviors of an individual and reviewing his past developmental history. The diagnosis usually involves a direct assessment of the child using standardized tasks and activities designed to elicit the particular communication, social, and play deficits of children with ASDs. This is usually complemented by a detailed developmental interview using the parent as the source of information to elicit information about past and current symptoms, as seen in different contexts and over time. An ASD diagnosis is made solely on the basis of behavioral and developmental abnormalities; there are no biological markers or medical tests that can confirm or disprove the diagnosis.

29. There is a high degree of consensus among world experts on the definition and the procedures required to diagnose and assess subjects with Autistic Disorder (Volkmar et al., 1994; Filipek et al., 2000), and the reliability of the diagnosis (i.e., the extent to which two independent clinicians would arrive at the same diagnostic conclusion) is high for the ASDs.

30. Although classification systems identify separate diagnostic categories or groupings within each class of ASD, there is increasing evidence that the boundaries and differences among these diagnostic categories are somewhat arbitrary and merely represent variations in intensity of the same core underlying deficits. In ongoing molecular genetic studies in which families are ascertained because at least two relatives are affected with an ASD, most research groups have identified families where the two relatives affected within the same family have different diagnoses (e.g., Autistic Disorder and Asperger's Disorder, or PDDNOS and Asperger's Disorder, etc.). The fact that ASD subtypes cluster in families indicates that ASDs have common causal mechanisms.

31. There appears to be no association with social class, as ASDs are found at all social class levels and occur in families with different educational backgrounds. It also appears that autism can occur in different ethnic groups; in all countries where autism has been investigated, cases have been found (Fombonne, 2003 & 2005). There is no evidence that the rates of autism differ across countries or nations, with perhaps one exception amongst the Inuit population of Northern Canada where a preliminary study failed to find any case of autism in a population of approximately 5,000 children (Fombonne et al., 2006).

### **Onset of Autistic Disorder**

32. The onset of Autistic Disorder is difficult to measure and, in most individual children, impossible to determine with precision. The diagnostic criterion of the DSM-IV is that

“onset” of some abnormalities must occur before the third birthday. Rather than being a direct measure of the onset of the disorder, this criterion refers to the time at which parents become aware that the development of their child is not entirely right. Age of parental recognition is influenced by several factors that pertain to the child’s disorder, as well as to other contextual factors. For example, children who have autism and severe mental retardation are more likely to be identified as abnormal by their parents at an earlier age because the child fails very early in his development to achieve some important milestones (i.e., sitting or walking) that are hard to miss. Other studies have also shown that when the autistic child is not the parents’ first-born, the parents’ recognition of autistic symptoms occurs earlier, as they have gained more experience about normal childhood development through their first child; they know what to expect; and they are more quick to recognize deviance or delay in the development of their subsequent child (DeGiacomo & Fombonne, 1998). As in many disorders in medicine (such as cancer), it is therefore likely that the onset of the disorder occurs long before the age at which the first symptoms become manifest to parental eyes.

33. Early manifestations of autism have been extensively studied in the last 20 years. Analyses of home videos and of first birthday parties have allowed early developmental abnormalities to be identified at the end of the first year of life, which characterize children later diagnosed with autism, and that separate them from both typically developing peers and non-autistic mentally retarded controls (Osterling et al., 2002; Werner et al., 2000; Werner & Dawson, 2005; Baranek, 1999; Mars et al., 1998). At 12 months of age, children later diagnosed with autism were more abnormal than control children in such behavior as looking at faces, orientation to their name, communicative babbling, and poorer joint attention behavior. Prospective studies of individual cases (Dawson et al., 2000; Klin et al., 2004) and of high-risk (younger siblings of

autistic children) infants have since confirmed that abnormalities can be detected at 12 months of age in eye contact and visual tracking, social orienting, imitation, social interest and smiling, fixation of objects, and motor and language skills (Zwaigenbaum et al., 2005; Landa & Garrett-Mayer, 2006). These abnormalities may or may not be recognized by parents at the time.

### **Regressive Autism**

34. While some autistic children fail to acquire skills expected as part of normal development (i.e., social smile), or display abnormal behaviors (i.e., hand and finger mannerisms), typically between the age of 9 and 18 months (Carter et al., 1998), there is a subgroup of children with ASDs who appear to develop relatively normally up to a certain age and then lose skills, specifically the use of words to communicate, that they had gained before the first autistic symptoms developed. The loss of words to communicate often co-occurs with the emergence of social deficits that may be less easy to observe and recall. This phenomenon, now called “regressive autism” and referred to as such in the rest of the report, occurs in about 20% of children with either an Autistic Disorder or a PDDNOS diagnosis (Lord et al., 2004; Fombonne & Chakrabarti, 2001). This regressive pattern appears to be highly specific to ASDs, as it is not reported in children who have developmental delays without autism or language disorders (Lord et al., 2004).

35. When the onset of autism occurs with a regressive pattern, parents have tried to identify events that occurred immediately before the regression in order to explain it. This is understandable, but temporal correlation does not mean causation. The emergence of the first symptoms of autism is variable but occurs, by definition, before 3 years of age, and in the majority of cases during the second year of life. For example, in a large study comparing autistic children with and without regression, the mean age of autistic symptom onset was 16.9 and 13.7 months

respectively (Richler et al., 2006). In another recent study of toddlers diagnosed with ASDs, the mean age of symptom recognition in 51 children with Autistic Disorder was 14.7 months (Chawarska et al., 2007). The MMR vaccination is given to children between the ages of 12 and 18 months (in the U.S., most commonly between 15 and 18 months of age). Therefore, the age of onset of autism and the date of MMR vaccination are constrained by an overlapping time window. Thus, it follows that, in many children, the onset of first autistic symptoms will occur just after the MMR vaccination, or in the weeks that follow.

36. It is noteworthy that studies of parental beliefs have shown that parents of children with regressive autism are more likely to believe that the MMR vaccination, or similar causes, are responsible for their child's autism (Lingam et al., 2003; Woo et al., 2004). In previous studies (when MMR was not under consideration), parents attributed the onset of autistic symptoms to various other events such as the birth of a younger sibling, moving house, mother's hospitalization, etc. (Kobayashi et al., 1998). Parents, and more generally, human beings, have a tendency to seek coherence in their life by ascribing personal events to external causes, even when there is no scientific basis for these 'correlations'.

37. It has often been assumed that 'regressive autism' occurs in children whose development was normal up to the point of the loss of skills. In fact, the loss of skills does not mean that the child's development was entirely normal before the regression. Recent studies have suggested that most children with regressive autism displayed subtle developmental abnormalities long before the regression occurred (Rogers, 2004). For example, in a U.S. study of 13 sites funded by the NIH, an evaluation of 163 autistic children with regression showed that 72% were not developing normally before the regression (Richler et al., 2006). Thus, abnormal development can

be documented in children with 'regressive autism' before the regression occurs even though the parents are unaware of it.

38. Even if a child's development were absolutely normal, as is perhaps the case in a small subset of children with regressive autism (Werner & Dawson, 2005), the regressive pattern of behavior does not mean that the cause of the regression is environmental. There are many genetic diseases that manifest only after a period of normal development, followed by a loss of function or regression. A close example to Autistic Disorder is Rett's Disorder, which has an onset between 6 to 24 months of age following a period of unambiguously normal development. Rett's Disorder is due in most cases to a gene defect that has now been identified (Amir et al., 1999). Another example is that of Huntington's disease, which is caused by a single gene mutation that leads to neurological problems and intellectual deterioration, but often not before the third or fourth decade of life.

39. It is well established in the behavioral genetic literature that genetic effects are not necessarily expressed early in life, as genes are programmed to be switched on and off at different times in the lifespan. Thus, the mere fact of a delayed onset of a disorder does not mean that the disorder is not genetic in origin. If regressive autism were triggered by environmental factors, as opposed to genetic ones, then one would expect the rate of autistic characteristics (known as the broad autism phenotype) in relatives of autistic individuals to be lower. However, this is not the case because, in both regressive and non-regressive autistic children, there is no difference in the percentage of their relatives who are also affected with the broad autistic phenotype (Lainhart et al., 2002).

### **Autism and Mental Retardation**

40. Mental retardation is determined based on performance on verbal and non-verbal standardized tests of intelligence, for which multiple batteries exist. When children with ASDs are tested with these standardized IQ tests, about 70% of children with Autistic Disorder score in the range of mental retardation (IQ is below 70). The rates of mental retardation for PDDNOS are slightly lower, but no robust estimate exists for this rather heterogeneous group of subjects. By definition in the DSM-IV, there is no mental retardation associated with Asperger's Disorder. Children with ASDs, and especially Autistic Disorder, also tend to have unusual cognitive profiles on these standardized tests.

### **Macrocephaly in Autism**

41. Children with ASDs have abnormal brain development early in their development. Macrocephaly, or enlarged head circumference, was noted in 5 of the 11 cases described by Kanner in 1943. This pattern of abnormal head growth was confirmed subsequently, with about 20% of subjects having macrocephaly or a head circumference that exceeds the 97<sup>th</sup> percentile of the distribution of head circumferences in typical children (Fombonne et al., 1999). Head circumference is closely correlated with brain volume from birth to age three (Bartholomeusz et al., 2002). Brain neuroimaging (Courchesne et al., 2003; Sparks et al., 2002) and neuropathology findings (Bailey et al. 1998) have confirmed patterns of abnormal brain growth, volume, and weight in autism. Specifically, head circumference is normal at birth; however, at around 4 months of age, enlargement of the brain becomes noticeable (Redcay & Courchesne, 2005). Increased rate of head growth is now well-documented during the first year of life, especially during the second semester of the first year, and recent data indicate that the rate of head growth decelerates in the second year of life where it does not differ from normal head growth (Dawson et al., 2007). Abnormal head growth precedes and overlaps with the appearance of the

first symptoms of autism, and the deceleration of head growth coincides with a worsening of autistic symptoms in the second year of life.

42. A recent, large multisite study in the U.S. has examined correlates of abnormal brain growth in autism, and has investigated the relationship between enlarged head circumference and height in autistic children compared with normally developing controls (Lainhart et al., 2006). An increase in the rate of absolute macrocephaly was reported in autistic children, as has been found in other studies. There was a high correlation between height and head circumference in both autistic and control subjects. When head circumference was compared to height, the rate of relative macrocephaly was high in the autistic group, indicating that abnormal head growth was not accounted for by a growth in height. In fact, a significant discrepancy was reported between height and head circumference, suggesting that the proportionality between height and head circumference is distorted in autistic children. Furthermore, there was no correlation between IQ and head circumference in autistic patients (it was amongst controls). Delayed onset of language was associated with macrocephaly in the autistic subjects.

### **Causation of Autistic Disorder and Other ASDs**

43. The actual cause of autism in approximately 5-10% of the diagnosed cases can be determined (Fombonne, 2003; Rutter et al., 1994). The known causes are enumerated below and do not include any postnatal environmental factor. Therefore, the cause or causes of the bulk (90-95%) of autism cases are unknown (idiopathic). Research into the causes has taken several different paths, including investigations into (a) the role of medical disorders, (b) the role of genetic factors, and (c) the role of environmental exposures.

44. Guidelines exist to investigate young children diagnosed with Autistic Disorder or other ASDs to search for genetic or medical causes of autism (Filipek et al., 2000).

45. Tuberoze Sclerosis and Fragile X are genetic disorders described in association with autism.

46. Other rare medical disorders have been described in association with autism such as phenylketonuria and a few other genetic conditions, particularly those associated with chromosome 15 abnormalities (isodicentric chromosome 15 q syndrome, Angelman syndrome). One medical syndrome, congenital rubella, has been described historically as leading to autistic syndromes in children affected prenatally by this infectious agent. These children were studied in the aftermath of a large U.S. epidemic in the 1960s. While many of them showed autistic traits, the symptoms subsequently abated (Chess, 1971, 1977). Currently, congenital rubella does not account for more than a handful of cases of autism, due to prevention through systematic vaccination against rubella.

47. Thus, the majority of autism cases are idiopathic (one cannot find a specific cause or associated medical condition). In those idiopathic cases, there is evidence that genes play a major role in the development of the disorder.

48. To date, there are no postnatal environmental factors that have been reliably demonstrated to play a role in Autistic Disorder or other ASDs.

49. The fact that genes do play a role in autism was established from several sets of studies. First, family studies have been performed in which the rate of autism in siblings of an autistic patient (proband) has been calculated. Many such studies demonstrate that once a family has a child with an ASD, there is a rate of about 3% for another sibling to be affected with Autistic Disorder, and an additional 3% risk for subsequent offspring to be affected with PPDNOS or Asperger's Disorder (Bolton et al., 1994). Current estimates of the sibling recurrence risk are around 6-15%, depending upon the particular assumptions behind the calculations (Szatmari et al.,

1998; Zwaigenbaum et al., 2005). This is a well-replicated finding, which shows that autism and other ASDs cluster in families and that the risk of autism in a family is at least ten times higher than in the general population.

50. Second, twin studies of autism have compared the concordance rates between same-sex twin pairs, who share either 50% of their genes (dizygotic (DZ) twins) or 100% of their genes (monozygotic (MZ) twins). As early as 1977, these twin studies identified a strong genetic contribution to autism (Folstein & Rutter, 1977). The most accurate and recent estimates suggest that the concordance rate in MZ pairs is about 70% compared to 0 to 5% in the DZ pairs (Bailey et al., 1995). This discrepancy between 5% and 70% in DZ and MZ concordance rates emphasizes the strong influence of genetic factors in autism.

51. Twin studies further indicate that multiple genes, rather than a single gene, are likely to be involved. Modeling of data from family and twin studies actually suggests that from 3 to 20 genes may be involved in the susceptibility to an ASD (Pickles et al., 1995; Risch et al., 1999). Medical geneticists calculate from these twin studies an index of heritability that, in the case of autism, is above 90% (Bailey et al., 1995; Szatmari et al., 1998). In most family or twin studies, investigators have also identified in those twins who appear to be unaffected by autism, or amongst the unaffected relatives of autism probands, a set of mild developmental abnormalities that may combine communication and language impairments, social difficulties, unusual interests, and a tendency for rigid/obsessive behaviors that are conceptually equivalent to the symptoms seen as part of full-blown autism, but are much milder in intensity. This phenotype is referred to as the broader phenotype of autism and appears to affect 10 to 20% of first-degree relatives, depending upon which definition is used (Bolton et al., 1994; Fombonne et al., 1997). It is believed that

subjects presenting with this broader phenotype carry some, but not all, of the genes involved in autism.

52. After it was established that genes play a predominant role in the development of autism, investigators started to explore the genome to identify the genes involved. I was part of the first international consortium that investigated autism using modern molecular genetic techniques and, in 1998, published the first results of a genome scan (IMGSAC, 1998). We followed an affected relative pair approach, whereby we recruited families in several countries in which two members (usually two siblings) were affected with an ASD. Precise phenotypic assessments were conducted, and DNA from all family members was extracted from blood samples. This approach was followed by several research groups.

53. Regions on several chromosomes have now been identified that likely harbor susceptibility genes for autism. Major research efforts in the molecular genetic studies of autism are currently ongoing (Muhle et al., 2004). Recently, research groups worldwide have put their efforts together, shared samples, and performed new genetic analyses on a much larger sample of multiplex families (Autism Genome Project, 2007). The results of the genome scan have identified new genes that are likely to be implicated in autism. In addition, the genetic heterogeneity of autism begins to be better understood because in 10 to 15% of the sample it appears that copy number variants, small structural changes in the DNA that were thus far undetected with cytogenetic techniques, and that represent de novo mutations, appear to explain autism in a substantial minority of families. A full understanding of the causal mechanisms leading to autism is therefore in progress, but much remains to be done to understand the pathophysiology of this devastating disorder.

54. Few prenatal environmental risk factors have been identified that appear to increase the risk of autism, including *in utero* exposure to thalidomide, valproic acid, misoprostol, and rubella virus infection. All the scientific evidence suggests that the impact of these risk factors occurs during the early weeks of gestation. Malformations seen in thalidomide exposed patients indicate that the developmental interference occurs between 20 and 24 days after conception, and the same is true for valproic acid. For the other exposures (misoprostol, rubella virus infection), the window of vulnerability occurs during the first 12 weeks of gestation (Rodier & Hyman, 1998; Rodier, 2004).

55. In addition, cranio-facial dysmorphology and dysfunction of the cranial nerves are common in children with autism (Rodier, 2004; Rodier, 2000). When children with idiopathic autism are compared with unaffected siblings, higher rates of anomalies such as posteriorly rotated ears, small feet, and large hands are observed to occur. Minor physical anomalies occur at high rates in children with autism. In their review of studies of minor physical anomalies (MPA), Smalley et al. (1996) concluded that MPAs result from either genetic or environmental insults that occur in the first trimester of pregnancy and are an indirect measure of abnormal early fetal development. More recent studies have also found that autistic children were more likely to have MPAs than normal or sibling controls (Bailey et al., 1995; Rodier et al., 1997). For example, Miles and Hillman (2000) reported that 20% of their sample of autistic children had clearly abnormal physical examinations that also correlated with MRI brain abnormalities. Such dysmorphic conditions or congenital anomalies result from disturbances during embryonic development; they do not arise postnatally.

56. Also reflecting the early prenatal onset of autism are several neuroanatomical findings. Several components of the limbic system (a set of forebrain structures involved in

memory and emotionality) show abnormally small and closely packed neurons (Kemper & Bauman, 2002). Malformations in the neocortex have also been reported (Bailey et al., 1998). In the cerebellum, a consistent finding is a decrease in the number of Purkinje cells in the cortex; abnormalities in the size and number of neurons in the deep cerebellar nuclei are also observed. However, while anomalies in the size of the neurons in the inferior olive of the brain stem also occur in autism, there is no corresponding loss of these neurons. This destruction of Purkinje cells without a concomitant loss of olivary neurons indicates that the injury occurred prior to the 28th week of gestation.<sup>1</sup>

57. An excessive number of minicolumns has also been described in the brain of autistic patients. Minicolumns are generated early in gestation by divisions of primordial cells lining the anterodorsal aspect of the embryonic ventricles, and the total number of minicolumns is attained in the first 40 days of gestation in primate species (Casanova et al, 2002 & 2002 and 2003), again suggesting that an early, prenatal, pathological process is involved in autism.

58. Providing further support for a prenatal onset of brain development abnormalities, a study by Nelson et al. (2001) showed that, compared to control children, neonatal concentrations of vasoactive intestinal peptide, calcitonin gene-related peptide, brain-derived neurotrophic factor and neurotrophin 4/5 were significantly elevated in archived neonatal blood of children with autistic spectrum disorders or mental retardation without autism. In 99% of children with autism, levels of at least one of these substances exceeded those of all control children.

Although the results were not specific to autism, they point unequivocally toward prenatal anomalies in children with autism or intellectual impairments.

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<sup>1</sup> Because very close neuronal connections between Purkinje cells and neurons in the inferior olive are established by week 28 of gestation, any loss of Purkinje cells after this point would necessarily result in a loss of olivary neurons. In autism, what is observed is a loss of Purkinje cells without a corresponding loss of neurons in the inferior olive. It can therefore be concluded that the injury that results in Purkinje cell destruction occurs prior to the 28th week of gestation (Kemper and Bauman, 2002).

### **Prevalence of ASDs in Human Populations**

59. Epidemiology is concerned with the study of the distribution of diseases in human populations and of the factors that influence it. There are several measures of disease occurrence used by epidemiologists. Incidence rates refer to the number of new cases (numerator) of a disease occurring over a specified period of time in those at risk of developing the disease in the population (denominator, in person x years). Cumulative incidence is the proportion of those who were free of the disease at the beginning of the observation period and developed the disease during that period. Measures of incidence are required to properly estimate morbidity due to a disease, its possible changes over time, and the risk factors underlying disease status. Prevalence is a measure used in cross-sectional surveys (there is no passage of time) and reflects the proportion of subjects in a given population who, at that point in time, suffer from the disease. Most epidemiological studies of autism have been prevalence, rather than incidence, studies. Ecological studies compare rates of the disorder and rates of the exposure at a population level without ascertaining the association between disease and exposure at the individual level. Ecological studies have been used to evaluate risk of autism in relation to various vaccines.

60. I recently reviewed the epidemiological literature on autism (Fombonne, 2005 & 2006). Overall, forty-two studies published between 1966 and 2004 were identified. Conservative estimates for the current prevalence of Autistic Disorder, PDDNOS, Asperger's Disorder, and CDD are: 13/10,000, 20.8/10,000, 2.6/10,000 and 0.2/10,000, respectively, with a minimum, conservative estimate of 36.6/10,000 for all ASDs. However, six recent epidemiological surveys yielded higher rates in the 60-70/10,000 range (Baird et al., 2000; Chakrabarti & Fombonne, 2001; Chakrabarti & Fombonne, 2005; Bertrand et al., 2001; Scott, 2002; Fombonne et al., 2006). Most of these surveys had specific methodological features, such as identifying the whole spectrum of ASDs in small populations of young children with very proactive ascertainment

techniques and new assessment methods. The convergence of surveys around the estimate of 60-70/10,000 for all ASDs combined is striking, especially when derived from studies with improved methods. In the U.S., the CDC has developed a surveillance program to monitor the prevalence of ASDs in different U.S. states. The first prevalence estimates from this epidemiological network were released recently, and they are consistent with the other surveys in showing an average rate of 67/10,000 in 8-year old U.S. children, in 2000, and an average rate of 66/10,000, in 2002 (CDC, 2007). This estimate (0.6-0.7%) appears to be the best estimate for the prevalence of ASDs currently available.

### **Childhood Vaccines and Autism**

61. Since 1998, concerns have been raised about childhood vaccines and the risk of autism. Two separate hypotheses have been advanced. One hypothesis relates to the measles component of the triple vaccine MMR. The other relates to thimerosal (a substance containing ethylmercury) that has been used in most other childhood vaccines since 1930. The hypotheses are independent because MMR never contained thimerosal (it is live attenuated vaccine). The petitioners' expert reports argue that MMR vaccine triggered autism in Michelle Cedillo. Accordingly, I will discuss extensively the scientific literature regarding the putative link between MMR and autism. I will then review more succinctly the literature addressing thimerosal.

### **The Epidemiology of Autism and MMR**

62. Following the publication of a small case series in 1998 (Wakefield et al., 1998), the hypothesis of a causal connection between exposure to the MMR vaccination and the development of autism has been raised. The initial study suffered from serious methodological weaknesses, including a lack of control group, a lack of standardized testing of children with autism, a lack of validation of retrospective parental reports on first symptoms and their date of

onset, to name only a few. It is worth noting that of Wakefield's 12 co-authors, 10 of them have subsequently retracted officially the original interpretation of the data that considered MMR vaccine as an etiological trigger for autism (Murch et al., 2004). Over the years, several claims were made by Wakefield et al. in various papers and/or communications that can be summarized as follows: 1) There is an epidemic of autism; 2) Rates of autism have increased when MMR has been introduced in immunization schedules; 3) MMR immunizations are not safe; 4) MMR increases the risk of inflammatory bowel disorders in children with autism; 5) The risk of autism is increased in children following exposure to MMR; 6) There is a new syndrome of regressive 'autistic enterocolitis'; and 7) Rates of regressive autism have increased as a result of the implementation of MMR vaccine. Each of these claims is now examined in turn. I limit the focus of this report to epidemiological studies. Biological studies have recently re-examined Wakefield and his colleagues' studies and have shown that their results could not be replicated due to basic flaws in their experimental methods (D'Souza et al., 2006; Afzal et al., 2006). However, I do not review these studies here.

### **Is There an Epidemic of Autism?**

63. I first wrote on the subject of whether or not there was a "true" increase in the number of autism cases (an epidemic) in 1996, and I conducted the first empirical investigation of this question in 1997. I concluded that there was no evidence for an increase in the incidence of autism because I found no difference in rates of autism in successive birth cohorts of children born from 1972 to 1985 (Fombonne et al., 1997). Further studies that I have performed myself, and systematic reviews of new evidence, have confirmed my initial conclusions (Fombonne, 2003 & 2005).

64. There are certain methodological standards that have to be maintained when looking to see if there is an increase of disease or an event over time. For example, if you wanted to know if the rate of juvenile crime increased in San Antonio, Texas from 1994 to 2004 you would have to look at the rates in 1994 and again in 2004. However, you would have to be sure that you were comparing apples to apples. A valid comparison of juvenile crime rates could be jeopardized for at least three reasons: (1) if what we define and count as a crime has changed; (2) if crime detection and reporting practices have changed; and (3) if changes occurred in the population at risk for criminal behavior. In this example, an artifactual increase in crime rates could be observed if new offenses have been added to the list of criminal offenses, or if the police force had been reinforced or given a strong mandate or incentive to identify and report crime, or if the proportion of young males increased disproportionately. It would obviously be wrong, under these circumstances, to claim that a crime epidemic was striking San Antonio.

65. The issue of a so-called epidemic in rates of autism is subject to the same methodological vulnerabilities. Both prevalence and incidence estimates of autism will be erroneously inflated if the case definition for autism is broadened and case ascertainment for autism is improved. In fact, both of those things have occurred.

66. Time trends in rates can therefore only be gauged in investigations that hold these parameters under strict control over time. This was achieved only in a handful of studies. In addition, factors such as development of services and support systems for children with autism, improved awareness by both professionals and lay persons, decreasing age of diagnosis, availability of information from the Internet, parent support groups, and the removal of the stigma all contribute to increasing rates of diagnosed ASDs. A few approaches have been employed to

evaluate time trends in rates of autism. These are: referral statistics, comparison of prevalence studies, and incidence studies.

### Referral Studies

67. Increasing numbers of children referred to specialist services, or known to special education registers, have been touted as evidence for an increased incidence of Autism Spectrum Disorders (California Department of Developmental Services, 1999, 2002 & 2003).

68. For example, as of January 6, 2003, there were 20,377 cases of autism identified in the public database (California Department of Developmental Services, 2003). In fact, this number is much lower than what one would predict based on epidemiological calculations (Fombonne, 2006). The fact that this number has increased rapidly in the past fifteen years has been repeatedly used to support the claims of an autism epidemic. Over that period of time, however, diagnostic practices changed, broader definitions of ASDs were employed, services were developed, services improved, and autism became subject to mandatory reporting (1990) as part of the U.S. Individuals with Disability Education Act (IDEA). Also contributing to increasing numbers of ASDs is the practice of “diagnostic substitution,” whereby children formerly diagnosed with a non-ASD (i.e., mental retardation, language disorder) will now receive an ASD diagnosis. An analysis of the U.S. Department of Education data over time has shown that the increasing use of the ASD category was paralleled with a decreasing use of the mental retardation category (Shattuck, 2006). Similarly, data obtained in the U.K. by Jick and Kaye (2003) showed that the incidence of diagnoses of developmental disorders, including language disorders, decreased by about the same amount as the incidence of diagnoses of autism in boys, born from 1990-1997, increased. Finally, there is evidence that the number of children identified in the school system for different conditions (i.e., ADHD) has increased, and that the rise is not specific to autism (Gurney

et al., 2003; Shattuck, 2006). On the whole, evidence from these referral statistics is very weak and cannot be used to determine changes in the incidence of the disorder.

### Comparison of Prevalence Studies

69. Each epidemiological survey of autism possesses unique design features that differ from study to study. These differences in study design could entirely account for the different prevalence rates each study generates. Case definition and case ascertainment are at the heart of these design differences. Time trends in rates of autism are, therefore, difficult to gauge from comparisons of published prevalence rates (Fombonne, 2005).

70. For example, earlier surveys relied on case definitions and classifications that tapped a narrow definition of autism. Changes in the classification systems in 1980, 1987, and 1994 progressively broadened the concept and definitions of autism and other ASDs. Asperger's Disorder only appeared as a diagnostic category in the 1994 version of DSM. It would be inappropriate, therefore, to compare rates from old studies using narrow definitions (Kanner's criteria) with more recent surveys that rely on broader based DSM-IV definitions of ASDs. To illustrate the impact of diagnostic criteria on prevalence rates, one only has to look at the Finnish study by Kielinen et al. (2000). Kielinen assessed the same children for autism using (1) Kanner's criteria, and (2) ICD-10 criteria. He found a two- to three- fold increase in the diagnosis of autism. These data from the same survey illustrate the huge impact that diagnostic definitions and criteria have on the rate of prevalence.

71. In an editorial for JAMA (Fombonne, 2003), I wrote that one of the least distorted comparisons over time that could be performed was to contrast the rate of ASDs obtained by Wing and Gould (1979), in a survey conducted in the mid-1970s in a London borough (about 21/10,000 for the autistic disorder and the triad of impairments), to our current best estimate for

ASDs (60/10,000). This comparison shows a three-fold increase over 30 years, and, as per the previous point, the increase could clearly be accounted for by changes in diagnostic criteria and improved ascertainment.

72. It can also be shown that rates in surveys conducted approximately at the same time can yield very different prevalence estimates with a ten-fold variation in rates or more (see Table ‘Study design impact on prevalence’).

<b>STUDY DESIGN IMPACT ON PREVALENCE</b>					
<b>U.K. STUDIES</b>					
		<b>Size</b>	<b>Age Group</b>	<b>Method</b>	<b>ASD Rate /10,000</b>
Chakrabarti and Fombonne, 2001	Staffordshire	15,500	2½ - 6½	Intense screening and assessment	62.6
Baird et al., 2000	South East Thames	16,235	7	Early screening + follow-up identification	57.9
Fombonne et al., 2001	England and Wales	10,438	5-15	National household survey of psychiatric disorders	26.1
Taylor et al., 1999	North Thames	490,000	0-16	Administrative records	10.1
<b>U.S. STUDIES</b>					
Bertrand et al., 2001	Brick Township, NJ	8,896	3 – 10	Multiple sources of ascertainment	67
Sturmev and James	Texas	3,564,577	6-18	Educational services	16
CDER, 1999	California	3,215,000	4-9	Educational services	15
Hillman et al., 2000	Missouri	---	5-9	Educational services	4.8

73. The only explanation for such variability in rates lies in the differences in methodologies employed in each of these surveys because the studies were conducted at the same time, in the same country, and of children of similar age (Fombonne, 2003 & 2005).

74. Typically, surveys that rely on passive, administrative methods to count subjects yield much lower rates than those studies that employ more comprehensive and systematic ascertainment procedures. As it is, therefore, very difficult to compare meaningfully rates between

recent surveys performed with different designs, it is even less valid to compare rates of studies conducted at different historical periods.

75. In some instances, it has been possible to compare prevalence rates in successive birth cohorts surveyed with rigorously identical methods for case definition and case ascertainment. Such comparisons reveal no increase in the prevalence of ASDs. We performed two separate surveys looking for ASDs in children born between 1992 and 1995, and between 1996 and 1998, in Staffordshire, in the U.K.

STAFFORDSHIRE SURVEYS							
	92-95 cohort N=15,500		96-98 cohort N=10,903		Combined samples N=26,403		
	N	P	N	P	N	P	95%CI
Autistic Disorder	26	16.8	24	22.0	50	18.9	14.1-25.0
PDDNOS	56	36.1	27	24.8	83	31.4	25.0-39.0
Asperger's	13	8.4	12	11.0	25	9.5	6.1-14.0
CDD	1	0.7	1	0.9	2	0.8	0.1-2.7
All ASD	96 <sup>1</sup>	61.9	64	58.7	160	60.6	51.6-70.7
<sup>1</sup> One girl with Rett's Syndrome has been excluded N = number      P = prevalence rate per 10,000      Chakrabarti and Fombonne (2005)							

76. The prevalence for all ASDs was comparable in the two birth samples and not statistically different in the two surveys, suggesting no upward trend in overall rates of ASDs during the studies' time interval. In another analysis of pooled survey data on 735,000 children from studies that strictly relied on comparable methods, age-specific prevalence rates showed no upward trend in cohorts born from 1972 to 1985 (Fombonne et al., 1997). If there had been an increase in the incidence of autism during that period, the prevalence in the most recently born children should have been higher than that amongst the older children.

77. A recent analysis of special educational disability from Minnesota showed a sixteen-fold increase in the number of children identified with an ASD from 1991-1992 to 2001-2002 (Gurney et al., 2003). However, in this study, it was not possible to adjust for changes in diagnoses or improved case ascertainment. In addition, the increase was not specific to autism because during the same period, an increase of 50% was observed for all disability categories (except severe mental handicap), especially for the category including ADHD. Gurney et al. (2003) further argued that this phenomenon coincided closely with the inclusion of ASDs in the federal Individual with Disabilities Educational Act (IDEA) funding and reporting mechanism in the U.S. The addition of high functioning autistics also accounts for some of the increase (Eagle, 2004). Similar conclusions were obtained by Shattuck (2006) in an analysis of trends in ASD categories in the U.S. using the Department of Education data for all 50 states.

#### *Incidence Studies*

78. Several recent studies provided ASD estimates (Powell et al., 2000; Kaye et al., 2001; Smeeth et al., 2004; Barbaresi et al., 2005). All showed an upward trend. For example, in the largest study of 1410 subjects, we found a ten-fold increase in the rate of first recorded diagnoses of ASDs in United Kingdom general practice medical records from 1988-92 to 2000-01 (Smeeth et al., 2004). The increase was more marked for ASDs other than autism, but the increase in autism was also obvious. However, none of these studies could control for confounding due to changes over time in diagnostic criteria, improved awareness, and service availability.

79. The available epidemiological evidence does not support the hypothesis that the incidence of autism has increased. As it stands now, the recent upward trend in rates of *prevalence* cannot be directly attributed to an increase in the *incidence* of the disorder. There is evidence that changes in diagnostic criteria, diagnostic substitution, decreasing age at diagnosis,

changes in the policies for special education, and the increasing availability of services are responsible for the higher prevalence figures. Most of the existing epidemiological data are inadequate to test properly hypotheses on changes in the incidence of autism in human populations. The studies that could more adequately control for alternative explanations have failed to detect an upward trend in rates of ASDs.

### **Is the Prevalence of Autism Related to the MMR Vaccination?**

80. Several epidemiological studies have tested this hypothesis, using an ecological design. In the U.K., Taylor et al. (1999) studied 498 cases of children diagnosed with an ASD under 60 months of age, and born between 1979 and 1992. In the U.K., MMR was introduced in 1988. The authors used a time-series analysis with Poisson regression modeling. There was no indication that the incidence of autism increased after the introduction of MMR. In this study, there was no temporal association between changes in vaccination coverage and changes in the incidence of autism since 1987. We conducted a comparable study on a large sample of the National Autistic Society from the U.K. (Chen et al., 2004). Using a sample of 2407 subjects, we examined the trend in births of autistic subjects in successive birth cohorts from 1959 to 1993. Following the introduction of MMR in 1988, there was no evidence of a step-up in incidence of autism (see Figure 3).

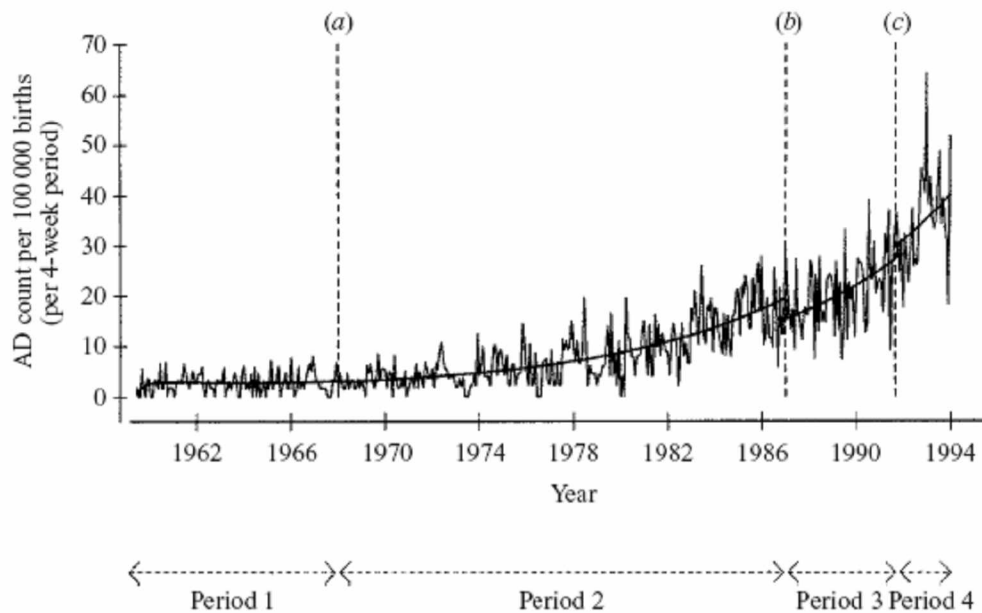


FIG. 3. Observed AD counts (per 100000 life births per 4-weekly period) from July 1959 to December 1993. The smooth line shows the long-term temporal trend fitted by the Poisson model used for the whole series (smoothed for seasonality), plus the estimated effects of changes in vaccination regimes. The broken vertical lines indicate the four different vaccination periods (Table 1). For time: (a) IRR of period 2 relative to period 1 = 96.1%, 95% CI from 67.2 to 137.3%,  $P=0.83$ ; (b) IRR of period 3 relative to period 2 = 78.8%, 95% CI from 66.7 to 93.1%,  $P=0.005$ ; (c) IRR of period 4 relative to period 3 = 109%, 95% CI from 95.4 to 124.7%,  $P=0.21$ .

In Sweden, where MMR was introduced in 1982 for children 18 months of age, and coverage rapidly reached 90%, two studies of samples, including ASD subjects (Gillberg & Heijbel, 1998) or children with epilepsy and learning disabilities with or without autism (Steffenburg, Steffenburg and Gillberg, 2003), examined if the prevalence of autism in these two samples had increased after 1982. None of these studies detected an increased proportion or prevalence of ASDs in the years following MMR introduction. The latter study also tested a possible increased risk for epilepsy/learning disability in relation to MMR and failed to identify such an association. In California, time trends in MMR immunization coverage rates for children born between 1980 and 1994 were compared to trends in autism caseloads for children born in the same years and enrolled in the regional service system of the California Department of Developmental Services (Dales et al., 2001). No correlation was observed between the two trends. A marked and sustained increase in autism caseloads was observed from 44/100,000 live births in 1980 to 208/100,000 in 1994, a 373% increase. By contrast, MMR coverage increased by a smaller extent, from 72% to 82%, a 14% increase. Dales et al. (2001) concluded that the data did not suggest an association between

autism and MMR. Another U.K. study relied on the GPRD, an electronic database of general practitioners' medical records, and examined trends over time in the prevalence of autism in relation to MMR uptake rates. As in other studies, the two trends were uncorrelated with the prevalence of autism rising regularly from 1988 to 1993 whilst the MMR uptake was steady and unchanged throughout the same period (Kaye et al., 2001). In another ecological study, rates of ASD were examined in children attending a school board in Montreal and born between 1987 and 1998 (Fombonne et al., 2006). The prevalence of ASD increased linearly about 10% each year during that interval. During the same period, there was a slight but significant trend toward a decrease in MMR uptake from 1988 to 1998 ( $P < .001$ ), with vaccine uptake dropping from 96.1% in the older birth cohorts (1988–1989) to 92.4% in younger birth cohorts (1996–1998). Again, the study concluded that the increase in the rate of ASD had no relationship to MMR vaccination.

81. In the U.S., two studies by Geier and Geier (2003 & 2004) reached different conclusions. In the first study (Geier & Geier, 2004), counts for autism caseloads from the U.S. Department of Education data were contrasted for different birth cohorts (1982, 1984, 1991, 1992, 1993, 1994, 1995, 1996) and correlated with estimated numbers of children having received measles-containing vaccines. The study reported a correlation that was difficult to interpret due to major methodological weaknesses. That study failed to account for various alternative explanations. The statistical analyses were very limited and of questionable validity. In the second study (Geier & Geier, 2003), the authors used the VAERS database and compared adverse events reported after MMR vaccination to those reported after DTP vaccinations. The authors reported a relative risk of 5.2 for MMR vaccinations and autism together with other epidemiologic figures. The study was seriously flawed in several respects, including using the VAERS data base to evaluate the association, an inappropriate use of epidemiological terms and calculations, and a lack

of transparency in the study reporting. Both studies have been regarded as non-contributory to the scientific debate by an ad hoc IOM Committee (IOM, 2004).

82. The history of MMR vaccination in Japan has been marked with complications occurring because of a strain of mumps virus (the Urabe AM9 strain) included in the triple vaccination, which led to complications (aseptic meningitis). MMR was initially introduced in Japan in April 1989, but was removed from the official vaccination recommendations in April 1993. This natural ‘experiment’ provided an opportunity to test whether or not rates of autism decreased following removal of the MMR vaccine. Honda et al. (2005) studied the cumulative incidence of ASDs in children from birth up to age seven in a population of 300,000 habitants living near Yokohama. The amount of MMR vaccinations decreased from 1988 to 1992 and stopped altogether from 1993 onwards. By contrast, the incidence of ASDs increased significantly from 1988 through 1996, with a most pronounced rise from 1993 onwards. This study shows clearly that removal of MMR vaccine does not reduce the incidence of autism and gives no support to the hypothesis of a causal link between MMR and autism.

83. *With the exception of 2 studies that were flawed in their design and conduct, all studies that have contrasted the prevalence of autism or other ASDs in periods with or without MMR vaccination have, in several different countries, shown no impact of MMR vaccination on the rates of autism.*

#### **Can Autism be a Complication of Measles Immunizations?**

84. Measles immunizations have been available since 1968 for monovalent vaccines and later for the triple vaccine MMR, with various dates of implementation in children’s immunization schedules in different countries. Vaccine safety is regularly reviewed by ad hoc committees and regulatory agencies such as the CDC and the World Health Organization. No

report by any public agency has ever described autism as an adverse effect of any vaccine, including vaccines against the measles virus.

85. In 1993-1994, a special review was conducted by the IOM to address the safety of different childhood vaccines (Stratton et al., 1994). MMR and monovalent vaccines were reviewed in this IOM report that predates the 1998 Wakefield article. The committee comprised scientists from various disciplines, including vaccinology, infectious diseases, epidemiology, and public health. Nowhere is the word autism mentioned in this report in either the text or the index.

86. In our U.K. National Autistic Society study, described above, we also examined if the incidence of autism was related to notifications of wild measles infections in England and Wales for the period 1968-1986. We tested for effects of natural measles virus exposure for different time windows. The exposure ranged from conception to the post-natal age of 18 months. There was no evidence for a statistically significant increase in the incidence of autism with exposure to wild measles infection for any timing of the exposure (Chen et al., 2004).

87. In that study (Chen et al., 2004), we also examined if the introduction of monovalent measles in the U.K., in 1968, led to an increase in the incidence of autism after that date. After adjustment on potential confounders, there was no evidence suggesting a step-up in the incidence of autism following introduction of the monovalent measles vaccine. Rather, the incidence rate ratio was 0.96, a slight and non-significant reduction in incidence.

88. Several surveillance systems exist worldwide to monitor the adverse effects of drugs or vaccinations. In Finland, for example, MMR adverse effects were evaluated from 1982 (date of the MMR introduction) through 1996, after 3 million doses had been given to 1.8 million individuals (Peltola et al., 2000). A total of 173 serious events were reported after the vaccination,

about half of them most probably unrelated to the vaccination. None of these adverse effects involved autism or other ASDs.

89. *The safety of MMR vaccination has been solidly established. Amongst the rare complications that can occur after MMR, autism has never been identified as one of them before the Wakefield article was published.*

### **Is There an Increased Risk of Inflammatory Bowel Disorders in Autistic Children?**

90. Before his controversial paper in 1998, Wakefield had conducted research on Crohn's disease and inflammatory bowel disorders (IBD) in adults. He had suggested that these inflammatory bowel disorders were increasing in incidence and that the measles virus was implicated in these trends. His research was not replicated by others. When reviewed by the Medical Research Council in the U.K., this hypothesis was clearly rejected. In his initial report on autism, from 1998, Wakefield described gastro-intestinal symptoms as an essential component of his MMR-induced autistic syndrome. Based on his ideas, if the measles virus was both increasing the risk of Crohn's disease or other IBD in humans, and increasing the risk of autism in children, it followed that autistic children should have a documented increased incidence of IBDs (Crohn's disease or ulcerative colitis).

91. We tested this hypothesis by comparing 936 children with ASDs selected in one U.K. clinical database from the Maudsley Hospital (762 children), and in one French epidemiological survey of childhood handicaps (174 children) (Fombonne, 1998). For both samples, appropriate control groups of children with non-autistic psychiatric disorders (N=8125) or non-autistic developmental handicaps or psychiatric conditions (N=5924) were available. Associated medical conditions were available in both studies, including Crohn's disease and other IBDs. In this study with a large power, no child in either ASD group had an IBD. Four children

had diagnosed IBDs, two in each control group. The prevalence of IBDs in the two samples was consistent with independent population estimates of IBD amongst children, suggesting that the study had not underestimated the prevalence of IBD.

92. A study by Black et al. (2002) examined the same issue, using an electronic database from the U.K., the General Practitioner Research Database (GPRD). The rate of gastro-intestinal disorders (including IBD, celiac disease, recurrent gastrointestinal symptoms, and food intolerance) was 9% in both the 96 autistic children and the 449 controls, leading to an odds-ratio of 1.0, indicative of no increase in risk.

93. In Finland, Makela et al. (2002) reported that of 352 children hospitalized with an autism diagnosis, none of them was hospitalized for an inflammatory bowel disease.

94. Of note is the recent study of a large sample of autistic children recruited from 13 research centers in the U.S. in which the frequency of gastro-intestinal disorders was compared in 164 children with regressive autism and 187 children with non-regressive autism (Richler et al., 2006). Of the 351 children, only 10 children had a diagnosed gastro-intestinal disorder (7 regressive autism, 3 non-regressive autism) with no statistically significant difference between the groups.

95. A Cochrane review of 31 studies published on MMR safety has concluded that “exposure to MMR was unlikely to be associated with Crohn’s disease, ulcerative colitis, autism” (Demicheli et al., 2005).

96. ***The evidence does not suggest that children with autism are at increased risk of developing chronic gastro-intestinal disorders.***

### **Does Exposure to MMR Increase the Risk of Autism in Vaccinated Children?**

97. Two large case-control studies and one retrospective cohort study have been conducted.

98. In the U.K., Smeeth et al. (2004) did a matched case-control study using the U.K. General Practice Research Database. Cases were subjects born in 1973 or later who had a first recorded diagnosis of ASD while registered with a contributing general practice between 1987 and 2001. In order to avoid biases due to the media impact of the 1998 Wakefield article, subjects had to be born before 1998. Up to 5 controls were matched with cases on age, sex, and general practice. 1294 cases and 4469 controls were included. The diagnoses of the electronic records were validated on a subsample by expert clinical review (Fombonne et al., 2004). 1010 cases (78.1%) had MMR vaccination recorded before diagnosis, compared with 3671 controls (82.1%) before the age at which their matched case was diagnosed. After adjustment for age at joining the database, the odds ratio for association between MMR and ASD was 0.86 (95% CI 0.68–1.09). Findings were similar when restricted to children with a diagnosis of autism, to those vaccinated with MMR before the third birthday, or to the period before media coverage of the hypothesis linking MMR with autism.

99. In the U.S., DeStefano et al. (2004) compared 624 ASD children with 1824 controls matched on cases for age, gender, and school. The distribution of age at MMR vaccination was similar in cases and controls. The authors examined the risk of autism in relation to MMR vaccination in different groups defined by age at MMR vaccination (before 18 months as recommended in the official schedule, before 24 months when symptoms of autism usually appear, and before 36 months when symptoms must be present for the diagnosis). Most cases (70.5%) and controls (67.5%) were vaccinated between 12 and 17 months of age. No association between autism was found for children vaccinated before 18 or 24 months of age. A significant odds-ratio

of 1.49 (95%: 1.04-2.14) was interpreted as reflecting the requirement of vaccination for children with autism entering early intervention programs. Of note is the fact that when analyses were restricted to the 80 children who experienced regression, no statistical association was found. The results of that study did not support the MMR-autism link.

100. In Denmark, Madsen et al. (2002) conducted a population based retrospective cohort study. Subjects included were born between 1991 and 1998, and information about their diagnostic status, immunization status and date was collected through the various national registers available in this country. Over half a million children were included, and 82% had received the MMR vaccination at a mean age of 17 months. After adjusting on several confounders, the relative risk for vaccinated children was 0.92 (95% CI: 0.68-1.24) for autistic disorder, and 0.83 (95%CI: 0.65-1.07) for ASDs, values which show that the risk is not different in vaccinated and unvaccinated children. In addition, the authors did not find clustering of autism cases following vaccination.

101. Smeeth et al. (2004) conducted a meta-analysis of the three previous controlled observational studies in order to derive a pooled estimate for the association between MMR and autism. There was no heterogeneity in the pooled studies, and the common risk estimate was 0.87 (95%CI:0.76-1.001, again strongly suggestive of no association (see Figure below)).

102. Another small case-control study comparing MMR and monovalent measles immunizations did not detect an increased risk associated with MMR (Takahashi et al. 2003). However, this study had several limitations.

103. ***Controlled observational studies (cohort and case-control studies) have been performed in different samples and different countries. None of these studies has shown an***

*increased risk of autism or ASD in children vaccinated with MMR as compared to unvaccinated children. All studies are consistent in their estimates of relative risk, and a metaanalysis shows a pooled estimate that strongly favours the rejection of the hypothesis of an association between MMR and autism or ASD.*

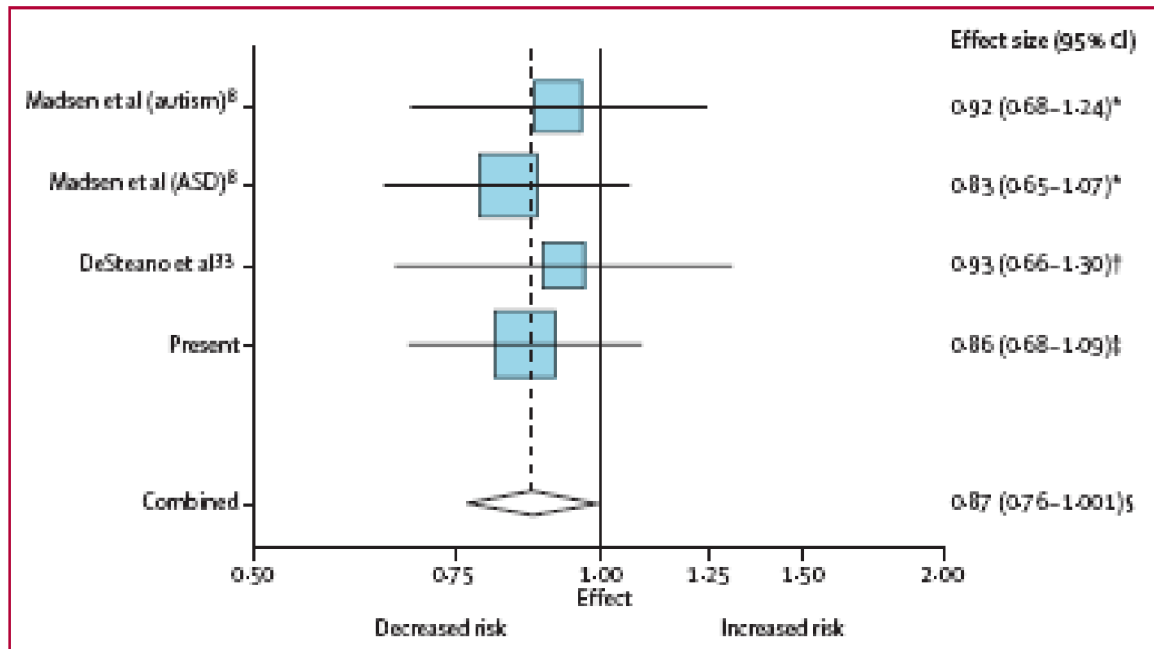


Figure 2: Meta-analysis of studies that compared risk of autism or other PDDs among vaccinated and unvaccinated individuals  
 ASD=other autistic spectrum disorders. Shaded boxes and horizontal lines correspond to effect size ratios and 95% CIs. Size of shaded box proportional to reciprocal of square of standard error of effect. <sup>\*</sup>Rate ratio, adjusted for age, calendar period, sex, birth weight, gestational age, mother's education and socioeconomic status. <sup>†</sup>Odds ratio, cases and controls matched on age, sex, and school, adjusted for birth weight, multiple gestation, maternal age, and maternal education. <sup>‡</sup>Odds ratio, cases and controls matched on age, sex, and general practice, adjusted for age registered with general practice. <sup>§</sup>Pooled relative risk.

### **Is There Evidence for a New 'Autistic Enterocolitis' Syndrome?**

104. Studies have been conducted to validate the putative syndrome described by Wakefield et al. in 1998 and beyond. The Wakefield et al. studies have been incomplete with respect to the characterization of autistic subjects included in the samples. Moreover, some of the

Wakefield et al. studies have also included children with other diagnoses such as schizophrenia or ADHD, which questions the overall interpretability of the data (Fombonne & Cook, 2002). At a minimum, if it has validity, the putative syndrome of 'autistic enterocolitis' should apply to children who have regressive autism with an onset shortly after MMR vaccination, associated with bowel symptoms and normal early (prevaccination) development. Several studies have tried to validate this putative phenotype or its components.

105. In Finland, Peltola et al. (1998) reported on a 14-year prospective surveillance of the MMR vaccine, introduced in Finland in 1982, whereby any adverse effect following the MMR vaccination was reported on a form sent to the National Public Health Institute, and followed up 2 or 3 weeks later by another report. After administration of 3 million doses of MMR, they could identify only 31 children for whom onset of gastro-intestinal symptoms (diarrhea, vomiting, gingivostomatitis, abdominal pain) was reported from 20 hours to 15 days after inoculation with MMR. At a mean follow-up interval of 9 years 3 months, further information was obtained. No child had been diagnosed with an ASD or an inflammatory bowel disease.

106. One component hypothesis of the putative new syndrome lies in the onset of autistic symptoms days after the MMR vaccination. DeWilde et al. (2001), using the Doctors Independent Network Database, examined the frequency at which 71 autistic and 284 matched control children were consulting with their family doctors 2 and 6 months before or after the MMR vaccination. In children who were later diagnosed with autism, there was no evidence of increased consultation with their GPs in the 2 or 6 months following the MMR vaccination compared to the same intervals before vaccination. By contrast, compared to the non-autistic controls, the autistic children showed an increased frequency of consultations with their GPs at age 3 and 4 years during

the 2 or 6 months that immediately preceded the diagnosis of autism. This study, therefore, provides no support for an onset of symptoms of autism immediately after MMR vaccination.

107. Similarly, Makela et al. (2002) studied hospitalizations of autistic children in Finland and did not detect a clustering of hospitalizations after MMR vaccination.

108. Taylor et al. (1999), in their North London study, examined if the timing of diagnosis, first parental concern, and regression of skills clustered around MMR vaccination dates. With the exception of one finding that reflected a recall artifact, all analyses were negative, suggesting no close temporal relation between these events. Further analyses also showed that the mean age at diagnosis was similar in children vaccinated before 18 months, after 18 months, or those unvaccinated. Further analyses of the same data, by Farrington et al. (2001), showed no increased incidence of regression, parental concern, or ASD diagnosis following MMR vaccination.

109. In a subsequent update of their study, Taylor et al. (2002) reported that 17% of a sample of 473 children had bowel symptoms, 25% had regression, and that an association was found between regression and bowel symptoms -- 26% vs 14% of children with and without regression were reported to have had bowel symptoms. However, further multivariate analyses showed no association between regression with bowel symptoms and MMR vaccination.

110. In our Staffordshire study, we examined the relationship between regression, as reported by parents on the standardized ADI, and bowel symptoms, as reported by parents and/or an experienced pediatrician (Fombonne & Chakrabarti, 2001). Gastrointestinal symptoms were reported in 18.8% of the sample. Bowel symptoms were not associated with regression (odds-ratio:0.63; 95%CI:0.06-3.2;  $p>0.50$ ).

111. We also posited that if there was a temporal relationship between MMR and the onset of autism, parental concerns in an MMR exposed group should occur, on average, earlier

than in unexposed children, since MMR is usually given in the U.K. around 13 months of age. (Fombonne & Chakrabarti, 2001). There was, however, no statistical difference in the mean age at first parental concern in an unexposed sample (19.5 months) and an MMR-exposed sample (19.2 months). Both samples were investigated by interviewers blind to the study hypothesis and who interviewed parents using the same standardized interview to evaluate first parental concern.

112. In the same study, we also examined, in our MMR exposed sample, the delay between MMR immunization and first symptoms in ASD children with or without regression. There was no statistical difference between the two groups (regressive: 248 days after MMR; non-regressive: 272 days after MMR; NS). This result does not support the hypothesis that MMR vaccine triggers autism in a child days or weeks after the vaccination.

113. Similar results were obtained in a U.S. collaborative study where the authors examined, in children whose onset of symptoms occurred after the MMR immunization, whether or not the onset of symptoms was closer to the vaccination date in children with regressive autism (Richler et al., 2006). No difference was found, again suggesting that the first symptoms of children with regressive autism are not temporally related to the vaccination. Further analyses using survival curves did not find differences in age at MMR vaccination for children with or without regression. Moreover, the interval between onset of symptoms and vaccination in those children with an onset after vaccination did not differ according to the presence or absence of regression. This study, based on a large sample, gives no support to a temporal relationship between MMR vaccination and autism, as postulated by Wakefield et al. (1998).

114. In the same study, the authors examined the relationship between gastro-intestinal symptoms and regression. They found that children with regressive autism reported more gastro-intestinal symptoms than non-regressive children (1 to 3 symptoms: 39.9% vs 33.9%; 4 or

more symptoms: 13.1% vs 5.8%;  $p < .05$ ). The most frequent gastro-intestinal symptoms were change in stool frequency, change in stool consistency, mucus in stool, recurrent diarrhea, and bloating. The authors noted that the information was based on parental reports and was not corroborated by medical records. Multiple testing may also have been a problem in the analyses reported (Richler et al., 2006).

115. In a large pediatric medical center serving a 10 county area in the midwestern U.S., Molloy and Manning-Courtney (2003) evaluated a sample of 137 children, age 24-96 months, classified as having autism or ASD by the Autism Diagnostic Observation Schedule. Twenty-four percent had a history of at least one chronic gastrointestinal symptom. The most common symptom was diarrhea, which occurred in 17 percent. There was no association between chronic gastrointestinal symptoms and a history of developmental regression.

116. In the recent multisite investigation of the network of autism research centers in the U.S., Richler et al. (2006) tested further the hypothesis of an MMR induced regressive autism by examining the early development of a subset of autistic children selected as the best candidates for the putative autistic enterocolitis phenotype. Specifically, they selected 24 children who had regressive autism, had experienced onset of autistic symptoms after regression, and had experienced at least one gastro-intestinal symptom of 3 months duration at any time. When these children were evaluated for their early development using the Communicative Development Inventory, all children showed abnormal development prior to regression. The authors concluded that there was no evidence for an MMR-induced autistic enterocolitis phenotype.

117. ***Taken altogether, the findings give no support to the validity of the putative autistic enterocolitis phenotype. There is no evidence of a close temporal relation between MMR vaccination and onset of regressive autism. There is mixed evidence for an association between***

*gastro-intestinal symptoms and regressive autism. However, there is evidence that children with regressive autism, with or without gastro-intestinal symptoms, have abnormal development prior to regression and prior to vaccination.*

**Have Rates of Regressive Autism Increased as a Function of MMR Vaccination?**

118. Regression in autism has been known for a long time, and it is not a new phenomenon. There are several examples in the early psychiatric literature of regressive patterns of autism being described by various clinicians and investigators worldwide.

TABLE 1. Regression in Autism: Not a New Phenomenon\*

Author/Year	Study Description	Description of the Regression	Rate (%)
Lotter, 1966 <sup>17</sup>	Epidemiologic (n = 32)	Developmental setback that included speech loss	31.3
Kurita, 1985 <sup>18</sup>	Clinical (n = 261)	Speech/gesture loss lasting over 6 months	37.2
Creak, 1963 <sup>19</sup>	Clinical (n = 100)	Setback in development	25.0
Wolff and Chess, 1964 <sup>20</sup>	Clinical (n = 14)	Setback in development	50.0
Wakabayashi, 1974 <sup>21</sup>	Clinical (n = 116)	Retregressive shift with speech disappearance	22.4
Kobayashi and Murata, 1998 <sup>22†</sup>	Clinical (n = 179)	Normal development followed by loss of words/interest for a minimum of 3 months	29.6

\* An appendix containing clinical descriptions of loss of skills and regression from this earlier literature can be obtained from the first author upon request.

† Subjects were born before 1975.

119. In the earlier studies, the rates of regressive autism in autistic series ranged from 20% to 50% (see Table; Rogers, 2004). These rates and descriptions were established before any concerns about immunizations were raised, at a time when measles vaccines, either as monovalent or MMR vaccines, were not yet available, and when the cumulative exposure of infants to thimerosal was much lower than in recent years. To give specific examples, Wolff and Chess made the following clinical observations about regression, in 1964:

Case 4	Began to speak before 12 months. Then after a separation from his mother he stopped speaking and did not say another word until 2½.
Case 5	Began to speak at 17 months but at 2 he lost all speech.
Case 6	Said single words at 12 months, smiled at people and reached out towards them. At 2 he lost all communicative speech and only repeated television commercials. His expression became blank.
Case 8	Began to speak at 10 months but stopped at 14 months and lost contact with people.
Case 9	At 21 months, following the birth of his brother, he no longer said the 4 words he had previously spoken and began to spend most of his time looking at magazines. He did not begin to speak again until he was 4.

(Wolff & Chess, 1964)

120. With the more stringent and reliable definitions used in recent research, the best estimate that we have for any regression or loss of skills in the developmental course of children with ASD is 20% (Fombonne & Chakrabarti, 2001; Lord et al., 2004). Specific investigations have been carried out recently to assess whether or not the frequency of regressive autism has increased over time.

121. We tested this hypothesis using data from our British survey of autism in Staffordshire and a clinical sample from the Maudsley Hospital (London, U.K.) (Fombonne & Chakrabarti, 2001). Both samples had been assessed by independent clinicians and researchers who were unaware at the time of collection of data that this study would be performed. In both studies, parents of diagnosed children were interviewed with a standardized diagnostic measure, the Autism Diagnostic Interview (ADI), that has become the standard in our field. The Maudsley Hospital sample comprised subjects who were born long before MMR was introduced in the U.K. and were, therefore, unexposed to it. The Staffordshire sample was born between 1992 and 1995, and almost all children had received the MMR vaccine between 12 and 15 months of age. Regression in the developmental course of subjects from the two samples was defined by parental answers to specific questions about regression in language or other skills included in the ADI. The

rates of reported regression were 18.4% in the Maudsley Hospital sample, and 15.6% in the Staffordshire sample, a non-significant ( $p > .70$ ) difference that does not support the hypothesis of increased regressive autism in MMR exposed autistic children.

122. In the U.K., Taylor et al. (2002) examined regression in a sample of 473 children born between 1979 and 1998. Regression was reported in 118 children (25% of the sample). MMR was introduced in the U.K. in 1988. No significant trend was found by year of birth ( $OR=0.98$ ;  $p=0.50$ ) during the 20 year time period of the study. In other words, the proportion of regressive autism remained constant before and after the introduction of MMR.

123. In the validation exercise we conducted for the U.K. case-control study of MMR and autism (Smeeth et al., 2004), we evaluated 178 medical records of autistic children born between 1973 and 1997 and rated the presence/absence of regression in their development. We then compared the proportion of regressive cases of autism over 5 five-year intervals spanning the years 1973 to 1997. Children born in 1987 or after were likely to have received MMR in our sample. A test for trend showed no significant ( $p > .75$ ) change in the proportion of cases with regression (Fombonne et al., 2004).

124. As explained above, MMR was initially introduced in Japan in April 1989 but removed from the official vaccination schedule in April 1993. This natural ‘experiment’ provided an opportunity to test whether or not regressive forms of autism increased during the 4 years of MMR administration (Uchiyama et al., 2006). These authors studied 904 children diagnosed with ASD and born between 1976 and 1999, including 292 children born between January 1985 and December 1991, who were likely to have received MMR (the MMR generation). The rate of regression was lower in children exposed to MMR than in unexposed children (27.8% vs 38.0%; odds-ratio=0.63, 95% confidence interval: 0.32-1.20,  $p=.15$ ). The rates of regression

were similar in the pre-MMR cohorts (34.0%), in the MMR generation (35.6%), and in the post-MMR cohorts (40.0%). No difference was found when comparing the rate of regression in the MMR generation to that of all birth cohorts unexposed to the vaccination (35.6% vs 38.9%; OR=0.87; 95%CI: 0.64-1.18, p=.36). The authors concluded that their findings disproved the hypothesis that MMR causes regression in ASD.

125. *Regression in autism has been described much before measles vaccines became available. Studies that have assessed trends over time in regressive autism have not shown an increase in regressive autism, and the introduction or removal of MMR at specific points in time in some countries has had no impact on rates of regressive autism.*

126. Reviews by independent scientific committees or authors have consistently concluded that the link between MMR and autism was not supported by the studies, leading to the rejection of this hypothesis (IOM, 2004; Medical Research Council, 2001; Demicheli et al., 2005; Taylor, 2006; Madsen & Vestergaard, 2004; DeStefano & Thompson, 2004).

#### **Epidemiology of Thimerosal-Containing Vaccines and Autism**

127. Several epidemiological studies have tested the hypothesis that the risk of ASD in children is increased as a function of the amount of thimerosal included in childhood vaccines. The studies have employed different designs, including cohort studies, case-control studies, and ecological studies. The studies are reviewed briefly in the following sections.

128. In Denmark, Hviid et al. (2003) compared the incidence rates of autism and ASD amongst over 460,000 children born between 1990 and 1996, using the national psychiatric and immunization registers. For autism, the incidence rate ratio was 0.85 (0.60-1.20) for autism and 1.12 (0.88-1.43) for ASD, showing no increase in the risk of the outcome following vaccination with a thimerosal-containing vaccine. When results were adjusted for age, calendar

period, gender, birthplace, birthweight, Apgar scores, gestational age, maternal age at birth, and maternal country of birth, the conclusions remained unchanged. The authors also conducted an analysis to test different levels of thimerosal exposure. There was no evidence of a dose response with increasing thimerosal exposure for either autism or ASD. Various potential sources of biases were considered in subsequent analyses that did not show they were likely to have resulted in these negative findings. The study was population-based and well-powered.

129. Two other controlled epidemiological studies were performed in the U.K. in similarly large population-based samples (Andrews et al. 2004; Heron et al. 2004). The first study, by Andrews et al. (2004), used data from approximately 110,000 children born between 1988 and 1997 and recorded in the General Practice Research Database (GPRD). The hazard ratios for cumulative exposure to thimerosal by 3, 4 or 6 months of age were all non-significant. Heron et al. (2004) used a prospective cohort of young children born in Avon followed from birth to school age. On a range of outcomes, no deleterious effect of thimerosal was reported in that study. Although ASD as a specific outcome was not examined, there was no association between thimerosal exposure and a statement of special educational needs, a category that would ordinarily comprise ASD children in the U.K.

130. In the U.S., Verstraeten et al. (2003) used data from the Vaccine Safety Datalink (VSD). The study was conducted in 2 phases. In the first phase, two HMOs (A and B) were enrolled in the study. HMO A had too few cases of autism to be analyzed according to a priori decisions made by the authors. HMO B had 202 autism cases, and the hazard ratios for 12.5 µg increases in thimerosal exposures at 1, 3, and 7 months were 1.16 (0.78-1.71), 1.06 (0.88-1.28), and 1.00 (0.90-1.09), respectively. Categorical analyses of cumulative exposure also showed no effect at age 3 and 7 months. In the second phase, a third HMO C was used to replicate any other

significant finding from phase 1, for autism or other outcomes. No significant increased risk for any of these outcomes was found.

131. A reanalysis of this study by petitioners' experts has shown that the original conclusions of Verstraeten et al. were entirely valid (Austin and Lally report, fall 2006).

132. In the U.K., Jick and Kaye (2004) examined records of children from the GPRD born between 1990 and 1998. ASD cases were matched to controls. The proportion of cases and controls exposed to three thimerosal-containing vaccine doses by age six months was comparable (92% vs 88%, respectively; OR = 1.6; 95% CI 0.7-3.3). This case-control study found no association between ASD and thimerosal-containing vaccines.

133. Madsen and al. (2003) conducted an ecologic study of thimerosal-containing vaccines and ASD using the Danish Registers of psychiatric hospitalizations since 1971, and all outpatient psychiatric visits since 1995. Thimerosal was removed from vaccines in Denmark in 1992, allowing for a comparison of rates of ASD before and after the use of thimerosal-containing vaccines. A clear increase in the incidence of ASD occurred after removal of thimerosal from vaccines. Stehr-Green et al. (2003) conducted a similar ecologic study of thimerosal-containing vaccines and autism in Sweden and Denmark during the 1980s and 1990s. Incidence rates of ASD in both countries began to rise slowly in the late 1980s when thimerosal-containing vaccines started to be used less often. ASD rates then markedly increased during the 1990s after cessation of thimerosal-containing vaccines (in Sweden, in 1993, and in Denmark, in 1992).

134. Other ecological studies have been conducted that showed a correlation between rising autism rates and increased use of thimerosal in childhood vaccines (Geier & Geier, 2003 & 2004; Blaxill, unpublished). None of these studies was controlled, and their methods have been reviewed and criticized by an ad hoc scientific committee appointed by the IOM. Detailed

descriptions of the methodological flaws in these studies can be found in the IOM's report (2004). These studies were considered to be uninformative and added nothing to the discussion on determining causality.

135. Reviews of this body of evidence by independent authors (Parker et al., 2004) and scientific committees (IOM, 2004) have concluded that the evidence favoured the rejection of the hypothesis of a link between thimerosal-containing vaccines and the development of autism in children.

136. We have since conducted another ecological study, in Quebec, where thimerosal in vaccines was removed altogether in 1996 due to the development of a new penta-vaccine that combined the polio vaccine with other vaccines (and, as a result, thimerosal could no longer be employed in the production of this vaccine). In an epidemiological study, we estimated the rates of autism for successive birth cohorts from 1987 to 1998. The rates of autism increased linearly during the whole period by about 10% each year. During the study period, the amount of thimerosal included in vaccines varied from a medium level from 1987 to 1991, to a high level from 1992 to 1995, and to a nil level from 1996 and beyond. As can be judged by a visual inspection of the data (see Figure below), and by statistical modeling of the data, we found no association between thimerosal and the risk of autism. This study adds to the existing body of evidence on the subject. Of note is the fact that the level of thimerosal included in vaccines in Quebec, from 1992 to 1995, was comparable to that used in the U.S. at the same time.

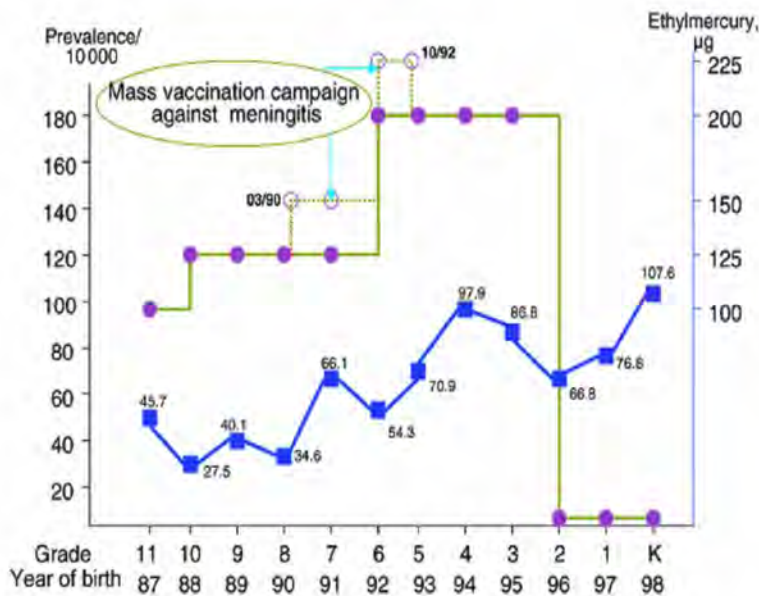


FIGURE 2  
Birth cohort prevalence rates and ethylmercury exposure. Dotted lines take into account the additional ethylmercury exposure because of a mass vaccination campaign against meningitis (see text).

*In sum, epidemiological evidence derived from well-conducted studies, by different groups of investigators, in different countries, has consistently failed to document an increased risk of ASD in relation to exposure to thimerosal, either as a categorical or a continuous exposure. All public health and scientific reviews of this question have rejected this hypothesis.*

### Michelle Cedillo

137. I have reviewed all available medical records of Michelle Cedillo. Michelle was born after a normal pregnancy. She was conceived after investigation of infertility in her parents and its treatment 4 weeks pre-conception with tubal insufflation. Birth circumstances were within normal limits. Birth weight, head circumference and vital functions were normal in the neonatal period, and she did not require any specific medical intervention.

138. Michelle was evaluated at Phoenix Children's Hospital at 2 years 11 months of age and diagnosed with autism according to both a standardized observational scale (the CARS)

and clinical examination using DSM-IV criteria (Exhibit 7: Letter from Dr Roth to Dr Matos, dated July 21, 1997). The diagnosis of Autistic Disorder was subsequently confirmed by Dr Lott, a child neurologist, on August 7, 1997 (Exhibit 4). It was also confirmed on subsequent evaluations by clinical experts, such as Drs Freeman and Cronin at UCLA, dated May 13, 1999, (Exhibit 31: pages 8-14), and the follow-up evaluation at UCLA, by Dr Freeman, dated August 21, 2000 (Exhibit 31: pages 1-7). In each clinical report, there are detailed behavioral descriptions that allowed me to rate DSM-IV criteria and confirm Michelle's diagnosis.

139. The severity of Michelle's condition is obvious from past and recent behavioral descriptions included in her medical file (Exhibits 4, 9, 31). At the initial evaluation by Dr Roth, Michelle obtained the very high score of 55 on the CARS (Childhood Autism Rating Scale), indicative of severe autism (Exhibit 4, pages 9-12). She displayed self-injurious behavior at age 5 and one-half and later (Exhibit 24, pages 5-7: letter from Mike and Theresa Cedillo, dated April 19, 2000). At age twelve, she remains an essentially non-verbal child, and she has profound and persistent impairments in her communication, social, and play skills.

140. Michelle's psychometric evaluations have also consistently shown that, in addition to her autism, she suffers from mental retardation to a severe degree. Thus, on the Bailey Scales of Infant Development, at the chronological age of 35 months, Michelle scored at the 4 month level, suggesting profound mental retardation, as indicated in Dr Roth's letter (Exhibit 7: Letter from Dr Roth to Dr Matos, dated July 21<sup>st</sup>, 1997). Later reevaluations, in 1999 and 2000, with an IQ test, the Mullens Scales of Early Learning, showed that Michelle's performance, in 1999, ranged from 6 to 10 months in age equivalents when she was age 56 months, and from 9 to 20 months, in 2000, when she was 71 months. (Exhibit 31: pages 1-14). Both results are indicative of severe mental retardation. Consistent with cognitive evaluations, parent-based evaluations of

Michelle's adaptive behavior with the Vineland Adaptive Behavior Scales consistently indicate performance in the retarded range in the domains of Communication, Socialization and Daily Living Skills, as indicated by age equivalents ranging from 1 to 11 months at 35 months of chronological age (Exhibit 7: Letter from Dr Roth to Dr Matos, dated July 21<sup>st</sup>, 1997); by age equivalents of 13 to 16 months at 56 months chronological age (Exhibit 31: page 10); and by age equivalents of 11 to 13 months at 71 months chronological age (Exhibit 31: page 4). Michelle is, therefore, severely mentally retarded as is often the case in girls with autism.

141. Michelle developed seizures at nine years old, a fact that is consistent with many studies which show that children with autism are at an increased risk for epilepsy, especially when they have severe autism associated with mental retardation, and that there exists a peak of onset of epilepsy during early adolescence.

142. The developmental history of Michelle is entirely consistent with a typical diagnosis of Autistic Disorder associated with mental retardation. Michelle's development and pattern of behavior are comparable to the children I have assessed during my entire career.

143. Michelle is an only child, and she is severely impaired. This has been and is understandably a source of extreme distress for her parents. Michelle's parents and relatives have been extremely committed to helping her achieve the best of her potential.

144. As is often the case with a severe developmental disorder such as autism, which has no specific cause that is yet known, Michelle's parents have sought advice about the causes and treatment of their daughter's handicap in a variety of ways. Like many other parents, they have tried different treatments amongst the dozens of interventions for autism of unproven efficacy. These included the secretin infusion (Exhibit 29), or the casein-free, gluten-free diet.

145. Michelle has been diagnosed over the years with a variety of other medical disorders that include pancreatitis, uveitis, Crohn's disease, obesity, gastritis, oesophagitis, osteoporosis, and arthritis. These medical disorders bear no relationship with autism, according to published medical literature. They just happen to co-occur in the same child, a child who has a diagnosis of autism. Having autism does not prevent etiologically independent conditions from occurring in the same person, as one can suffer concurrently from diabetes, cancer of the skin and myopia, all conditions being completely causally unrelated. There is a body of epidemiological evidence that is available and has not shown a relation between autism and the other medical disorders diagnosed in Michelle. One single case illustrating the co-occurrence of several medical conditions in one person cannot be taken as evidence for a causal association among them. Dr Kinsbourne's (petitioners' expert) comment on this issue is scientifically invalid.

146. Detailed comments about the co-occurring medical conditions in Michelle's medical history are provided in reports by other experts.

147. Petitioners' expert reports allude to different biological effects of thimerosal and of MMR that, in their view, might increase the risk of autism. However, there is no model of causation that is clearly argued in the expert reports, and there is no medical literature cited to support their theories or to describe convincingly the relevant biological mechanisms underpinning their comments. The petitioners' experts also failed to evaluate a large body of epidemiological literature that has consistently shown no association between MMR or thimerosal-containing vaccines and autism. Dr. Kinsbourne completely ignores the vast body of epidemiology by incorrectly asserting that it does not apply to Michelle Cedillo's case.

148. With this background, it is important to note the following facts about the appearance of signs of autism in Michelle's development, her vaccination history, and several

observations pertaining to her family history or her personal medical history. The petitioners' experts rely entirely on the assumption that Michelle had unambiguously normal development until her MMR vaccination on December 20, 1995, following which she experienced, only days after the vaccination, a regression and loss of skills that led to full blown autism. They further assume that Michelle's other medical conditions, especially those involving the gastrointestinal tract, developed after the MMR vaccination and are a consequence of it. Even if that were the case, this temporal coincidence would not be sufficient to establish a causal relationship. In fact, for reasons explained below, these assumptions do not hold true in Michelle's case.

149. In reviewing her medical file and history, it is important to identify the different sources and dates of information for various claims that are made, and to evaluate the degree of reliability and consistency between informants and sources of information. Recognition of the emergence of autistic symptoms in a child is highly subjective and reports can be contaminated by various sources of bias, especially when they are retrospective. It is, therefore, important to seek consistency of reporting and validation of retrospective accounts by independent and objective sources.

150. In Michelle's medical file, there is evidence of inconsistency and bias in several parental and professional reports about various aspects of her medical history. For example, taking the straightforward example of a milestone such as sitting without help (usually occurring before age 8 months), Ms Cedillo reports that Michelle was sitting alone by 6 or 7 months of age (Exhibit 25, page 10: form completed 1/12/99), whereas, based on the Initial Developmental Evaluation, it appears that Michelle reached this milestone at 11 months of age. (Exhibit 7; Dr Roth's letter dated July 21, 1997, page 2).

151. As is usually the case, the first symptoms of autism that worried Michelle's parents are difficult to date with precision. In the initial developmental evaluation by Dr Roth, the parents noticed the changes in Michelle three weeks after the two bouts of fever that followed the MMR immunization (Exhibit 7, page 2 of Dr Roth's letter). Later, however, the evaluation states that the "youngster seemed to develop normally up to about her 18<sup>th</sup> month" (Exhibit 7, page 3 of Dr Roth's letter). In the pediatrician's records, there is no mention at the January 6, 1996 visit of behavioral changes, a visit that occurred 16 days after the MMR vaccination. Behavioral changes are noted only at the March 15, 1996 visit, at age 18.5 months (Exhibit 8, page 1: "Talks less since ill in January"). In the report dated May 28, 1998, by Catherine Brown, a speech pathologist who evaluated Michelle, Mr and Ms Cedillo reported at that time that they "noticed a change in Michelle's behavior a few weeks after her illness following the MMR vaccination" (Exhibit 5, page 2). According to a note written by Ms Cedillo on April 24, 1997, in order to provide professionals with more detailed accounts of Michelle's development, "Michelle developed normally up to about her 18th month or so" (Exhibit 18, page 3). Later in the same note Ms Cedillo states, "it wasn't until she started to get better from fever, rash, and teeth that we realized that she wasn't talking like she used to" (Exhibit 18, page 4). All these convergent accounts make it clear that the parents started to recognize the first symptoms, in the form of a gradual change in Michelle's communication skills, progressively, sometime between early January 1996 and March 1996.

152. A very different account is provided by Ms Cedillo in a typed, undated (but written after June 2000) note included in the Good Samaritan Medical Center medical records. The note ends on Ms Cedillo's comment that "although not diagnosed, she [Michelle] has the symptoms of autistic enterocolitis discovered by Dr Andrew Wakefield" (Exhibit 21, page 12). As shown in other medical notes, Ms Cedillo, in late 1998, "discovered Wakefield's work, called & spoke to

Andy,” then “discovered Dr Cindy Schneider,” leading to “1<sup>st</sup> endoscopy” in May 2000 and in 2001, first “DAN conference, met Andy eventually got scoped - & discovered LNH.” (Exhibit 41, page 7). Ms Cedillo’s account regarding the first autistic symptoms in Michelle changed after she embraced Dr Wakefield’s theories, and she provides a narrative that is now consistent with Dr Wakefield’s earlier accounts, but which is totally inconsistent with her own previous accounts and those of several professionals collected before Dr Wakefield’s theories became known to the Cedillos. For example, to be consistent with the presumed onset of gastro-intestinal symptoms following the MMR vaccination, Ms Cedillo states that “on approximately that date, [Michelle] began a history of constipation.” The pediatric records, however, document multiple gastrointestinal symptoms in Michelle before the MMR vaccination, including an episode of constipation at 9 months of age that led to a prescription of glycerin suppositories by her doctor (Exhibit 8, page 3: note of 6/2/95: “extremely constipated on 2% milk, molasses and glycerin suppositories”), and to follow-up interventions for the same problem at age 12 months (Exhibit 8, page 2: Sept 6 1995: 2 tea spoons of mineral oil , molasses .....Stayed with whole milk....Gassy).

153. The first professionally documented symptoms of Michelle’s autism appeared in the pediatrician’s consultation of March 15, 1996, when Michelle was age 18.5 months (Exhibit 8, page 1: “Talks less since ill in Jan(uary)”). Based on previous notes from the pediatrician (“several words” at the September 6, 1995 visit: Exhibit 8, page 2), on Dr Roth’s developmental evaluation (“She had about ten words that she said mostly in imitation”; Exhibit 7, page 2), and on Ms Cedillo’s account (“At the 3/18/96 visit with Dr Cannell, I mentioned that she had quit talking...”; Exhibit 18, page 4), it appears that Michelle stopped using some words to communicate around the March 15, 1996 visit. As explained before, the precise date of this change is impossible to determine, but several accounts suggest that it occurred between January and

March 1996. Consistent with most descriptions of loss of language skills in autism during the second year of life, Michelle's loss of words was associated with other social and behavioral symptoms, i.e. she started to refuse to go out of her home unless for strolling or riding in wagons, and she became engrossed in watching Sesame Street on television (Exhibit 18, page 4). It is, therefore, likely that Michelle experienced regression in her developmental course, with loss of communicative and social skills associated with behavioral changes. This, however, does not mean that she was developing entirely normally prior to this loss or that regression was the first sign of autism.

154. Petitioners' experts argue that Michelle Cedillo was developing entirely normally prior to her MMR vaccination. However, the review of her medical records indicates early abnormalities both in her behavioral and social development, and in her biological development, as is explained in the next three paragraphs.

155. During the first developmental evaluation, Dr. Roth noted that Michelle "was a very good baby who cried little, and awakened to be fed. She could cry when she wanted to, but she appeared to be 'very content.' Michelle didn't smile until 4 to 6 months of age..." and "she had about 10 words that she said mostly in imitation". (Exhibit 7, page 2 of Dr Roth's letter). These descriptions are typical of the early manifestations of autism that have been reported retrospectively by parents, in the autism literature. Babies later diagnosed with autism are described as less socially responsive or active, and language, when it develops, progresses very slowly, lacks spontaneity and consistency, and relies on various parental prompts to occur (Bryson et al., 2007; Watson et al., 2007). Michelle's description as a baby fits the literature well. Therefore, it is likely that Michelle showed early, albeit mild signs, of social-communicative

impairments that are consistent with the early signs of dysfunction reported in the first year of life in children later diagnosed with autism.

156. In addition, Michelle showed unusual motor development as “she got in and out of an independent sitting position after 11 months of age,” and she did not walk before 16 months of age (Exhibit 7, page 2 of Dr Roth’s letter). She had excessive, and probably restricted, food intake to the point that her diet was discussed at her medical check-ups at 9, 12 and 15 months, with rising concerns about obesity (Exhibit 8). Michelle also displayed gastrointestinal symptoms during the same period, including constipation and gassiness, documented in pediatrician records as early as 9 months. As quoted by her mother, Michelle “has always been an easy one to throw up . . . she can taste something she doesn’t like and she vomits,” and “once they (antibiotics) hit her stomach, she vomits about 4 times in a row.” (Exhibit 18, page 8: Miscellaneous paragraph, dated May 29, 1997). At her 9 month pediatric visit, the pediatrician noted that Michelle had been vomiting on two consecutive days in the absence of a fever and that she had loose stools (Exhibit 28, page 265). Therefore, according to the medical records, before Michelle received her MMR vaccination there was evidence of gastrointestinal dysfunction, probable abnormal dieting patterns, and slight motor delay.

157. The monitoring of Michelle’s head circumference (HC) during her first year of life shows unambiguous signs of brain developmental abnormalities in the first semester of life (Exhibit 8, pages 7-8). At her 2 month check-up, Michelle’s HC was already on the 95<sup>th</sup> percentile. From 6 to 18 months, the HC chart shows clearly that Michelle’s HC is consistently off the chart and far beyond the 97<sup>th</sup> percentile that defines macrocephaly, with a maximal rate of head growth in the second semester of life. This abnormal head growth cannot be solely attributed to the general overgrowth syndrome displayed by Michelle (shown in her length and weight curves), as the HC

abnormal growth clearly exceeds that of body length. This pattern has been described in the literature on autism (Lainhart et al., 2006). This abnormally large HC is noted by her pediatrician for the first time when Michelle is six months old (Exhibit 8, page 4: 27 April 1995 visit). When evaluated by a child neurologist at 2 years 11 months of age, Michelle's HC was 53.5 cm (Exhibit 4, Dr Lott's report). Dr Lott notes that "as an infant, she was investigated for a large head circumference, but it is now closer to the normal range." Dr Lott reports the HC of Michelle's parents (58 cm for father, 55 cm for mother) compared to the Nellhaus charts for HC are both in the normal range for adults. This emphasizes the fact that the accelerated head growth during Michelle's infancy represents an abnormal developmental process that does not appear to have a familial basis. Dr Lott relates Michelle's abnormal HC to her diagnosis of autism, and he requires further neuroimaging examination to further investigate such abnormal findings (Exhibit 4, page 3). Michelle's HC chart and Dr Lott's findings clearly point toward abnormal brain development in Michelle's first year of life. The pattern of overgrowth in head circumference observed in Michelle is typical of the specific pattern of head overgrowth described in the autism literature, both in terms of timing in the developmental course and for its lack of proportionality to height.

158. Michelle's history of autistic symptoms is remarkably comparable to those medical records or histories of children whom I have assessed where exposure to thimerosal through the immunization schedule was either lower than in the U.S. (as in the U.K.) or nil (as in Quebec). Similarly, Michelle's history of autistic symptoms is comparable to those medical records or histories of children whom I have assessed and/or reviewed who had not received the MMR vaccine. It is a case, plain and simple, of classic autism.

### **Conclusion**

159. It is my opinion, to a reasonable degree of scientific and medical certainty, that thimerosal-containing vaccines and MMR vaccine neither caused nor contributed to Michelle Cedillo's autism. The claim that there is an autism epidemic caused by thimerosal-containing vaccines, or by MMR, is unfounded, without reliable scientific support, and is not generally accepted in the autism epidemiologic community. There is no reliable scientific or medical basis to support a conclusion that there is an association or a causal relationship between MMR or thimerosal-containing vaccines and ASDs, and the evidence favors rejection of such a causal relationship. There is strong evidence that signs of abnormal brain development and of autism were present in Michelle Cedillo before she received her MMR vaccination.



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## REFERENCES

1. Afzal MA, Ozoemena LC, O'Hare A, Kidger KA, Bentley ML, Minor PD. *Absence of detectable measles virus genome sequence in blood of autistic children who have had their MMR vaccination during the routine childhood immunization schedule of UK.* J Med Virol. 2006 May; 78(5): 623-30.
2. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. *Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2.* Nat Genet. 1999 Oct; 23(2): 185-8.
3. 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 Sep; 114(3): 584-91.
4. Autism Genome Project Consortium (with E. Fombonne). *Mapping autism risk loci using genetic linkage and chromosomal rearrangements.* Nat Genet. 2007 Mar; 39(3): 319-28. Epub 2007 Feb 18, 1-10.
5. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. *Autism as a strongly genetic disorder: evidence from a British twin study.* Psychol Med. 1995 Jan; 25(1): 63-77.
6. Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. *A clinicopathological study of autism.* Brain. 1998 May; 121 ( Pt 5): 889-905.
7. Baird G, Charman T, Baron-Cohen S, Cox A, Swettenham J, Wheelwright S, Drew A. *A screening instrument for autism at 18 months of age: a 6-year follow-up study.* J Am Acad Child Adolesc Psychiatry. 2000 Jun; 39(6): 694-702.
8. Baranek GT. *Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age.* J Autism Dev Disord. 1999 Jun; 29(3): 213-24.
9. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. *The incidence of autism in Olmsted County, Minnesota, 1976-1997: results from a population-based study.* Arch Pediatr Adolesc Med. 2005 Jan; 159(1): 37-44.
10. Bartholomeusz HH, Courchesne E, Karns CM. *Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults.* Neuropediatrics. 2002 Oct; 33(5): 239-41.

11. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. *Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation*. Pediatrics. 2001 Nov; 108(5): 1155-61.
12. 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 Aug 24; 325(7361): 419-21.
13. Blaxill M. *Thimerosal-containing vaccines and neurodevelopmental outcomes: testimony of Mr. Mark Blaxill, July 16, 2001*. Immunization Safety Review Committee, Public Meeting, 2001. 1-5.
14. Bolton P, Macdonald H, Pickles A, Rios P, Goode S, Crowson M, Bailey A, Rutter M. *A case-control family history study of autism*. J Child Psychol Psychiatry. 1994 Jul; 35(5): 877-900.
15. Bryson SE, Zwaigenbaum L, Brian J, Roberts W, Szatmari P, Rombough V, McDermott C. *A prospective case series of high-risk infants who developed autism*. J Autism Dev Disord. 2007 Jan; 37(1): 12-24. Epub 2007 Jan 9.
16. California Department of Developmental Services (DDS). *Changes in the population of persons with autism and pervasive developmental disorders in California's Developmental Services System: 1987 through 1998*. A Report to the Legislature, March 1, 1999 (19 pages). Available at: <http://www.dds.ca.gov/Autism/main/incidencrptfinal.pdf>.
17. California Department of Developmental Services (DDS). *Autistic spectrum disorders/ changes in the California caseload/ an update: 1999 through 2002*. April 2003 (25 pages). Available at: <http://www.dds.ca.gov/Autism/pdf/AutismReport2003.pdf>.
18. California Department of Developmental Services (DDS). Report to the legislature on the principle findings from the epidemiology of autism in California. A comprehensive pilot study. October 17, 2002 (70 pages). Available at: [http://www.dds.ca.gov/autism/pdf/study\\_final.pdf](http://www.dds.ca.gov/autism/pdf/study_final.pdf).
19. Carter AS, Volkmar FR, Sparrow SS, Wang JJ, Lord C, Dawson G, Fombonne E, Loveland K, Mesibov G, Schopler E. *The Vineland Adaptive Behavior Scales: supplementary norms for individuals with autism*. J Autism Dev Disord. 1998 Aug; 28(4): 287-302.
20. Casanova MF, Buxhoeveden DP, Switala AE, Roy E. *Minicolumnar pathology in autism*. Neurology. 2002 Feb 12; 58(3): 428-32.
21. Casanova MF, Buxhoeveden DP, Switala AE, Roy E. *Neuronal density and architecture (Gray Level Index) in the brains of autistic patients*. J Child Neurol. 2002 Jul; 17(7): 515-21.

22. Casanova MF, Buxhoeveden D, Gomez J. *Disruption in the inhibitory architecture of the cell minicolumn: implications for autism*. *Neuroscientist*. 2003 Dec; 9(6): 496-507.
23. Centers for Disease Control and Prevention. *Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, Six Sites, United States, 2000; Surveillance Summaries, Feb. 9*. *MMWR*, Vol. 56, (SS-1)(2007).
24. Centers for Disease Control and Prevention. *Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2002; Surveillance Summaries, Feb. 9*. *MMWR*, Vol. 56, (SS-1)(2007).
25. Chakrabarti S, Fombonne E. *Pervasive developmental disorders in preschool children*. *JAMA*. 2001 Jun 27; 285(24): 3093-9 (pages 1-14).
26. Chakrabarti S, Fombonne E. *Pervasive developmental disorders in preschool children: confirmation of high prevalence*. *Am J Psychiatry*. 2005 Jun; 162(6): 1133-41.
27. Chawarska K, Paul R, Klin A, Hannigen S, Dichtel LE, Volkmar F. *Parental recognition of developmental problems in toddlers with autism spectrum disorders*. *J Autism Dev Disord*. 2007 Jan; 37(1): 62-72.
28. Chen W, Landau S, Sham P, Fombonne E. *No evidence for links between autism, MMR and measles virus*. *Psychol Med*. 2004 Apr; 34(3): 543-53.
29. Chess S. *Autism in children with congenital rubella*. *J Autism Child Schizophr*. 1971 Jan-Mar; 1(1): 33-47.
30. Chess S. *Follow-up report on autism in congenital rubella*. *J Autism Child Schizophr*. 1977 Mar; 7(1): 69-81.
31. Courchesne E, Carper R, Akshoomoff N. *Evidence of brain overgrowth in the first year of life in autism*. *JAMA*. 2003 Jul 16; 290(3): 337-44.
32. D'Souza Y, Fombonne E, Ward BJ. *No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder*. *Pediatrics*. 2006 Oct; 118(4): 1664-75.
33. Dales L, Hammer SJ, Smith NJ. *Time trends in autism and in MMR immunization coverage in California*. *JAMA*. 2001 Mar 7; 285(9): 1183-5.

34. Dawson G, Osterling J, Meltzoff AN, Kuhl P. *Case study of the development of an infant with autism from birth to two years of age.* J Applied Developmental Psychology, 2000 21(3): 299-313.
35. Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. *Rate of head growth decelerates and symptoms worsen in the second year of life in autism.* Biol Psychiatry. 2007 Feb 15;61(4):458-64.
36. De Giacomo A, Fombonne E. *Parental recognition of developmental abnormalities in autism.* Eur Child Adolesc Psychiatry. 1998 Sep; 7(3): 131-6.
37. Demicheli V, Jefferson T, Rivetti A, Price D. *Vaccines for measles, mumps and rubella in children.* Cochrane Database Syst Rev. 2005 Oct 19; (4): CD004407. 1-33.
38. DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C. *Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta.* Pediatrics. 2004 Feb; 113(2): 259-66.
39. DeStefano F, Thompson WW. *MMR vaccine and autism: an update of the scientific evidence.* Expert Rev Vaccines. 2004 Feb; 3(1): 19-22.
40. DeWilde S, Carey IM, Richards N, Hilton SR, Cook DG. *Do children who become autistic consult more often after MMR vaccination?* Br J Gen Pract. 2001 Mar; 51(464): 226-7.
41. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS – FOURTH EDITION (DSM-IV). American Psychiatric Association, Washington, D.C., 1994. 69-84.
42. Eagle RS. *Commentary: Further commentary on the debate regarding increase in autism in California.* J Autism Dev Disord. 2004 Feb; 34(1): 87-8.
43. Farrington CP, Miller E, Taylor B. *MMR and autism: further evidence against a causal association.* Vaccine. 2001 Jun 14; 19(27): 3632-5.
44. Filipek PA, Accardo PJ, Ashwal S, Baranek GT, Cook EH Jr, Dawson G, Gordon B, Gravel JS, Johnson CP, Kallen RJ, Levy SE, Minshew NJ, Ozonoff S, Prizant BM, Rapin I, Rogers SJ, Stone WL, Teplin SW, Tuchman RF, Volkmar FR. *Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society.* Neurology. 2000 Aug 22; 55(4): 468-79.
45. Folstein S, Rutter M. *Infantile autism: a genetic study of 21 twin pairs.* J Child Psychol Psychiatry. 1977 Sep; 18(4): 297-321.

46. Fombonne E, du Mazaubrun C. *Prevalence of infantile autism in four French regions. Soc Psychiatry Psychiatr Epidemiol.* 1992 Aug; 27(4): 203-10.
47. Fombonne E. *Anorexia nervosa. No evidence of an increase. Br J Psychiatry.* 1995 Apr; 166(4): 462-71.
48. Fombonne E. *Depressive disorders: Time trends and possible explanatory mechanisms.* In: PSYCHOSOCIAL DISORDERS IN YOUNG PEOPLE: TIME TRENDS AND THEIR CAUSES. Rutter M & Smith D (Eds.). Wiley & Sons, 1995. 544-615.
49. Fombonne E. *Eating disorders: Time trends and possible explanatory mechanisms.* In: PSYCHOSOCIAL DISORDERS IN YOUNG PEOPLE: TIME TRENDS AND THEIR CAUSES. Rutter M & Smith D (Eds.). Wiley & Sons, 1995. 616-685.
50. Fombonne E. *Is bulimia nervosa increasing in frequency? Int J Eat Disord.* 1996 Apr; 19(3): 287-96.
51. Fombonne E. *Is the prevalence of autism increasing? J Autism Dev Disord.* 1996 Dec; 26(6): 673-6.
52. Fombonne E, Bolton P, Prior J, Jordan H, Rutter M. *A family study of autism: cognitive patterns and levels in parents and siblings. J Child Psychol Psychiatry.* 1997 Sep; 38(6): 667-83.
53. Fombonne E, Du Mazaubrun C, Cans C, Grandjean H. *Autism and associated medical disorders in a French epidemiological survey. J Am Acad Child Adolesc Psychiatry.* 1997 Nov; 36(11): 1561-9.
54. Fombonne E. *Increased rates of psychosocial disorders in youth. Eur Arch Psychiatry Clin Neurosci.* 1998; 248(1): 14-21.
55. Fombonne E. *Epidemiological surveys of autism.* In: AUTISM AND PERVERSIVE DEVELOPMENTAL DISORDERS. Volkmar F.R. (Ed.). Cambridge University Press, 1998. 32-63.
56. Fombonne E. *Time trends in affective disorders.* In: HISTORICAL AND GEOGRAPHICAL INFLUENCES ON PSYCHOPATHOLOGY. Cohen P, Slomkowski C, Robins L (Eds.). Lawrence Erlbaum Associates, 1998. 115-139.
57. Fombonne E, Roge B, Claverie J, Courty S, Fremolle J. *Microcephaly and macrocephaly in autism. J Autism Dev Disord.* 1999 Apr; 29(2): 113-9.

58. Fombonne E. *The epidemiology of autism: a review*. Psychol Med. 1999 Jul; 29(4): 769-86.
59. Fombonne E. *Is there an epidemic of autism?* Pediatrics. 2001 Feb; 107(2): 411-3.
60. Fombonne E, Chakrabarti S. *No evidence for a new variant of measles-mumps-rubella-induced autism*. Pediatrics. 2001 Oct; 108(4): E58 (8 pages).
61. Fombonne E. *Epidemiological trends in rates of autism*. Mol Psychiatry. 2002; 7 Suppl 2: S4-6.
62. Fombonne E. *Prevalence of childhood disintegrative disorder*. Autism. 2002 Jun; 6(2): 149-57.
63. Fombonne E. *The prevalence of autism*. JAMA. 2003 Jan 1; 289(1): 87-9.
64. Fombonne E, Cook EH. *MMR and autistic enterocolitis: consistent epidemiological failure to find an association*. Mol Psychiatry. 2003 Feb; 8(2): 133-4.
65. Fombonne E, Simmons H, Ford T, Meltzer H, Goodman R. *Prevalence of pervasive developmental disorders in the British nationwide survey of child mental health*. Int Rev Psychiatry. 2003 Feb-May; 15(1-2): 158-65.
66. Fombonne E. *Epidemiological surveys of autism and other pervasive developmental disorders: an update*. J Autism Dev Disord. 2003 Aug; 33(4): 365-82.
67. Fombonne E, Heavey L, Smeeth L, Rodrigues LC, Cook C, Smith PG, Meng L, Hall AJ. *Validation of the diagnosis of autism in general practitioner records*. BMC Public Health. 2004 Mar 3; 4: 5 (9 pages).
68. Fombonne E. *The Changing Epidemiology of Autism*. J Applied Res Intellectual Disabilities. 2005; 18: 281-94.
69. Fombonne E. *Epidemiology of autistic disorder and other pervasive developmental disorders*. J Clin Psychiatry. 2005; 66 Suppl 10: 3-8.
70. Fombonne E. *Epidemiological studies of pervasive developmental disorders*. In: HANDBOOK OF AUTISM AND PERVASIVE DEVELOPMENTAL DISORDERS THIRD EDITION. Volkmar FR, Paul R, Klin A, & Cohen D (Eds.). Wiley & Sons, 2005. 42-69.

71. Fombonne E. *The epidemiology of pervasive developmental disorders*. In: THE NEUROBIOLOGY OF AUTISM, 2ND EDITION. Bauman M & Kemper T (Eds.). Johns Hopkins University Press, 2005. 3-22.
72. Fombonne E. *The epidemiology of pervasive developmental disorders*. In: RECENT DEVELOPMENTS IN AUTISM RESEARCH. Casanova MF (Ed.). Nova Science Publishers, Inc., 2005. 1-25.
73. Fombonne E, Morel J, MacArthur J. *No autism amongst Inuits from Northern Quebec?* International Meeting for Autism Research (IMFAR), Montreal, June 1-3, 2006.
74. Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D. *Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations*. Pediatrics. 2006 Jul; 118(1): e139-50.
75. Fombonne E. *Past and Future Perspectives on Autism Epidemiology*. In: UNDERSTANDING AUTISM: FROM BASIC NEUROSCIENCE TO TREATMENT. Moldin S.O. & Rubenstein J (Eds.). CRC Press, Taylor & Francis Group, 2006. 25-48.
76. Fombonne E. *Epidemiology in child psychiatry*. In : LEWIS'S CHILD AND ADOLESCENT PSYCHIATRY : A COMPREHENSIVE TEXTBOOK, FOURTH EDITION. Martin A, Volkmar F.R., Lewis M (Eds.). Lippincott Williams & Wilkins 2007.
77. Frith U. AUTISM: EXPLAINING THE ENIGMA (COGNITIVE DEVELOPMENT), SECOND EDITION. Blackwell Publishing 2003.
78. Geier DA, Geier MR. *Response to JR Mann*. Exp Biol Med. 2003; 228(1): 993-94.
79. Geier MR, Geier DA. *Thimerosal in childhood vaccines, neurodevelopment disorders, and heart disease in the United States*. J Amer Phys Sur 2003 8(1): 6-11.
80. Geier DA, Geier MR. *An assessment of the impact of thimerosal on childhood neurodevelopmental disorders*. Pediatr Rehabil. 2003 Apr-Jun; 6(2): 97-102.
81. Geier MR, Geier DA. *Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication*. Exp Biol Med (Maywood). 2003 Jun; 228(6): 660-4.
82. 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.* Med Sci Monit. 2004 Mar; 10(3): PI33-9.
83. Gillberg C, Heijbel H. *MMR and autism.* Autism 1998; 2: 423-4.
  84. Gurney JG, Fritz MS, Ness KK, Sievers P, Newschaffer CJ, Shapiro EG. *Analysis of prevalence trends of autism spectrum disorder in Minnesota.* Arch Pediatr Adolesc Med. 2003 Jul; 157(7): 622-7.
  85. Heller T. *Dementia infantilis.* Zeitschrift für die Erforschung und Behandlung des Jünglichen Schwachsinn 1908 2: 141-65.
  86. Heron J, Golding J; ALSPAC Study Team. *Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United Kingdom does not support a causal association.* Pediatrics. 2004 Sep; 114(3): 577-83.
  87. Honda H, Shimizu Y, Rutter M. *No effect of MMR withdrawal on the incidence of autism: a total population study.* J Child Psychol Psychiatry. 2005 Jun; 46(6): 572-9.
  88. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. *Association between thimerosal-containing vaccine and autism.* JAMA. 2003 Oct 1; 290(13): 1763-6.
  89. INTERNATIONAL CLASSIFICATION OF DISEASES, TENTH EDITION (ICD-10), Version 2007. Chapter 5: Mental and behavioural disorders (F00-F99), Disorders of psychological development (F80-F89). World Health Organization, 2006 (5 pages).
  90. Institute of Medicine (IOM). *Immunization Safety Review: Vaccines and Autism.* 2004; Washington, D.C.: National Academies Press (filed as Respondent's Exhibit JJ).
  91. International Molecular Genetic Study of Autism Consortium. *A full genome screen for autism with evidence for linkage to a region on chromosome 7q.* Hum Mol Genet. 1998 Mar; 7(3): 571-8.
  92. Jick H, Kaye JA, Black C. *Changes in risk of autism in the U.K. for birth cohorts 1990-1998.* Epidemiology. 2003 Sep; 14(5): 630-2.
  93. Jick H, Kaye JA. *Epidemiology and possible causes of autism.* Pharmacotherapy. 2003 Dec; 23(12): 1524-30
  94. Jick H, Kaye JA. *Autism and DPT vaccination in the United Kingdom.* N Engl J Med. 2004 Jun 24; 350(26): 2722-3.

95. Kaye JA, del Mar Melero-Montes M, Jick H. *Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis.* BMJ. 2001 Feb 24; 322(7284): 460-3.
96. Kemper TL, Bauman ML. *Neuropathology of infantile autism.* Mol Psychiatry. 2002; 7 Suppl 2: S12-3.
97. Kielinen M, Linna SL, Moilanen I. *Autism in Northern Finland.* Eur Child Adolesc Psychiatry. 2000 Sep; 9(3): 162-7.
98. Klin A, Chawarska K, Paul R, Rubin E, Morgan T, Wiesner L, Volkmar F. *Autism in a 15-month-old child.* Am J Psychiatry. 2004 Nov; 161(11): 1981-8.
99. Kobayashi R, Murata T. *Setback phenomenon in autism and long-term prognosis.* Acta Psychiatr Scand. 1998 Oct; 98(4): 296-303.
100. Lainhart JE, Ozonoff S, Coon H, Krasny L, Dinh E, Nice J, McMahon W. *Autism, regression, and the broader autism phenotype.* Am J Med Genet. 2002 Dec 1; 113(3): 231-7.
101. Lainhart JE, Bigler ED, Bocian M, Coon H, Dinh E, Dawson G, Deutsch CK, Dunn M, Estes A, Tager-Flusberg H, Folstein S, Hepburn S, Hyman S, McMahon W, Minshew N, Munson J, Osann K, Ozonoff S, Rodier P, Rogers S, Sigman M, Spence MA, Stodgell CJ, Volkmar F. *Head circumference and height in autism: a study by the Collaborative Program of Excellence in Autism.* Am J Med Genet A. 2006 Nov 1;140(21):2257-74.
102. Landa R, Garrett-Mayer E. *Development in infants with autism spectrum disorders: a prospective study.* J Child Psychol Psychiatry. 2006 Jun; 47(6): 629-38.
103. Lingam R, Simmons A, Andrews N, Miller E, Stowe J, Taylor B. *Prevalence of autism and parentally reported triggers in a north east London population.* Arch Dis Child. 2003 Aug; 88(8): 666-70.
104. Lord C, Shulman C, DiLavore P. *Regression and word loss in autistic spectrum disorders.* J Child Psychol Psychiatry. 2004 Jul; 45(5): 936-55.
105. 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.* N Engl J Med. 2002 Nov 7; 347(19): 1477-82.
106. 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 Sep; 112(3 Pt 1): 604-6.
107. Madsen KM, Vestergaard M. *MMR vaccination and autism : what is the evidence for a causal association?* Drug Saf. 2004; 27(12): 831-40.
  108. Makela A, Nuorti JP, Peltola H. *Neurologic disorders after measles-mumps-rubella vaccination.* Pediatrics. 2002 Nov; 110(5): 957-63.
  109. Mars AE, Mauk JE, Dowrick PW. *Symptoms of pervasive developmental disorders as observed in prediagnostic home videos of infants and toddlers.* J Pediatr. 1998 Mar; 132(3 Pt 1): 500-4.
  110. Medical Research Council (MRC). *MRC review of autism research/epidemiology and causes.* Dec 2001; London, United Kingdom: 92 pages.
  111. Miles JH, Hillman RE. *Value of a clinical morphology examination in autism.* Am J Med Genet. 2000 Apr 10; 91(4): 245-53.
  112. Molloy CA, Manning-Courtney P. *Prevalence of chronic gastrointestinal symptoms in children with autism and autistic spectrum disorders.* Autism. 2003 Jun; 7(2): 165-71.
  113. Muhle R, Trentacoste SV, Rapin I. *The genetics of autism.* Pediatrics. 2004 May; 113(5): e472-86.
  114. Murch SH, Anthony A, Casson DH, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Valentine A, Davies SE, Walker-Smith JA. *Retraction of an interpretation.* Lancet. 2004 Mar 6; 363(9411): 750.
  115. Nelson KB, Grether JK, Croen LA, Dambrosia JM, Dickens BF, Jelliffe LL, Hansen RL, Phillips TM. *Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation.* Ann Neurol. 2001 May; 49(5): 597-606.
  116. Osterling JA, Dawson G, Munson JA. *Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation.* Dev Psychopathol. 2002 Spring; 14(2):239-51.
  117. Parker SK, Schwartz B, Todd J, Pickering LK. *Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data.* Pediatrics. 2004 Sep; 114(3): 793-804.
  118. 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 Dec; 19(12): 1127-34.

119. Peltola H, Patja A, Leinikki P, Valle M, Davidkin I, Paunio M. *No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study.* Lancet. 1998 May 2; 351(9112): 1327-8 (4 pages).
120. Peltola H, Davidkin I, Paunio M, Valle M, Leinikki P, Heinonen OP. *Mumps and rubella eliminated from Finland.* JAMA. 2000 Nov 22-29; 284(20): 2643-7.
121. Pickles A, Bolton P, Macdonald H, Bailey A, Le Couteur A, Sim CH, Rutter M. *Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: a twin and family history study of autism.* Am J Hum Genet. 1995 Sep; 57(3): 717-26.
122. Powell JE, Edwards A, Edwards M, Pandit BS, Sungum-Paliwal SR, Whitehouse W. *Changes in the incidence of childhood autism and other autistic spectrum disorders in preschool children from two areas of the West Midlands, UK.* Dev Med Child Neurol. 2000 Sep; 42(9): 624-8.
123. Redcay E, Courchesne E. *When is the brain enlarged in autism? A meta-analysis of all brain size reports.* Biol Psychiatry. 2005 Jul 1; 58(1): 1-9.
124. Richler J, Luyster R, Risi S, Hsu WL, Dawson G, Bernier R, Dunn M, Hepburn S, Hyman SL, McMahon WM, Goudie-Nice J, Minshew N, Rogers S, Sigman M, Spence MA, Goldberg WA, Tager-Flusberg H, Volkmar FR, Lord C. *Is there a 'regressive phenotype' of Autism Spectrum Disorder associated with the measles-mumps-rubella vaccine? A CPEA Study.* J Autism Dev Disord. 2006 Apr; 36(3): 299-316 (18 pages).
125. Risch N, Spiker D, Lotspeich L, Nouri N, Hinds D, Hallmayer J, Kalaydjieva L, McCague P, Dimiceli S, Pitts T, Nguyen L, Yang J, Harper C, Thorpe D, Vermeer S, Young H, Hebert J, Lin A, Ferguson J, Chiotti C, Wiese-Slater S, Rogers T, Salmon B, Nicholas P, Petersen PB, Pingree C, McMahon W, Wong DL, Cavalli-Sforza LL, Kraemer HC, Myers RM. *A genomic screen of autism: evidence for a multilocus etiology.* Am J Hum Genet. 1999 Aug; 65(2): 493-507.
126. Rodier PM, Bryson SE, Welch JP. *Minor malformations and physical measurements in autism: data from Nova Scotia.* Teratology. 1997 May; 55(5): 319-25.
127. Rodier PM, Hyman SL. *Early environmental factors in autism.* MRDD Res Revs 1998; 4: 121-28.
128. Rodier PM. *The early origins of autism.* Sci Am. 2000 Feb; 282(2): 56-63.

129. Rodier PM. *2003 Warkany Lecture: Autism as a birth defect*. Birth Defects Res A Clin Mol Teratol. 2004 Jan; 70(1): 1-6.
130. Rodier PM. *Autism as a birth defect: Reply to Dr. Simon*. Birth Defects Res A Clin Mol Teratol 2004; 70(6): 417.
131. Rogers SJ. *Developmental regression in autism spectrum disorders*. Ment Retard Dev Disabil Res Rev. 2004; 10(2): 139-43.
132. Rutter M, Bailey A, Bolton P, Le Couteur A. *Autism and known medical conditions: myth and substance*. J Child Psychol Psychiatry. 1994 Feb; 35(2): 311-22.
133. Scott FJ, Baron-Cohen S, Bolton P, Brayne C. *Brief report: prevalence of autism spectrum conditions in children aged 5-11 years in Cambridgeshire, UK*. Autism. 2002 Sep; 6(3): 231-7.
134. Shattuck PT. *Diagnostic substitution and changing autism prevalence*. Pediatrics. 2006 Apr; 117(4): 1438-9.
135. Smalley SL, Collins F. *Brief report: genetic, prenatal, and immunologic factors*. Autism Dev Disord. 1996 Apr; 26(2): 195-8.
136. Smeeth L, Hall AJ, Fombonne E, Rodrigues LC, Huang X, Smith PG. *A case-control study of autism and mumps-measles-rubella vaccination using the general practice research database: design and methodology*. BMC Public Health. 2001; 1: 2 (7 pages).
137. 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 Sep 11-17; 364(9438): 963-9.
138. Smeeth L, Cook C, Fombonne PE, Heavey L, Rodrigues LC, Smith PG, Hall AJ. *Rate of first recorded diagnosis of autism and other pervasive developmental disorders in United Kingdom general practice, 1988 to 2001*. BMC Med. 2004 Nov 9; 2: 39 (8 pages).
139. Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, Maravilla KR, Giedd JN, Munson J, Dawson G, Dager SR. *Brain structural abnormalities in young children with autism spectrum disorder*. Neurology. 2002 Jul 23; 59(2): 184-92.
140. Steffenburg S, Steffenburg U, Gillberg C. *Autism spectrum disorders in children with active epilepsy and learning disability: comorbidity, pre- and perinatal background, and seizure characteristics*. Dev Med Child Neurol. 2003 Nov; 45(11): 724-30.

141. Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D. *Autism and thimerosal-containing vaccines: lack of consistent evidence for an association.* Am J Prev Med. 2003 Aug; 25(2): 101-6.
142. Stratton KR, Howe CJ, Johnston RB Jr. *Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine.* JAMA. 1994 May 25;271(20):1602-5.
143. Szatmari P, Jones MB, Zwaigenbaum L, MacLean JE. *Genetics of autism: overview and new directions.* J Autism Dev Disord. 1998 Oct; 28(5): 351-68.
144. Takahashi H, Suzumura S, Shirakizawa F, Wada N, Tanaka-Taya K, Arai S, Okabe N, Ichikawa H, Sato T. *An epidemiological study on Japanese autism concerning routine childhood immunization history.* Jpn J Infect Dis. 2003 Jun; 56(3): 114-7.
145. Taylor B, Miller E, Farrington CP, Petropoulos MC, Favot-Mayaud I, Li J, Waight PA. *Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association.* Lancet. 1999 Jun 12; 353(9169): 2026-9.
146. 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. 2002 Feb 16; 324(7334): 393-6.
147. Taylor, B, Rutter M. *Classification: Conceptual issues and substantive findings.* In: CHILD AND ADOLESCENT PSYCHIATRY. Rutter M & Taylor E (Eds.). Blackwell Science Ltd. 2002. 3-17.
148. Taylor B. *Vaccines and the changing epidemiology of autism.* Child Care Health Dev. 2006 Sep; 32(5): 511-9.
149. Uchiyama T, Kurosawa M, Inaba Y. *MMR-vaccine and regression in autism spectrum disorders: negative results presented from Japan.* J Autism Dev Disord. 2007 Feb; 37(2): 210-7.
150. 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 Nov; 112(5): 1039-48.
151. Volkmar FR, Klin A, Siegel B, Szatmari P, Lord C, Campbell M, Freeman BJ, Cicchetti DV, Rutter M, Kline W, et al. *Field trial for autistic disorder in DSM-IV.* Am J Psychiatry. 1994 Sep; 151(9): 1361-7.

152. 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 Feb 28; 351(9103): 637-41.
153. Watson LR, Baranek GT, Crais ER, Steven Reznick J, Dykstra J, Perryman T. *The first year inventory: retrospective parent responses to a questionnaire designed to identify one-year-olds at risk for autism.* J Autism Dev Disord. 2007 Jan; 37(1): 49-61.
154. Werner E, Dawson G, Osterling J, Dinno N. *Brief report: Recognition of autism spectrum disorder before one year of age: a retrospective study based on home videotapes.* J Autism Dev Disord. 2000 Apr; 30(2): 157-62.
155. Werner E, Dawson G. *Validation of the phenomenon of autistic regression using home videotapes.* Arch Gen Psychiatry. 2005 Aug; 62(8): 889-95.
156. Wing L, Gould J. *Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification.* J Autism Dev Disord. 1979 Mar; 9(1): 11-29.
157. Wolff, S, Chess, S. *A Behavioural Study of Schizophrenic Children.* Acta Psychiatr Scand. 1964; 40: 438-66.
158. Wolff, S. *The first account of the syndrome Asperger's described?* Translation of a paper entitled Die schizoiden Psychopathien im Kindesalter by Dr. GE Ssucharewa, 1926 – Monatsschrift für Psychiatrie und Neurologie 60: 235-61. European Child and Adolescent Psychiatry 1996; 5: 119-32.
159. Woo EJ, Ball R, Bostrom A, Shadomy SV, Ball LK, Evans G, Braun M. *Vaccine risk perception among reporters of autism after vaccination: vaccine adverse event reporting system 1990-2001.* Am J Public Health. 2004 Jun; 94(6): 990-5.
160. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. *Behavioral manifestations of autism in the first year of life.* Int J Dev Neurosci. 2005 Apr-May; 23(2-3): 143-52.