

# **Respondent's Exhibit MM**

**Eric Fombonne, M.D., F.R.C.Psych**

Canada Research Chair in Child Psychiatry

Professor of Psychiatry McGill University

Director of the Department of Psychiatry at the Montreal Children's Hospital

**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 or pharmaceutical companies.

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 Medical Research Council (MRC) Child Psychiatry Unit 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 also conducted research on child and adolescent depression and headed a clinical service for depressed youths in addition to my clinical activities in autism. 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 1995a and 1995b), I published several scientific articles on the topic (i.e., Fombonne, 1995c; Fombonne, 1996a; Fombonne, 1998a & 1998b). In 1996, I published on the issue of secular changes in the incidence or prevalence of autism in an editorial column (Fombonne, 1996b). 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., 1997b). 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, 2001c).

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 of the only Canadian team funded in the new genetic research initiative funded by the U.S.-based Simons Foundation. 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. With the support of Autism Speaks, I am currently consulting with public health authorities in Mexico to design the first epidemiological study of autism there. I am also planning the first survey of autism in Belarussia using data already collected on over 13,000 children in a Canadian-funded research study.

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 in different countries.

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. I am on the Advisory Editorial Board of the new scientific journal *Autism Research* that was launched in 2008 by the International Society for Autism Research (ISAR).

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. I was an invited consultant to an American Psychiatric Association workshop in Sacramento, CA (3-5 February 2008) to set up the future research agenda for autism research and advice on changes in diagnostic

concepts and criteria that will appear in 2010 in the new (fifth) edition of the *Diagnostic and Statistical Manual of Mental Disorders*.

14. I have published over 170 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 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 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 whom 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, 2002a). 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, and on average close to 3 years of age (Volkmar, 1992), 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 ultimately 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, 2003a, 2005a, and 2005b). 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., 2006a).

#### **Onset of Autistic Disorder**

32. The onset of Autistic Disorder is difficult to measure. 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). Vaccinations are given to children between birth and two years of age. Therefore, the age of onset of autism and the date of vaccinations are constrained by an overlapping time window. Thus, it follows that, in many children, the onset of first autistic symptoms will occur just after their routine vaccinations, 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 vaccinations, or similar causes, are responsible for their child's autism (Lingam et al., 2003; Woo et al., 2004). In previous studies (when vaccinations were 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 (Luyster et al., 2005; 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. This was further illustrated in a recent study documenting clearly abnormal patterns of head growth before the first birthday in a sample of autistic children. This unusual acceleration of head growth was seen with similar frequency in the regressive group as compared to the early-onset group (Webb et al., 2007). This finding again illustrates both the presence of objective developmental abnormalities before the regression and the similarity between the regressive and non-regressive groups.

39. 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.

40. 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 entirely triggered by environmental factors, as opposed to only genetic ones, then one would expect the rate of autistic characteristics (known as the broad autism phenotype) in relatives of individuals with regressive autism to be lower than in those of non-regressive individuals. 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).

41. Even if one postulates that regressive autism is triggered by environmental factors in genetically susceptible individuals, several testable predictions could be made if thimerosal-containing vaccines were hypothesized to be such an environmental trigger. First, the parents of children with regressive autism born in the 1990s were exposed to much smaller doses of thimerosal in vaccines than were their children. Thus, if the above postulate were true, we would expect to see a lower rate of autism in these older individuals than in relatives of non-regressive autistic children, but that is not the case (Lainhart et al., 2002). Second, one would expect that the proportion of regressive autism would have increased over time as a function of increased exposure to higher doses of thimerosal in vaccines, which has not occurred. Third, the proportion of regressive autism should be higher in countries like the U.S. where exposure to thimerosal was higher than in countries (i.e., in Europe) with lower cumulative doses of thimerosal in childhood

vaccines, which is also not the case. Finally, one would expect to see a decrease in rates of autism in the population, especially of the regressive form, following discontinuation of use of thimerosal-containing vaccines, which, again, has not been found (see below).

### **Autism and Mental Retardation**

42. 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). Subjects with autistic disorder who have an IQ within the normal range (IQ>70) are often designated as having “high-functioning autism” (HFA) but HFA represents merely a convenient descriptor and is not a subtype or separate diagnostic variant of autistic disorder. 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**

43. 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.

44. 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.

45. In a more recent study documenting abnormal head growth during the end of the first year of life in children later diagnosed with autism, the abnormal pattern of head growth

occurred at similar frequencies in regressive and non-regressive children (Webb et al., 2007). This finding is important as it confirms that developmental abnormalities occur in children with regressive autism much before the loss of skills.

### **Natural History and Outcome**

46. Follow-up studies have consistently shown that autistic symptoms persist throughout one's life span even though marked improvements can sometimes be seen in subjects with good language and cognitive skills (Eisenberg, 1956; Lotter, 1978; Lockyer and Rutter, 1969; Howlin et al., 2004). In more recent studies, diagnostic stability has been confirmed from preschool years to mid-school age for Autistic Disorder (Lord et al., 2006; Charman et al., 2005), whereas some optimal outcomes have been described in up to 10% of children with an initial PDDNOS diagnosis – some children lose their initial ASD diagnosis even though they present with persisting language or attentional difficulties (Fein et al., 2005; Kelley et al., 2006). These findings are important for two reasons. First, improvement occurs in autism as a function of both biological maturation and of access to treatments with documented efficacy (i.e., early intensive behavioral interventions). Thus, interpreting a positive change in an individual child is virtually impossible because a clinician cannot tease apart the effects of the natural history of the disorder and those of treatment (and, when multiple treatments are simultaneously administered, no causal inference about the effect of one treatment regarding the change can be made at all). Second, improvements have been documented in generations of children exposed to the 1990s' regimen of thimerosal-containing vaccines, who were not chelated, thereby suggesting that mercury exposure bears no relationship with these trajectories.

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

47. The actual cause of autism in approximately 5-10% of the diagnosed cases can be determined (Fombonne, 2003a; 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.

48. 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).

49. Tuberosc Sclerosis and Fragile X are genetic disorders described in association with autism.

50. 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 and 1977). Currently, congenital rubella does not account for more than a handful of cases of autism, due to prevention through systematic vaccination against rubella.

51. 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.

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

53. 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.

54. 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.

55. 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., 1997a). It is believed that subjects presenting with this broader phenotype carry some, but not all, of the genes involved in autism.

56. 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.

57. 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; Freitag, 2007). 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 (either microdeletions or microduplications) in the DNA that were thus far undetected with conventional cytogenetic techniques, and that represent *de novo* mutations, appear to explain autism in a substantial minority of families. These findings have been replicated in other studies (Sebat et al., 2007; Marshall et al., 2008) and new deletions and duplications on the short arm of the chromosome 16 have been shown recently to account for as much as 1% of ASD cases (Weiss et al., 2008). 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.

58. 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, 2004a & 2004b).

59. In addition, cranio-facial dysmorphism and dysfunction of the cranial nerves are common in children with autism (Rodier, 2000, 2004a & 2004b). 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.

60. 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>

61. 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

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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).

attained in the first 40 days of gestation in primate species (Casanova et al, 2002a, 2002b, & 2003), again suggesting that an early, prenatal, pathological process is involved in autism.

62. 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.

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

63. 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.

64. I recently reviewed the epidemiological literature on autism (Fombonne, 2005a, 2005b, 2005c, 2005d, 2005e, & 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., 2006b). 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 (Centers for Disease Control and Prevention, 2007a & 2007b). This estimate (0.6-0.7%) appears to be the best estimate for the prevalence of ASDs currently available.

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

65. 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., 1997b). Further studies that I have performed myself, and systematic reviews of new evidence, have confirmed my initial conclusions (Fombonne, 2003a & 2005b).

66. 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.

67. 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.

68. 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

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

70. 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; Atladottir et al., 2007). 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

71. 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, 2005b & 2005c).

72. 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.

73. 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.

74. 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 & 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
Sturme & James, 2001	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

75. 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).

76. 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.

77. 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 & Fombonne (2005)							

78. 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., 1997b). 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.

79. 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*

80. 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 1988-1992 to 2000-2001 (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.

81. A more recent study deriving from the Danish National Psychiatric register provided cumulative incidence data for autism and ASDs together with data on Tourette syndrome,

hyperkinetic disorder, and obsessive-compulsive disorder (OCD) (Atladottir et al., 2007). The population size of children born between 1990 and 1999 was 669,995 children. Outcome data for each birth cohort were collected from 1995 through 1999, a period in which ICD-10 codes were in use and both inpatient and outpatient data were included in the National register. Statistically significant increases were reported for successive birth cohorts for all disorders except OCD. The study was uninformative about the possible causes of these trends but clearly showed that the increase over time was not specific to autism or ASDs, but rather applied to a range of neurodevelopmental disorders.

82. The available epidemiological evidence does not support the hypothesis that the incidence of autism has increased for reasons other than changes in diagnostic practices and improved detection. 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.

## Have Rates of Regressive Autism Increased?

83. 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)	Retrogressive 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.

84. In the earlier studies, the rates of regressive autism in autistic series ranged from 20% to 50% (see Table 1 above from Fombonne and Chakrabarti, 2001c; Rogers, 2004). These rates and descriptions were established before any concerns about immunizations were raised and when the cumulative exposure of infants to thimerosal was much lower than in recent years. To give specific examples, in 1964, Wolff and Chess made the following clinical observations about regression:

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)

85. 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 about 20% (Fombonne & Chakrabarti, 2001c; 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.

86. 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, 2001c). 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 mostly in the 1970s. The Staffordshire sample was born between 1992 and 1995. 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 an increase in regressive autism over a 20-year period.

87. 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). 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 during this interval.

88. 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. A test for trend showed no significant ( $p > .75$ ) change in the proportion of cases with regression (Fombonne et al., 2004).

89. In Japan, Uchiyama et al. (2007) studied 904 children diagnosed with ASD and born between 1976 and 1999. The study was designed to test the relationship between MMR exposure and regressive autism. 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 rightly concluded that their findings disproved the hypothesis that MMR causes regression in ASD. Irrespective of the MMR question, the value of this study is that it adds to the evidence of stability over time in the proportion of regressive autism cases.

90. *Regression in autism was described a long time ago. Studies that have assessed trends over time in regressive autism have not shown an increase in regressive autism.*

### Childhood Vaccines and Autism

91. 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 a live attenuated vaccine). 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; D'Souza et al., 2006; Afzal et al., 2006; Baird et al., 2008). I now review epidemiological studies that are relevant to the hypothesis of an increased risk of ASD following exposure to thimerosal-containing vaccines.

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

92. 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. These studies are reviewed in the following sections.

93. 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. The sample was ascertained over the whole country and yielded a large sample of 440 cases with autism in particular, and 787 cases of ASDs in general. In Denmark, the vaccine schedule involved three immunizations at 5 weeks, 9 weeks, and 10 months of age with the first dose containing 50 $\mu$ g of thimerosal and the following two doses each containing 100 $\mu$ g of thimerosal. Thus, as thimerosal contains about 50% ethylmercury, the total exposure at 10 months of age was 125 $\mu$ g of ethylmercury. Of note, at 3 months of age, Danish children were exposed to 75 $\mu$ g of ethylmercury, which is comparable to the exposure of children in the U.S. in the 1990s. The recruitment of an unexposed group in that study was facilitated by the fact that, in Denmark, thimerosal was discontinued in vaccine production in 1992. Therefore, the unexposed cohort is less likely to represent a biased or atypical group of children who are not

following the immunization schedule because they are at risk of some sort of neurodevelopmental disorder.

94. For autism, after adjusting for calendar period and age, the incidence rate ratio was 0.85 (95%CI: 0.60-1.20) for autism, and 1.12 (95% CI: 0.88-1.43) for ASDs. This shows no increased risk following vaccination with any thimerosal-containing vaccine as compared to that following vaccination with only thimerosal-free vaccines. When results were adjusted for age, calendar period, gender, birthplace, birth weight, 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 ethylmercury exposure. There was no evidence of a dose response with increasing ethylmercury exposure for either autism or ASD. Thus, the rates ratio for any increase of 25 $\mu$ g in the level of ethylmercury exposure were 0.98 (95% CI: 0.90-1.06) for autism, and 1.03 (95% CI: 0.98-1.09) for ASDs. Various potential sources of biases (to test for misclassification on exposure in 1992, for diagnostic heterogeneity, or for missing values) were considered in subsequent analyses that did not show they were likely to have resulted in these negative findings. In addition, a time trend analysis showed statistically significant increases in age-adjusted risk ratios for autism (RR=1.24; 95% CI: 1.17-1.31) and for ASDs (RR=1.21; 95% CI: 1.16-1.27) during the study period. As new data from outpatient clinics were added to the national database in the course of the study, the authors tested whether or not these changes in ascertainment could have affected the results. They conducted an additional time trend analysis restricting the sample to a time period (1995-2000) where no change occurred in the registry. The time trends analysis in this restricted sample showed rigorously comparable and statistically significant increases in age-adjusted risk ratios for autism (RR=1.24; 95% CI: 1.16-1.32) and for

ASDs (RR=1.20; 95% CI: 1.13-1.26). The study was population-based, well-powered, and published in the renowned scientific journal, JAMA.

95. 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). To be eligible to participate in the study, children had to be followed from birth until age 2 or more and could not have any pre-, peri-, or post-natal conditions or negative developmental outcomes in the first six months of life. Exposure to thimerosal was ascertained from the electronic records using information about DTP and DT vaccines received by the study subjects. A validation study was conducted on a small sample recruited from 152 general practices and 80% of the GPRD diagnoses for neurodevelopmental disorders were confirmed by independent inspection of medical records.

96. The hazard ratios for cumulative exposure to thimerosal by 3, 4 or 6 months of age were all non-significant. More specifically, after adjustment on date of birth and gender, the hazard ratios for autism were 0.89 (95% CI: 0.65-1.21) and 0.94 (95%CI: 0.73-1.21) for receiving an additional vaccine dose by 3 and 4 months of age, respectively. An analysis of thimerosal exposure using a composite continuous index yielded an adjusted hazard ratio of 0.99 (95%CI: 0.88-1.12), showing no dose response relationship. The Andrews et al. (2004) study was published in the very respected journal, *Pediatrics*.

97. Heron et al. (2004) used a prospective cohort of about 13,000 young children born in Avon followed from birth to school age. The exposure to thimerosal was calculated at 3, 4, and 6 months of age on children who were exposed to the normal U.K. immunization schedule. On a range of outcomes collected over time between 6 and 91 months of

age, no deleterious effect of thimerosal was reported. 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. (see Heron et al., 2004, page 578, paragraph on Special Needs). The adjusted odds ratios for the likelihood of a Local Educational Authority statement at 91 months of age were nonsignificant at 3 months of age (OR=0.78, 95%CI: 0.60-1.02), at 4 months of age (OR=0.83, 95%CI: 0.67-1.04), and also when the cumulative exposure to thimerosal was examined as a continuous variable (OR=0.87, 95%CI: 0.78-0.96). In fact, the last results indicated a significant result indicative of a protective effect of higher thimerosal exposure at 6 months for a statement of special needs. This unexpected finding applied to four of the five other significant results and the authors also noted that a majority of analyses indicated trends towards a protective effect of thimerosal exposure.

98. In the U.S., Verstraeten et al. (2003) used data from the Vaccine Safety Datalink (VSD) to conduct a retrospective cohort study funded by the CDC. The study was conducted in two phases: the first phase screened two HMOs to identify potential associations that would then be confirmed in the second phase, using another HMO to replicate the findings. In the first phase, two HMOs (A and B) were enrolled in the study. Children had to be born and continuously enrolled in the HMOs during their first year of life and had to have received at least two polio vaccines during that first year. Infants with low birth weight, congenital disorders, or serious maternal illnesses were excluded. The cumulative exposure to thimerosal was evaluated at 1, 3, and 7 months of life at ages where exposure relative to body weight is at its peak. The cumulative dose, therefore, ranged from 12.5µg in the first month up to a maximum of 187.5µg at 6 or 7 months. A validation study of medical records was conducted showing accuracy of the diagnosis of autism in 92.3% of the cases in HMO A, and in 81.3% of the cases in HMO B.

99. HMO A had a relatively small population of 13,337 subjects and had too few cases (N=21) of autism to be analyzed according to *a priori* decisions made by the authors. HMO B had 202 autism cases (out of a sample size of 110,833), and the hazard ratios for 12.5 µg increases in ethylmercury exposure at one, three, and seven months of age were 1.16 (95% CI: 0.78-1.71), 1.06 (95% CI: 0.88-1.28), and 1.00 (95% CI: 0.90-1.09), respectively. Categorical analyses of cumulative exposure to ethylmercury also showed no effect at age 3 and 7 months.

100. In the second phase of this study, a third HMO was used to replicate any significant findings from phase one, including stammering, Attention Deficit Disorder, speech and language delay, tics, and sleep disorders. HMO C had a cohort size of 16,717 children and none of the 15 analyses conducted on the five neurodevelopmental outcomes were significant with respect to cumulative thimerosal exposures at 1, 3, and 7 months, examined as a continuous variable.

101. Concerns have been raised about differences in results obtained at different stages of the study before its final publication. However, it is common in the conduct of epidemiological studies to go through different iterations and obtain intermediate findings that may change as new analyses are conducted, and new confounder variables are identified that need to be considered in modeling the data. One concern about the Verstraeten et al. (2003) study pertained to pooling of the data from the two HMOs, A and B, during phase one. However, a reanalysis of this study by petitioners' experts has shown that the original conclusions of Verstraeten et al. were entirely valid (Austin & Lally report, 2006).

102. In the U.K., Jick and Kaye (2004) conducted a case-control study in which they examined records of children from the GPRD born between 1990 and 1998. ASD cases (N=122) were matched to controls (N=587) on gender, age, general practice, and index date of registration. 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.

103. Madsen et al. (2003) conducted an ecologic study of thimerosal-containing vaccines and ASD using the Danish National Register of psychiatric hospitalizations since 1971, and all outpatient psychiatric visits since 1995. All children between age 2 and 10 years with a diagnosis of autism received between 1971 and 2000 were included, giving a total sample of 956 children with autism over the study interval. Due to changes in the immunization schedule in Denmark, children born between 1961 and 1970 in that study had received 200 $\mu$ g of ethylmercury by age 15 months. During the period 1970 to 1992, they had received 125 $\mu$ g of ethylmercury by 10 months of age. Thimerosal was then removed from vaccines in Denmark in 1992, allowing for a comparison of rates of ASD before and after the use of thimerosal-containing vaccines. The incidence rates were relatively stable from 1970 to 1990. Thereafter, the incidence increased in all age groups until 1999. The change in incidence occurred around 1990 at a time when no change occurred in the vaccine immunization schedule. Similarly, the discontinuation of thimerosal in 1992 had no impact on the ascending trend in rates of autism: incidence rates had started to increase in 1990 and 1991, and kept increasing at the same pace after discontinuation of thimerosal. To examine the impact of adding outpatient data in 1995, the authors restricted their analysis to inpatient data only and again reported the same trend of regular increase of rates of ASD from 1990 to the end of the study period (although the specific data were not included in the article).

104. 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, which they compared to trends from California public services. In Sweden, thimerosal was discontinued in vaccines in 1993, and in Denmark, in 1992. Swedish data were limited to inpatient statistics, but

the recording system did not change during the study period (unlike in Denmark). In California, exposure to thimerosal increased during the study period. Interestingly, the incidence rates of ASD in the 3 datasets began to rise slowly in the mid-to-late 1980s and then increased more steadily in the 1990s. When thimerosal-containing vaccines were discontinued in Denmark and Sweden, there was no deceleration in the rate of increased incidence of ASD in those two countries. In fact, the increase continued or accelerated after the discontinuation of thimerosal in vaccines. The findings suggest that the similar patterns of increased incidence in the three datasets have no relationship with thimerosal exposure, but rather reflect changes in diagnostic practices, and availability and access to services.

105. We have 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. Children were selected because they attended one the schools of an Anglophone schoolboard of West Montreal in October 2003, from kindergarten through grade eleven. The children with an ASD diagnosis were classified as special need students identified through a specific administrative code. Exposure to thimerosal was estimated by calculating the cumulative dose of ethylmercury received by the children from birth to age three, if they followed the official immunization schedule. The rates of autism increased linearly during the whole period by about 10% each year. During the study period, the amount of ethylmercury included in vaccines varied from a medium level (100 to 125  $\mu\text{g}$ ) from 1987 to 1991, to a high level (200  $\mu\text{g}$ ) 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 in paragraph 106), and by statistical modeling of the data, we found no association between thimerosal and the risk of autism.

106. We conducted several analyses to test for the effect of misclassification on exposure or diagnostic status and found the results to be robust. This study adds to the existing body of evidence on the subject in showing: a) that changes in levels of ethylmercury exposure

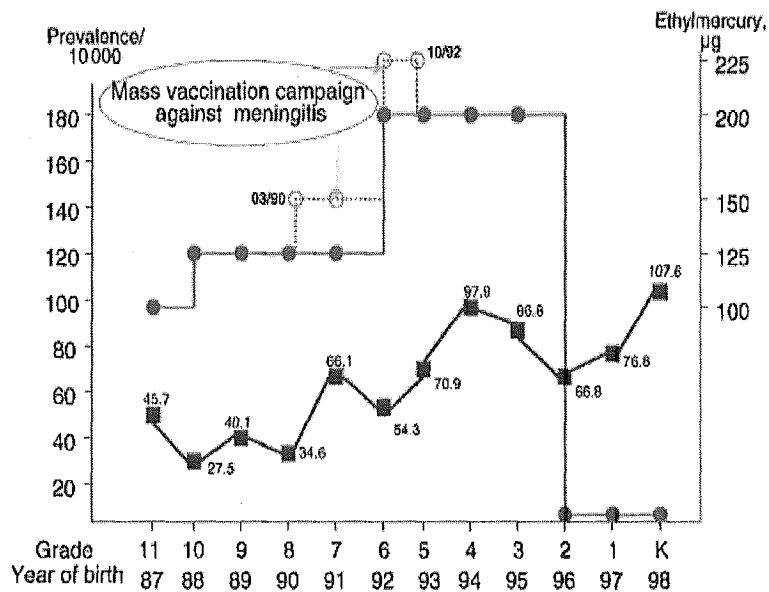


FIGURE 2  
Birth cohort prevalence rates and ethylmercury exposure. Dotted lines take into account the additional ethylmercury exposure because of a mass vaccination campaign against meningitis (see text).

from medium (European countries) to high (U.S.) levels had no impact on the rates of autism and their trend over time; and b) that, like other discontinuation studies (see Stehr-Green, 2003; Madsen et al., 2003; Schechter & Grether, 2008), removal of thimerosal from vaccines does not result in any deflection in the rates or trends of autism and ASDs. 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.

107. Recently, Schechter and Grether (2008) published results from an analysis of prevalence by age and birth cohort of children with autism who were active status clients of the California DDS from January 1, 1995, through March 31, 2007. As thimerosal-containing vaccines

were discontinued in the U.S. in 2001, it had been predicted by proponents of the autism-thimerosal hypothesis that rates of autism should fall as a result of the discontinuation of thimerosal, a trend that Geier and Geier (2006a) claimed to have detected. The study precisely tested this prediction with a sound set of methods and analyses, and Schechter and Grether showed that the time trends in California provided no support to the thimerosal/autism hypothesis. Specifically, they found that for children born between 1989 and 2003, the prevalence of autism increased consistently during the periods in which exposure to thimerosal decreased. Moreover, since 2004, the period at which a decline in autism should have been observed if thimerosal contributed to the cause of autism, in children ages three to five years, the prevalence of autism in fact increased at a steadier pace than that for other developmental disabilities (see Figure below). This study adds a consistently negative result to previously published discontinuation studies. Its particular significance is the fact that the study's data came from the California database that proponents of the thimerosal/autism hypothesis abundantly used in support of their claim (Fombonne, 2008). In addition, like the Canadian study (Fombonne et al., 2006b), and in contrast to European studies, the California study examines the effects of discontinuation of thimerosal in populations of children who were exposed previously to presumably "high" levels of thimerosal.

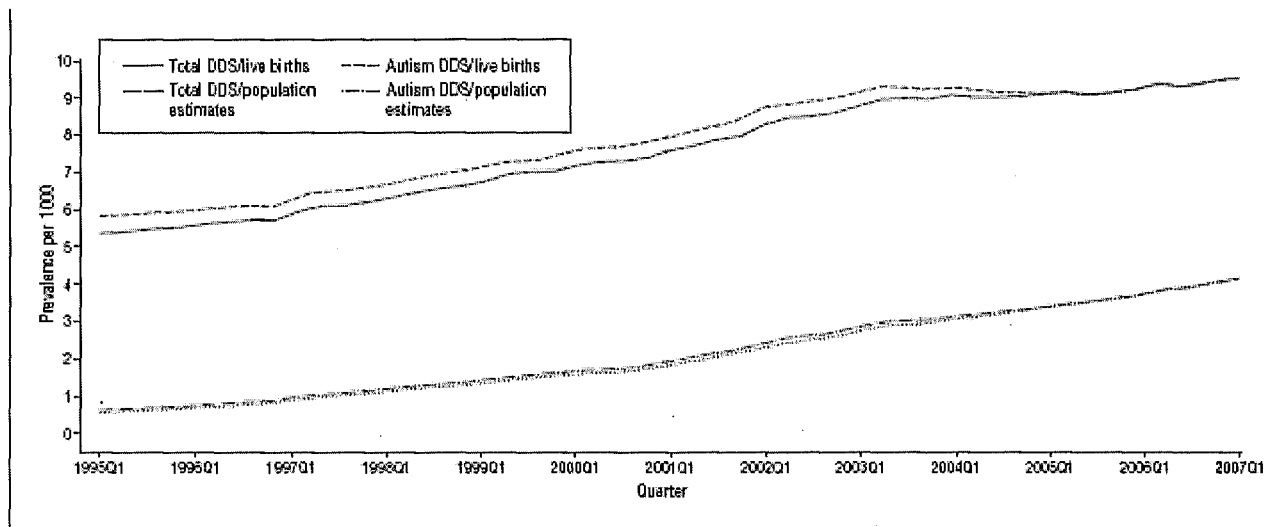


Figure 3. Prevalence of autism and total California Department of Developmental Services (DDS) client enrollment reported by the DDS for children aged 3 to 5 years by reporting quarter (Q), January 1, 1995, through March 31, 2007. Prevalence is estimated by dividing the number of active status children with autism<sup>24</sup> by the number of live births in California for each quarterly cohort from 1993 to 2003<sup>25</sup> (solid and dotted lines) and the number of children estimated to reside in California for each quarter from 1995 to 2004<sup>27</sup> (hashed lines).

108. Although not examining the association between autism and thimerosal exposure per se, another published study recently conducted by the CDC is worth mentioning (Thompson et al., 2007). There, the authors included 1,047 children in the U.S., ages seven to ten years, selected from four HMOs participating in the VSD, and performed direct testing of 42 neurological outcomes, blind to exposure status. Because some of these outcomes (i.e., speech and language measures, intellectual and cognitive functioning) could be regarded as component parts of the ASD phenotype, the study's results are relevant here. Further, this study is the first to examine the neurodevelopmental outcomes in childhood, in humans, following earlier exposure to thimerosal-containing vaccines. Exposure to thimerosal was calculated by pre-natal exposure through the mother's treatment with immune globulins or her receipt of thimerosal-containing vaccines, and postnatally through computerized immunization records supplemented by other information sources. Thimerosal doses were related to the weight of the child at the time of vaccine administration. Three exposure windows were created (prenatal exposure, birth-to-7 months, birth- to-28 days). There was no consistent pattern of results, with few associations

reaching the level of statistical significance, but being of small magnitude and representing an equal number of positive or negative effects. Thus, this well-powered study provides no support for an increased incidence of negative neurodevelopmental outcomes as a result of thimerosal exposure amongst school age American children exposed to the immunization schedule in place in the U.S. in the 1990s.

109. In line with Thompson et al. (2007) regarding the lack of an association between risk of neurodevelopmental outcomes and prenatal exposure to thimerosal, Miles and Takahashi (2007) studied 214 mothers of children with an ASD with complete records, including blood group status and RhIg exposure. In mothers of children with autism, Rh(-) status was no more frequent than in the general population. Similarly, exposure to antepartum RhIg, preserved with thimerosal, was not higher for children with autism, and pregnancies were no more likely to be Rh incompatible. Importantly, this was also true for children with a regressive onset and for autism subgroups defined by other behavioral characteristics that included gender, IQ, head circumference, or dysmorphology. These findings invalidate the results obtained by Geier and Geier (2007) on a limited and biased sample.

110. To address claims raised by petitioners' experts, it is also useful to extract from the published epidemiological studies data and results that directly challenge assumptions made by those experts. Some epidemiological studies have been criticized because the overall levels of exposure to ethylmercury were lower in European countries than in the U.S. in the 1990s. This, however, is not always a correct assumption. For example, Madsen et al. (2003) comment on the levels of ethylmercury received by Danish children born from 1961 through 1970: the cumulative dose of ethylmercury was 200 $\mu$ g by 15 months of age. It is clear from the incidence data shown in the 1970s, in their Figure 1, that no 'epidemic' of autism resulted in the birth cohorts

exposed to these high levels. Second, to consider as uninformative studies that have a limited range of exposure would be appropriate if some form of threshold effect (by which the exposure increases the risk of the outcome only after a certain 'dose' has been reached) had been demonstrated in other studies. No such demonstration exists, however. In fact, all dose-response analyses conducted thus far, including studies in which the exposure range included higher levels (i.e., Verstraeten et al., 2003), have consistently failed to show such a dose-response relationship. Third, whichever conflicting theories are embraced by petitioners' experts (the 10% clearly regressive subgroup, or the thimerosal-induced increase in rates of all ASDs), they both lead to predictions of a detectable decline in rates of autism following discontinuation of thimerosal use in vaccine production. There are now four studies that have all failed to document such a trend, including two (Fombonne et al., 2006b; Schechter & Grether, 2008) in which thimerosal exposure was at its highest levels before discontinuation. Fourth, rates of regressive autism have not changed over time, and rates of regression are comparable in countries with moderate exposure to ethylmercury (U.K.: Fombonne and Chakrabarti, 2001c; Fombonne et al., 2004) to those countries with higher exposure levels (Lord et al., 2004).

111. 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, 2005, 2006a & b; 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.

112. Other ecological studies have examined patterns of associations between environmental levels of mercury and rates of autism (Palmer et al., 2006; Windham et al., 2006). Of note, these two studies did not test specifically the effects of exposure to ethylmercury (contained in thimerosal) and, therefore, are not directly informative to an examination of the putative association between thimerosal-containing vaccines and ASDs. However, because they reported correlations between environmental mercury and rates of autism, they are briefly discussed here.

113. Palmer et al. (2006) reported positive correlations between the amount of mercury released in the environment and rates of children with autism who were enrolled in special education classes. The strongest associations in that study were between rates of autism and urban/rural residence, illustrating the notorious difficulty in controlling for confounding variables in this type of ecological study. Further, the rates of autism in children enrolled in Texas schools, in 2001, from kindergarten to grade twelve were correlated with environmental releases of mercury in 2001. Obviously, children included in this study were born sometime between 1983 and 1995, and autism became manifest in these children between 1986 and 1998 (as it is a diagnostic requirement that symptoms occur before age three). Thus, this study reports on correlations between a disease and an exposure that occurred after disease onset in study subjects. Besides indicating a poor study design, this flaw also points to the general difficulty in inferring causality from ecological correlations.

114. The Windham et al. (2006) study suffers from the same limitations. There, environmental exposures were measured two years after the birth of the children included in the sample. In addition, the risk of autism was slightly increased in relation to several highly intercorrelated exposures to environmental substances that included, in addition to mercury,

cadmium, nickel, and chlorinated solvents. This lack of specificity, the absence of a dose-response relationship, and several other limitations acknowledged by the authors, make this study non contributory to an examination of the role of mercury exposure as a risk factor for ASDs.

115. Reviews of this body of evidence by independent authors (Parker et al., 2004; Rutter, 2005; Doja & Roberts, 2006; Hviid, 2006; Taylor, 2006; DeStefano, 2007) and scientific committees (IOM, 2004; National Advisory Committee on Immunizations, 2007) 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.

116. 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. What is striking is the consistent replication of negative findings across investigations that otherwise differed with respect to their sample sizes and selection, design, countries, investigators, and other critical variables.

### **Dr Greenland's Report**

117. I have read Dr Sander Greenland's expert report dated August 13, 2007. The following comments are in response to several statements and opinions that he expressed in that report.

118. Having reviewed the epidemiologic literature on mercury-containing vaccines (MCV) and autism, Dr. Greenland, at the beginning and in the conclusion of his report, rejects the association: (see page 1, Introduction: "while the epidemiologic literature to date has not detected an association of MCV with autism in general or autistic spectrum disorders..."; and page

16, point 8, Conclusion section: “the brief overview given above supports the idea that the association of MCV with autism is small or non-existent”).

119. After Dr Greenland wrote his report, more studies were published that reach the same conclusion of no causal association. In particular, the study by Schechter and Grether (2008) discussed above has shown no decline in rates of children with autism enrolled in the public system of services, in California, after thimerosal was removed from vaccines in the United States. This ecological study clearly establishes that thimerosal-containing vaccines did not contribute to the increasing trends since in the 1980s and 1990s in the number of young children diagnosed with an ASD (Fombonne, 2008).

120. Having concluded that published epidemiologic studies investigating the association between MCV and autism have been negative, Dr Greenland posits that controlled epidemiological studies have not tested separately the possibility of an association between MCV and regressive autism and, therefore, the possibility of a specific association between MCVs and regressive autism has not been rejected. Dr Greenland calculates that assuming there is a two-fold increase in the risk of a subtype of autism applicable to 10% of the cases (a subtype he describes as “clearly regressive autism”), the true association specific to that subtype would remain undetected in epidemiological studies that do not test specifically for an association between the exposure and this subtype. Dr Greenland then reviews the results of published epidemiological studies and concludes that based on the upper limits of the confidence intervals for published risk ratios, a small association between MCVs and clearly regressive autism cannot be entirely ruled out. According to Dr. Greenland, if such an association existed, it would only lead to a marginal increase in the risk ratio, and would be diluted by tests that only look for an association between MCVs and ASDs in general.

121. Whilst the technicalities of Dr Greenland's report are accurate, certain technical aspects merit modification. More substantial conceptual flaws with his opinion are discussed below.

a. Dr Greenland uses a hypothetical rate of 10% for a subtype of autism that he contends could be specifically associated with MCVs. However, he provides no reference in support of this particular figure. Based on recent published data (Lord et al, 2004; Fombonne & Chakrabarti, 2001c), the frequency of regression in the developmental course of children later diagnosed with autism can be estimated at around 20%. The most extensive study of the developmental course of children with a regressive autistic pattern has shown that 72% had abnormal development prior to the regression or loss of skills (Richler et al, 2006). Therefore, a more accurate figure to use would be 6% ( $0.20 \times 0.30$ ) to index a group that Dr. Greenland terms "clearly regressive autism."

b. This 6% figure represents an upper bound limit for the true proportion of children with regressive autism and (apparently) previously normal development. It is highly probable that the sensitivity of the techniques used to evaluate prior abnormalities in the development of autistic children prior to their loss of skills is imperfect. This would lead to an overestimation of the proportion of children with so-called "clearly regressive autism," who are presumed to be completely normal before the loss of skills.

c. If one admits that the proportion of "clearly regressive autism" cases is 6% or lower, and if we further assume that this now very small subgroup has a unique and specific association with MCVs, the dilution bias described by Dr Greenland in his report would even be greater.

d. Dr Greenland is incorrect when he states that considering a broader category, such as all ASDs in general, necessarily dilutes a true association between MCVs and clearly regressive autism. As discussed previously, ASDs include Autistic Disorder, PDDNOS, Asperger's Disorder, Rett's Disorder, and CDD. Autism and PDDNOS together account for a large majority of ASDs, and regression has been shown to be comparable in those diagnosed with Autistic Disorder or with PDDNOS (Lord et al, 2004). Accordingly, Dr. Greenland's comment on page 15 of his report about the Fombonne et al. (2006b) study is inaccurate. He states that one would expect to find only

about a dozen cases of regressive autism. Yet if one looks for regression in both PDDNOS and autism, one would expect to find much more than twelve cases. In fact, based on a 20% rate of regression, we would expect to find at least thirty cases of regressive autism alone.

e. Dr Greenland uses the well-known textbook example of phenylketonuria to indicate that genetic and environmental factors act together to lead to the onset of a disorder known to have a genetic origin. I have no disagreement with this example, but Dr Greenland misses the essential point of my previous testimony (Fombonne, 2007, paragraphs 37 to 39). I quoted the Lainhart et al. (2002) study, which showed that 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. What the study shows is that the data do not support the hypothesis that regressive autism is a distinct form of the disorder entirely induced by an environmental trigger. Several advocates of the hypothesis of a mercury-induced autism have posited this hypothesis (one which may not be embraced by Dr Greenland), but the hypothesis is clearly not consistent with the evidence. In addition, as already noted above, this and other studies' results are not consistent with the hypothesis that thimerosal-containing vaccines act as environmental triggers of autism in a subgroup of genetically susceptible individuals.

f. In reviewing controlled epidemiological studies, Dr Greenland fails to emphasize the consistency of risk ratio point estimates obtained by independent investigators analyzing independent datasets. The two most powered, controlled studies showed risk ratio estimates for the association between MCVs and ASDs of 0.85 and 0.99: the upper limit of the 95% confidence limits in both studies being 1.20 and 1.12. If a meta-analysis of these studies were to be conducted, the upper limit would undoubtedly be closer to 1.0. Although this does not rule out entirely a specific association with a very small subset of the disorder going undetected, it makes it less likely, especially considering the conservative assumption of a two-fold increase in the risk taken by Dr Greenland. This is at variance with claims made by petitioners' other experts, who hypothesized a much larger increase in risk. If the increase in risk for a specific subtype of autism with respect to exposure to MCV was four or five fold, it should have been detected in these large, controlled epidemiological studies, all of which consistently

found no association. Nor did these studies find even the beginning of a hint of an association in a specific subgroup. Following Dr Greenland's calculations (pages 5 and 6 of his report), I have calculated that if one assumes "clearly regressive autism" occurs in 6% of the cases, and that MCV exposure increases the risk of this subtype five-fold, it would translate into a risk ratio of 1.24 for ASD in general. This is not consistent with the two most powered, controlled studies currently available.

g. Dr Greenland cites the Heron et al. (2004) study and finds it uninformative. That study reported a negative association between the cumulative exposure to ethylmercury by six months of age and the likelihood of an identification for special educational needs (adjusted OR = 0.87; 95% CI: 0.78–0.96). Recent research by Golding (2007) reported on the rate of ASDs in this particular birth cohort, and the investigators found a prevalence estimate of 62/10,000 that is consistent with recent estimates, and corresponds to more cases of ASDs (n = 86) than those postulated by Dr Greenland.

122. As there is no empirical data to support his opinion, Dr Greenland tries to draw parallels with cancer. He argues that cancer is a broad category of which there are distinct types or forms (Dr Greenland's report page 4, section 3). Dr Greenland never defines what he refers to as (1) a disease category, (2) a distinct type or form, or (3) the criteria that are necessary to ascertain the distinctiveness of types or forms within a disease category. He uses the example of cancer (the broad category) within which two types or forms (respiratory system cancers and skin cancer) have a differential association with smoking. He then goes on to apply this comparison to the disorder of autism and attempts to dissect the disorder into a non-regressive *versus* regressive phenotype; the latter being further subdivided into "clearly regressive autism" and a not-so-clearly-regressive autism. This analogy between cancer and autism is patently incorrect and is inconsistent with biological and medical knowledge. Broncho-pulmonary cancers and skin cancers are different diseases. In addition to having different symptomatology, they affect different organs and different cells; their epidemiology (incidence over time and place, age groups, and gender) is vastly different; the patho-physiological mechanisms are different; the association with known

environmental risk exposure (smoking versus sun exposure) are strikingly different; their genetic backgrounds are most likely different; and the treatments are different, as are the outcomes and the mortality rates. Broncho-pulmonary cancers and skin cancers represent two different diseases that are distinct not only in their symptoms or phenomenology, but in their causes, correlates, treatments and outcomes. Broncho-pulmonary cancers and skin cancers are subsumed into the same broad category of “cancers” in the same manner as HIV, flu, the common cold, malaria or streptococcal infection are subsumed into the broad category of “infectious diseases.”

123. By contrast, within the category of ASDs, there is no evidence to separate regressive from non-regressive autism. The main difference is definitional only and relies on patterns of symptom onset. In classical autism, there is no identifiable loss of skills whereas in regressive autism, there is an apparent loss of skills that usually occurs during the second year of life. It was assumed for a long time that the development of children who were losing skills during their second year of life, and who fit this description of regressive autism, was normal up to the time of the regression or loss of skills. We now know that is not the case (Lord et al., 2004; Rogers et al., 2004; Werner & Dawson, 2005; Richler et al., 2006). In fact, in the majority of cases, the onset of autistic symptoms occurs prior to the loss of skills, thus blurring the phenomenological difference between the two clinical presentations. As explained above, recent studies (Richler et al., 2006) suggest that up to 72% of children with regressive autism have abnormal development before the loss of skills. As studies become more precise in identifying early symptoms of autism, this proportion is likely to grow, and it is a true possibility that, with advancing technologies, all children who regress or lose skills will in fact be shown to have abnormal brain and/or behavioral development prior to their regression or loss of skills. For example, a similar pattern of abnormal

head circumference growth between 7 and 10 months of age has now been reported by Webb et al. (2007), with no difference between regressive and non-regressive autism.

124. Even if one assumes there is a very small subset of children who regress after apparently normal development, this is not sufficient to establish this phenotype as a distinct disease, disorder, or syndrome. Medicine in general, and psychiatry in particular, has made progress in establishing the validity of disorders using a certain number of approaches to differentiate disorders. The phenomenology of syndromes is usually not a sufficient characteristic to establish the validity of a psychiatric or developmental disorder (Rutter, 1978). For example, there is no difference between a spider phobia or a dog phobia: both are simple phobias. Similarly, Rett's syndrome can develop in a young girl at age eight months or at age fifteen months, yet no one would claim that these represent two distinct types of Rett's syndrome. Rather, one needs to establish that the two disorders, which can be identified reliably by their clinical descriptions, also differ with respect to correlates (i.e., social class, age, gender), age of onset, genetic or social background, course and natural history, and response to treatment and long-term outcome in order to establish their distinctiveness. To give two examples, the phenomenology of schizophrenia and bipolar disorder can be very similar in young children, but the differentiation between these two syndromes in young people has been made possible by long-term outcome studies or treatment-response studies. Conversely, depression in children and in adults presents phenomenologically in different ways, but outcome studies showing a high degree of recurrence of depression as an adult following a depressive episode in childhood have indicated that these conditions are similar (Fombonne et al., 2001a). In other words, in order to argue that a syndrome or disorder represents similar or different types or forms of a disease, it is not sufficient to rely upon the clinical

phenomenology or symptom presentation. One needs also to provide other data establishing the discriminate validity or the uniqueness of the two types or forms.

125. In the case of ASDs, the pattern of regression has been known for over 50 years. All studies that have looked at regressive versus non-regressive autism have failed to differentiate these two phenotypes for critical features that would support their distinctiveness. Studies have been performed comparing regressive autism and non-regressive autism on a range of correlates (i.e., family history of the autism phenotype, Lainhart et al. (2002); symptom severity, course, and intellectual functioning, Lord et al. (2004), Fombonne & Chakrabarti (2001c); presence or absence of epilepsy, Tuchman & Rapin (2002); abnormal brain growth during first year of life, Webb et al. (2007); familiarity in multiple and singleton families, Parr et al. (2002); Lainhart et al. (2002)). The pattern of regressive autism represents only a symptomatic variation in the clinical presentation that does not carry any other known meaning based on current knowledge. Therefore, the analogy with broncho-pulmonary cancer and skin cancer is incorrect. A more appropriate analogy would be to compare regressive and non-regressive autism with different profiles of symptom onset within broncho-pulmonary cancer, i.e., one broncho-pulmonary cancer in an individual might have a slow progressive onset with coughing, repetitive bronchitis and progressive weight loss, or the same cancer disease could manifest itself suddenly through a massive pulmonary hemorrhage in an up-to-then asymptomatic individual. In this example, these two distinct “forms” of broncho-pulmonary cancer only differ in the pattern of first symptoms but not on other key characteristics of the disease, especially with respect to their cause, prognosis, and management. There is no need to invoke different etiologies of these two “forms” of broncho-pulmonary cancer to account for the variability in mode of onset.

126. As there is no evidence that the slight difference in symptom onset in regressive autism as opposed to non-regressive autism is a valid subtyping of ASD, and as Dr Greenland fails to provide any preliminary evidence that exposure to mercury or thimerosal-containing vaccines increases the risk of autism, one wonders what the starting point of this hypothesis is. Dr Greenland describes a new form or type of autism that he calls “clearly regressive autism,” but he provides no operational definition for this entity and no demonstration that it can be reliably and validly measured. Absent such evidence, his recommendation to conduct further controlled epidemiological studies on this issue (page 16, last paragraph) is meaningless.

127. When several controlled epidemiological studies have failed to reject the null hypothesis, as has been the case for MCV and autism, it will always be possible to hypothesize that within the disease phenotype studied, there may be a subgroup (maybe 1% or 1 per 1,000 individuals having this disease), defined by a particular set of clinical or biological characteristics, who nevertheless have a unique, specific association with the exposure under study. For example, in the case of autism, it is possible not only to stratify any sample by regression status but also by multiple other phenotypic characteristics, such as bands of intellectual functioning; gender; presence or absence of epilepsy; presence or absence of macrocephaly; multiple versus singleton families; family history positive or negative for the broader autism phenotype; language level; and response to early behavioral intervention. Autism research findings have shown that stratification using these characteristics is indeed much more meaningful than stratification using regression status alone. Each sample set of autistic children could possibly be stratified using a *combination* of these characteristics that may lead to hundreds of putative, distinct types or forms of autism. Only then could Dr Greenland or others easily claim that one form (for example children with autism and epilepsy and macrocephaly and moderate mental retardation) or several forms of the

disorder have a specific association with the exposure. This, however, would likely lead to an endless collection of hypotheses or wild speculations about particular “vulnerable” subtypes or subgroups. Unless the claim for one hypothesized subtype is anchored on preliminary, convincing biological or epidemiological evidence, epidemiologists would ordinarily not engage to test these multiple “hypotheses” that are not informed by a defensible disease model or a plausible biological theory. In fact, the multiple testing associated with such “fishing expeditions” carries the well-known danger that the testing may give rise to a high number of false positive findings. In experimental studies (randomized clinical trials), epidemiologists are well aware of these dangers and require that a small number of predefined analyses are conducted on *a priori* selected primary and secondary outcome measures in order to test the efficacy of an intervention. In these studies, the analytical plan is rigorous and concentrates on the plausibly hypothesized relationship between the intervention and the outcome, and on variables that can be measured reliably. Dr Greenland’s hypothesis has no preliminary data to demonstrate its plausibility, and it refers to a speculative phenotype for which no reliable measurement is even available. It would, therefore, be unwise and in fact, not feasible, to conduct controlled epidemiological studies to test Dr Greenland’s hypothesis.

128. Dr Greenland points out well-known limitations of ecological studies.

However, ecological studies that evaluate trends over time in a disease during periods where there is substantial variation in the exposure (especially when the exposure is eliminated) are much less susceptible to their known biases. For example, three studies conducted independently in three different countries (Madsen et al. 2004; Fombonne et al., 2006b; Schechter & Grether, 2008) have all shown that when thimerosal is removed entirely from vaccines, the rates of autism do not decline. In fact, those rates continue to increase at the same pace as before (Fombonne, 2008). If,

as postulated by Dr Greenland, there was a two-fold increase in the risk of a type of autism occurring in 10% of the cases, which is due to thimerosal containing vaccines, one should expect a fall of about 10% in the rates of autism following the discontinuation of thimerosal in vaccines (assuming complete vaccine coverage in the child population). No such fall has been documented. In fact, in two of the studies, the levels of thimerosal exposure before its elimination from vaccines were at U.S. levels (Schechter & Grether, 2008; Fombonne et al., 2006b). Furthermore, the rates of regression in ASDs in studies of children who were exposed to the U.S. levels of thimerosal are about 20% (Lord et al., 2004). This is no different from rates that have been reported in British studies where thimerosal levels were lower (Taylor et al, 2002; Fombonne & Chakrabarti, 2001c; Fombonne et al., 2004). There is no evidence that the proportion of regressive autism has decreased after the discontinuation of thimerosal in vaccines.

129. In sum, Dr Greenland makes in his report a methodological remark that is technically correct but remains purely hypothetical, has no empirical grounding to support it, and ultimately lacks the essential pre-requisites that would make it a workable scientific hypothesis.

#### **Jordan King**

130. Jordan King was born on September 29, 1997. He was the product of an uncomplicated pregnancy. His mother, then age thirty-six, presented with a spontaneous membrane rupture, and during delivery had a high fever (101 degrees) treated with antibiotics. Jordan's birth weight was 7lbs, 14oz, and his Apgar scores were 8 and 8. He passed his two-week and two-month developmental check-ups with his doctor, Dr Lauren Roberts, without problems (exhibit 2, page 34).

131. Sleeping and bowel problems were noted at his four-month check-up with dry stools and constipation and (difficult to read) sleeping descriptions. At six months of age

(exhibit 2, page 33), sleeping problems were still reported, but he seemed to be developing well, generally. Jordan had an episode of diarrhea, in August 1998, at eleven months of age (four months after his last immunization series). He passed his one-year check-up well, and his doctor noted that he babbled and understood well.

132. At sixteen months of age, Jordan had an infectious episode that was investigated in the Emergency Room of the Providence Portland Medical Center (exhibit 3, pages 77 and 78), with a resulting diagnosis of a viral syndrome.

133. Dr Roberts saw Jordan, on March 17, 1999, at the age of 17½ months, for coughing and a febrile episode. His mother's description indicated that Jordan seemed lethargic. Dr Roberts noted that Jordan was "sleepy now but wandering/exploring drawers" (exhibit 2, page 27).

134. On July 1, 1999, at the age of twenty-one months, Dr Reagan evaluated Jordan for another viral illness. Dr Reagan's notes indicated that Jordan appeared "actually surprisingly open-minded and moderately comfortable" (exhibit 2, page 25).

135. On October 25, 1999, at almost twenty-five months of age, Dr Roberts identified significant developmental concerns with Jordan, including the fact that he did not talk at all; he made a lot of noise, such as grunts and humming on and on; and he had no language. Dr. Roberts noted possible autism, which required a developmental evaluation, and indicated that Jordan had previously used single words (exhibit 2, page 23).

136. Jordan received the normal immunization schedule recommended at the time, including MMR at one year of age, and the complement of other vaccines.

137. Jordan was referred to the Pediatric Development and Rehabilitation Program, in November 1999, at twenty-six months of age. His mother completed a questionnaire

and indicated her concern that Jordan did not speak at all. She further indicated that Jordan babbled normally and used single words around one year of age and then stopped. She also noted that he did not relate well to non-family members, preferred to play alone in group settings, seemed to be annoyed by the loud babbling of his baby sister, and did not come when called (exhibit 7, page 9).

138. Jordan's regression is difficult to assess. He apparently started to use single words around his first birthday, although the exact age varies from nine months (exhibit 1, page 41) to thirteen months (exhibit 8, page 168). The extent of his vocabulary at that age is difficult to evaluate, although examples ("shoes," "juice") are found in some records. There is not much evidence that his language progressed between the ages of 12 and 18 months. In fact, his pediatrician's notes are remarkable for their lack of reference to language development during that period. It is then asserted that Jordan lost his skills in June 1999, around twenty months of age. Although his parents indicated he was a "normal child until around age 20 months" (exhibit 8, page 189), they wrote to Dr Budden that they noticed the first changes in Jordan at 18 months of age when he "would not stay with the group and instead would wander over to the boom box and play with the buttons" (exhibit 8, page 189). This corresponds to the age (17.5 months) at which Dr Roberts's notes indicated that Jordan is "sleepy now but wandering/exploring drawers" (exhibit 2, page 27). Although it appears likely that Jordan lost the few language skills that he had acquired (a few single words), it is probable that his development was not normal before the loss at 18 or 20 months of age, and before the emergence of clear autistic symptoms. His language failed to progress between 12 and 18 months of age, and according to his parents' comparative comments with regard to his sister's behavior, Jordan "was never a babbler. His vocalisations were fairly limited compared to her articulations." (exhibit 8, page 189).

139. Jordan was evaluated with the Rossetti Infant-Toddler Language Scale at two years, three months of age, which documented a delay in language skills and social skills, and raised the possibility of a PDD spectrum diagnosis. He was subsequently referred for speech therapy. A second language assessment at twenty-nine months of age with the Preschool Language Scale (PLS)-3 documented significant delays in expressive (age equivalent: 3 months) and receptive (age equivalent: 7 months) language skills. (exhibit 8, pages 168-169).

140. On January 25, 2000, at the age of 2 years, 3 months, Jordan had a cognitive assessment with the Battelle Developmental Inventory, which showed a standard score of 65 (percentile 1), corresponding to an age equivalent of 14 months (for adaptive skills) (exhibit 8, page 101). He obtained nearly identical results on personal social skills. In motor skills, he had a standard score of 82 for gross motor skills and 75 for fine motor skills.

141. Jordan was diagnosed with autism in early 2000 after the speech and language evaluation and his first contact with the Early Intervention Programs of Portland. The diagnosis was later confirmed by a pediatric psychiatrist, Dr Stubbs, and by Dr Budden, a pediatrician, in August 2000 (exhibit 8, pages 56-60).

142. As soon Jordan received an autism diagnosis, the records indicate that his parents understandably began an active search for a biomedical explanation for their son's difficulties that spanned different organs and mechanisms, including pancreatic deficiency, digestive problems, abnormal metabolism, and toxic exposures (exhibit 2, pages 18 and 21). Like many parents who are searching for a cause, Jordan's parents requested that he be seen by a naturopath, Dr Pamela Jeanne, and by Dr John Green, who both began treating Jordan. It is important to note that multiple investigations were performed that led to negative or inconsistent results, and to Jordan being prescribed many supplements and medications that were administered

at a very early stage. Jordan's parents also started him on a gluten-free and casein-free diet in January 2000. Equally important is the fact that an early intervention program using speech therapy and, later, behavioral techniques was started in early 2000.

143. There were, therefore, multiple interventions that were immediately implemented that involved both behavioral and educational measures, and a range of biomedical treatments. The constant changing of biomedical treatments together with the fact that behavioral treatments were taking place at the same time renders it impossible to evaluate the efficacy of each component of Jordan's multifaceted treatment programme.

[REDACTED]

144. [REDACTED]

[REDACTED]

[REDACTED]

145. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

146. [REDACTED]

[REDACTED]

147. [REDACTED]

[REDACTED]

148. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

149. [REDACTED]

[REDACTED]

[REDACTED]

150. [REDACTED]

[REDACTED]

151. [REDACTED]

[REDACTED]

[REDACTED]

152. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

153. [REDACTED]

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[REDACTED]

[REDACTED]

154. [REDACTED]

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155. [REDACTED]

[REDACTED]

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156. [REDACTED]

[REDACTED]

157. [REDACTED]

[REDACTED]

158. [REDACTED]

[REDACTED]

159. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

160. [REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

William Mead

161. William Mead was born on May 5, 1998, at St. Vincent Hospital at thirty-nine weeks' gestation. His birth weight was 9lbs 4oz, and his Apgar scores were 8 and 9. His parents were 36 and 37 years of age when William was born. Newborn screening test results were normal. There were no complications during the neonatal period.

162. There is a positive family history for arthritis, thyroid dysfunction, asthma, and allergies on the maternal side, and of cancer and alcohol problems on the paternal side.

163. William passed his check-up visits at 4 and 6 months with no problems identified besides intermittent and benign colds or upper respiratory infections.

164. He was given the normal immunization schedule, and received MMR and Varivax at 1 year, 5 days of age.

165. The first developmental concerns appear in the medical notes at William's 2-year check-up on May 15, 2000. The doctor mentioned "no speech" (exhibit 1, page 22). The

doctor further comments that William “hears well,” “acts on language,” “responds to commands,” “plays ball, rolling it back etc.” (exhibit 1, page 22). There is also a mention that there are “no words,” and that William “does not point or know body parts.” The doctor recommends “floor time” for mother and William, 10 minutes at a time, and suggests a reassessment in 3 or 4 months if there is no verbal progress (exhibit 1, page 22).

166. On August 29, 2000, at approximately 28 months of age, it is noted that William is not talking, and an audiology referral is obtained. William underwent an audiological examination on September 25, 2000, and the examiner observed that William did not make eye contact or engage in play. In the weeks that followed, he was referred to the Autism Clinic for a developmental assessment.

167. On November 28, 2000, at 2½ years of age, an evaluation by Dr Alvan Pang confirmed the autism diagnosis. Based on parental reports, the developmental history now indicates that the symptoms occurred after the MMR immunization at 1 year of age with gastrointestinal illness followed rapidly by deterioration in social, motor, and intellectual skills. On that date, William’s parents had already started him on nutritional supplements, including DMG. William had also been started on a casein- and gluten-free diet, and his parents wanted to pursue hypotheses regarding heavy metal toxicity, immune dysfunction, candida overgrowth, and similar issues.

168. In a letter dated January 17, 2001 (exhibit 4, pages 42-43), Dr Pang indicates a different developmental history with a dramatic decrease in verbal abilities and loss of language noted by the parents in August 2000 (i.e., at the age of approximately 27 months). This account of language loss in the summer of 2000 is further documented in a letter by William’s father to Dr John Green, dated November 30, 2000 (exhibit 4, page 26).

169. In the same letter from January 2001, an account is given of William attending, during the 1999-2000 academic year, a "Mommy and Me" school program where William's teachers noted lack of age appropriate social or cooperative play, and the fact that William was becoming increasingly isolated. The director of this program asked that William be withdrawn from the program and placed more appropriately elsewhere. This suggests anomalies in the social and play domains that occurred before the alleged loss of language in August 2000, and probably before the two-year medical check-up in which William's speech delay was first noted as a concern.

170. An assessment performed at the Autism Clinic of the Oregon Health Sciences University, in December 2000, included a summary of William's speech and language assessment performed previously at 29 months of age. This showed receptive language at the equivalent of 9 months of age, and expressive language skills at the equivalent of 12 months of age. On the re-evaluation two months later with the same test, William showed an improvement from 2 to 5 months in his language skills. In addition, William began applied behavioral analysis training at Buiding Bridges for 30 hours per week in late 2000.

171. In the psychiatry report (exhibit 4, page 35), Williams's parents give an account of absolutely normal development up to 18 months of age, at which point William would have already received his MMR vaccination. I note that the MMR vaccination was given on May 10, 1999 (at 12 months of age). This parental report is, therefore, inaccurate. Moreover, the description given of William's development before age 18 months is improbable -- that of a child having three- to four-word phrases, pointing at objects, making good eye contact, and even having a vocabulary of 60 words that was subsequently completely lost.

172. During the same evaluation, on December 12, 2000, Dr Stubbs, a child psychiatrist, reports a different developmental history with loss of words occurring in August 2000 (at 27 months of age) (exhibit 4, page 35). Dr Stubbs confirmed the diagnosis of Autistic Disorder (exhibit 4, pages 37-38).

173. In the fall of 2000, William was receiving different types of intervention, including up to 30 hours per week of applied behavioral analysis using the discreet trial method, and a series of biomedical treatments that more or less followed the DAN! protocol (DMG, amino acids, cod liver oil, melatonin, glutation, vitamin B5, and other compounds).

174. The evaluation of William's possible regression and loss of language skills is made very difficult because of highly inconsistent reports in his medical file. According to his pediatrician's notes, the first concerns are noted at age two in the form of speech delay. There is no evidence from the previous visits during William's second year of life that he had developed any speech, or that he had developed and then lost speech. If he had indeed developed up to 60 words and subsequently lost those words at 18 months, this would certainly have been reported in the pediatrician's file, which is not the case. Further, there are inconsistencies in the dates of the supposed regression. Based on parental accounts, professionals report either a loss of skills occurring at 18 months in a child who was developing normally until then, or they report language loss occurring at 27 months, in August 2000. Because it is highly implausible that William would have had 60 words at 18 months of age and then lost them, and because the connection the parents make with the MMR vaccination at 18 months of age is wrong according to the medical records (MMR was given at one year of age), it is more likely that the parents recognized changes and autistic symptoms in William during the summer of 2000. However, it is unclear how much speech he might have lost at this time. Even if some loss of words could be established at 27 months of

age, it is clear that William's prior development was not normal. His pediatrician noted speech delay at two years of age, and William was asked to leave a daycare program during the 1999-2000 school year, most likely before his second birthday. It is, therefore, likely that William's first autistic symptoms occurred in the form of a lack of speech development during his second year of life, associated with delays in play and social skills, which became gradually more evident to both the parents and the pediatrician, who identified them for the first time at age two. It is difficult to establish whether or not loss of skills occurred at 27 months of age. If it did, the loss of skills occurred after the onset of William's first autistic symptoms.

175. In 2001, William continued to be treated by a combination of behavioral techniques and multiple compounds prescribed by Dr Green that were changed frequently. He also received IVIG, auditory integration therapy, chelation therapy, and secretin infusion, to name only a few interventions. It is impossible to draw any conclusions about the efficacy of interventions or the causes of William's autism from this medical history.

#### **Dr Mumper's Reports**

176. I have reviewed all available medical records of Jordan King, William Mead, and [REDACTED] I have also read the three reports of the petitioners' expert, Dr Elizabeth Mumper.

177. In her three reports, Dr Mumper makes a number of statements that are not substantiated in the scientific literature or in the clinical experience. Some examples of faulty reasoning are as follows:

a. Dr Mumper ignores all the published scientific evidence that does not support her "causal" theory. In particular, she makes no mention of the range of controlled epidemiological studies that have all failed to show an increase in the risk of autism in

children following exposure to various doses of thimerosal received as part of the routine immunization schedule in the United States during the 1990s. The fact that controlled studies in human subjects have consistently yielded negative results is not evaluated by Dr Mumper. Moreover, the fact that rates of autism have not declined following the removal of thimerosal in childhood vaccines in Scandinavia (Madsen et al, 2004; Stehr-Green et al, 2003), in Canada (Fombonne et al, 2006b), and now in the U.S. (Schechter & Grether, 2008) is even not considered. As Dr Mumper appears to be a proponent of the hypothesis of an autism epidemic triggered by childhood vaccines ( [REDACTED]

[REDACTED] King's report, page 7, paragraph 6), it is puzzling that she pays no attention to population-based, well-controlled epidemiological studies and time trends that contradict it.

b. Dr Mumper fails to examine alternative causal explanations for the Mead, King, and [REDACTED] children's autism. This is particularly apparent when she wrongly asserts that the absence of signs of dysmorphology or the presence of normal results for genetic testing regarding karyotype, the MECP2 gene, argue for a role of an environmental factor in these three cases. This statement is incorrect and fails to recognize that if the presence of dysmorphic signs or of a genetic abnormality, when found, positively points at early abnormal embryogenic development or abnormal genetic background, the absence of such abnormalities does not rule out prenatal onset or a genetic cause of autism. This is well-illustrated in recent genetic findings (Weiss et al., 2008; Autism Genome Project, 2007) where microdeletions and microduplications have been found on several chromosomes which account for up to 10% or 15% of autism cases. Such abnormalities were unknown two years ago because techniques to detect them were just not available.

c. The failure to account for alternative causal explanations is also obvious in the lack of attention Dr Mumper paid to alternative environmental exposures. Most obviously, if one assumes for purposes of argument that exposure to ethylmercury can induce autism, Dr Mumper cannot rule out other sources of mercury to which William Mead, Jordan King, and [REDACTED] were exposed. In fact, in the case of Jordan King, Dr Mumper admits that his medical records indicate he ate a lot of tuna and that he was exposed to other neurotoxicants. These other environmental exposures presumably fit within her view of an environmental cause of Jordan's autism.

d. Dr Mumper misinterprets scientific studies in an attempt to buttress her lack of evidence for causation. For example, she repeatedly quotes studies by Mundy et al., Dawson et al., Fein et al., and Kelley et al. that describe optimal outcomes in children diagnosed with autism or PDD in preschool years. Dr Mumper argues these studies indicate that environmental components are demonstrated by these positive outcomes. This reflects an ignorance of the natural history of autism which is, at times, associated with spectacular improvements, irrespective of interventions received and of the causal mechanisms involved. Secondly, in none of the studies mentioned has the author referred to vaccination theories or mercury-induced autism. If anything, these authors, in their discussion of these good trajectories, argued that early detection, which is now taking place, and access to early intensive behavioral interventions, are the likely factors accounting for these positive outcomes.

e. Dr Mumper further misinterprets the supposed effects of chelation therapy. She wrongly infers that because autistic children occasionally excrete higher amounts of mercury following chelation, this is somehow proof that these children suffer from mercury

overburden that could be the cause of their autism. This is plainly wrong. In these observations collected in the course of clinical practice, there is not even baseline pre-chelation mercury excretion data that could help interpret the post-treatment excretion figure. Secondly, it is clear from the literature that administration of a chelating agent to anyone (autistic or not) will be followed by increased excretion of mercury. This does not mean that the mercury is a cause of any health problem in the subject undergoing chelation. To provide a simple analogy, if autistic children were treated with diuretics, they would certainly display increased urine output. It would not, however, follow from this observation that the children's autism resulted from fluid retention or renal insufficiency.

f. Dr Mumper makes statements supporting the implementation of so-called treatments, although there is no evidence of their efficacy. The only evidence from which she quotes is that of her own clinical experience. It must be noted, however, that the clinical experience of most autism specialists contradicts Dr Mumper's opinions. There are standards to establish the efficacy of interventions in medicine through the use of controlled studies, particularly using methodology known as randomized, double-blind, placebo-controlled clinical trials. Most of the interventions that Dr Mumper supports and claims to have been efficacious in the treatment of Jordan King, [REDACTED] and William Mead have not been subjected to any scientifically rigorous testing for their efficacy. Moreover, some of these interventions, such as secretin infusion, have a history worth noting. After the report of three cases of apparent improvements in autistic symptomatology following secretin infusion, multiple families and practitioners began using this treatment for autistic children. Parents and practitioners reported improvements, and a number of people believed that an efficacious therapy had been found. Yet when

secretin was rigorously tested for its efficacy in three separate randomized clinical trials, with evaluators being blind to treatment status, none of the studies showed any beneficial value to secretin. This history, and others like it, suggest that the clinical experience, or the informal observations made by families or practitioners, can often be seriously misleading. None of the methods supported by Dr Mumper has been shown, through scientifically reliable testing, to be efficacious in the treatment of autism.

178. The histories of autistic symptoms in Jordan King, [REDACTED] and William Mead are remarkably comparable to those medical records or histories of children whom I have assessed in settings 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).

### Conclusion

179. It is my opinion, to a reasonable degree of scientific and medical certainty, that thimerosal-containing vaccines neither caused nor contributed to Jordan King's, William Mead's, and [REDACTED] autism. The claim that there is an autism epidemic caused by thimerosal-containing vaccines is unfounded, without reliable scientific support, and is not generally accepted in the autism community. There is no reliable scientific or medical basis to support the conclusion that there is an association or a causal relationship between thimerosal-containing vaccines and ASDs, and the evidence favors rejection of such a causal relationship. There is no basis for the claim that a subgroup of individuals with regressive autism and previously normal development represents a valid subtype and that it would have a unique association with thimerosal-containing vaccines that would not have been detected in existing studies. In fact, the replicated observation that the discontinuation of thimerosal from childhood vaccines in several

countries was not followed by a downward trend in rates of autism argues clearly for a lack of an association.

A handwritten signature in black ink, appearing to read "Eric Fombonne". The signature is written in a cursive style with a long, sweeping horizontal line above the name.

Eric Fombonne, M.D., F.R.C.Psych

Date: February 25<sup>th</sup> 2008

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