

# **Respondent's Exhibit BB**



**Omnibus Autism Proceeding - Expert Report  
Brian J Ward**

**Michelle Cedillo Case**

**A. Limited Chronology of Early Events**

***Early Events***

Michelle’s parents had experienced some difficulty conceiving and a number of interventions were attempted over a three-year period (eg: Clomid, tubal insufflation). Michelle was born on August 30, 1994. The pregnancy was reported to be uncomplicated and her birth records indicate a vacuum assisted delivery with APGAR scores of 9 and 9. According to the limited medical records available, she seemed to have a relatively uneventful first 15 months of life. There is considerable variability in the various reports of the timing of events that took place around Michelle’s MMR vaccine at ~15 months of age. For example:

***Mother’s narratives regarding fever onset:***

- Apr 24, 1997 (Pet Ex 14-pg 5) ‘[Michelle] got the MMR on 12/20/95. Exactly 14 days later; she got high fever (106 and 105.6)’
- Apr 21, 2001 (Pet Ex 54) MMR administered on 12/20/95 and first fevers on December 27-28.

***Expert reports on fever onset:***

- Drs Kinsbourne & Krigsman state the first fever occurred on Dec 27, 1995
- Dr Byers states that Michelle was irritable with fever on Dec 23, 1995
- Dr S. Gupta’s record suggest that Michelle developed a fever of 101°F 2 days after her MMR (Pet Ex 3-pg3).

As Dr Kinsbourne points out in his first expert opinion (Pet Ex 28-pg251), ‘There is a dearth of contemporaneous medical records on which to base an opinion’. The only hard data in the medical record that I can find for the 2-3 week period after Dec 20, 1995, is a very limited Yuma Pediatrics note that Michelle was brought to the Pediatrician in the first days of January 1996 (Pet Ex 8 – date obscured in my copy). This was presumably Jan 6, 1996 since Michelle’s mother states in her affidavit (Pet Ex 54-pg4-point 19), ‘I showed up at the pediatricians office without an appointment’ on January 6<sup>th</sup>, 1996. Michelle was found to have a purulent nasal discharge at this visit and was treated with cefazol. She was also found to have 8 teeth coming in simultaneously (Pet Ex 14-pg 5). Michelle subsequently developed an odd, possibly irritation rash around her nose associated with scratching/rubbing. As a result, it seems like the most likely chronology of early events was:

Vaccine	Dec 20, 1995
Red cheeks, fever	Dec 27, 1995
Fever	Dec 28 – 29, 1995
Mild fever, vomiting, diarrhea, rash	Dec 29, 1995
Fever gone, vomiting	Dec 30, 1995
Vomiting	Dec 31, 1995
Doing reasonably well	Jan 1-4, 1996
Fever	Jan 5, 1996
Purulent nasal d/c, fever, stomach rash, teething	Jan 6, 1996



***First signs of behavioural change:***

In the expert reports and most of the later parental narratives, the behavioural changes are all described as having occurred abruptly following the onset of fever in the first week after the MMR immunization (not speaking, distant, persistent crying, word loss, etc).

However, there are repeated references in the documentation provided of a more gradual onset of behavioural changes. For example:

Mar 15, 1996 (Pet Ex 8)

Another short Yuma Pediatrics note states that Michelle ‘talks less well since ill in Jan’

Aug 1997 (Pet Ex 4)

According to Dr Lott, ‘Within 3-4 weeks, [Michelle’s] behaviour was markedly abnormal and [she] went on to be diagnosed as a severe form with prominent GI symptoms.’

July 1997 (Pet Ex 7-pg5)

Dr Emilia Matos wrote that ‘the parents are concerned that [Michelle] seemed to develop normally up to about 18 months of age’

Apr 24, 1997 (Pet Ex 14-pg5)

In the mother’s narrative, she states that ‘Michelle developed normally up until about her 18<sup>th</sup> month or so’

May 28, 1998 (Pet Ex 5-pg 3)

In a language assessment ‘Mr & Mrs Cedillo noticed a change in Michelle’s behaviour beginning a few weeks after her illness following the MMR vaccine’.

?? Date (Pet Ex 21-pg17)

In another of the mother’s narratives, she states that ‘I believe that we may have seen symptoms as early as 3 days following the MMR vaccination. On December 23, 1995 at a family Christmas party, my husband and I noticed Michelle began trembling and crying when we entered a room full of people’ ‘This occurred before the onset of the fever’

July 7, 2004 (Pet Ex 41)

Total Life Center evaluation reported the parents as saying that ‘within 3 months of MMR, [Michelle] stopped responding to name, manifested obsessive behaviour, was [sic] crabby, transitions became a problem ...’

As a result, it is actually very difficult from the available records to be certain how Michelle’s behaviour changed around the time of her MMR immunization and at what pace. However, it seems very clear to me that Michelle did not suddenly regress and start acting abnormally on Dec 27, 1995, as some of the expert reports would suggest.

Thereafter, however, her language, behaviour and development *did* deteriorate over time in the months after the MMR vaccine such that she was diagnosed with severe ASD in her third year of life and went on to be diagnosed with Crohn’s disease with uveitis, rheumatologic problems, seizures and many other serious medical complications through childhood. I can find no CNS imaging studies in her records until very late (CAT scans Dec 2005, Mar 2006 and MRI Sept 2005), all of which were essentially normal. To my knowledge, no lumbar puncture was ever performed. A truly stunning number and variety of tests were performed on this child between the ages of 3 and 11. Some of the most interesting include:

Serum TNF $\alpha$  level (Apr 30, 2004)      normal      (Pet Ex 27)

Hair mercury level (Jul 27, 2004)	undetectable	(Pet Ex 28-pg 342)
Hair mercury level (Mar 27, 2006)	undetectable	(Pet Ex 43–pg121)
Anti-MBP levels (7/26/04)	neg IgG/A/M	(Pet Ex 28- pg 359)

Michelle had multiple endoscopic procedures (both upper and lower) during her first 11 years of life. The first (June 12, 2000) showed erosive esophagitis/gastritis with some eosinophil infiltration. Dr Dodge reported ‘focal lymphoid aggregate formation ... as expected’ in the ileum as well as the colon. There was ‘no increase in inflammatory cells in the lamina propria’ and he reported the colon as having ‘histologically unremarkable colonic mucosa’ (Pet Ex 28-pg 199). An ileum biopsy obtained at another endoscopy performed by Dr Krigsman (Jan 31, 2002) was sent to Unigenetics Inc where it was reported to be positive for the measles F gene (1.67x10E5 copies/ng total RNA: Pet Ex 28-pg179). Although blood was apparently also sent to Unigenetics at this time, there is no report of its having been tested. Minor changes are noted in some of the 16 biopsies obtained (occasional lymphoid follicles in gastric antrum and ileum)(Pet Ex 28-pg451-55).

**B. General Comments on the Expert Reports**

Three of the petitioners’ expert reports in this case are remarkably self-referential (Byers, Krigsman, Kinsbourne). Each of these reports refers extensively to the opinions of the others in support of the conclusions. The overall effect is one of slipping effortlessly from hypothesis to established fact in several aspects of the Cedillo case. This circularity also results in considerable repetition of the core hypothesis (actually a series of hypotheses).

The petitioners’ argument rests on a cascade of unproven and controversial hypotheses:

- First That thimerosal in the vaccines Michelle received caused her to be immunosuppressed, hence susceptible to a persisting measles virus infection
- Second That measles virus did indeed persist in Michelle’s case following MMR vaccination leading to a long-term infection of her gut, her immune system and her brain
- Finally That this persisting, vaccine-strain infection of her brain and gut (and other tissues) led to her clinical manifestations of autism with enterocolitis

There is no scientifically reliable evidence that *any* of these hypotheses are true either alone or as a whole. Furthermore, arguments that rely on a convergence of unlikely events should be viewed with skepticism.

**C. *The Individual Reports***

**C.1 *Dr V Aposhian***

I understand that a toxicologist will comment in more detail regarding Dr. Aposhian’s report; however, I would like to note, on the basis of my work with vaccine development, that Dr Aposhian overstates the FDA ‘case’ against thimerosal by selectively quoting the FDA to support the argument ‘that thimerosal is not safe.’ The FDA is discussing thimerosal’s possible use in over-the-counter (OTC) medications, not vaccines. With OTC medications, control of the substance is essentially lost once they are licensed, and administration of the product is unrestricted. The FDA must consider that an OTC product may be used more frequently, at higher doses and for applications that were not intended. Dr. Aposhian implies that thimerosal itself is unsafe because it has not achieved ‘generally recognized as safe’ (GRAS) status. Not achieving GRAS status does not mean that a particular product is unsafe: it simply means that it is not known to be safe for widespread and unregulated use.

### ***C.2 Dr A Krigsman***

Dr Krigsman dates Michelle's problem onset as precisely 7 days after her MMR at 15 ¾ months of age ('on December 27<sup>th</sup>, 2005') when he reports that she had a high fever for 4 days with vomiting, lethargy and irritability. [note: Dr Krigsman likely means 1995).

It is Dr Krigsman's opinion that 'The most compelling factor implicating receipt of the live virus MMR vaccine in the development of Michelle's enterocolitis is the simple chronology of the events'. This is a common error in causality assessment. In fact, simple temporal associations are far from compelling when the natural timing of the events overlap as is the case for MMR administration and the clinical onset of ASD.

In his limited review of the evidence for measles virus persistence, Dr Krigsman refers primarily to the Uhlmann paper (Uhlmann 2002). He then cites a 2006 International Meeting For Autism Research (IMFAR) abstract by Walker as having confirmed 'the reliability of [the Uhlmann] assay as an accurate predictor of the presence of measles virus RNA'. Apparently, the Walker abstract proves that 'measles RNA products generated by use of the Uhlmann assay [are] those of vaccine not wildtype measles RNA' and that 'base pair sequencing of the RNA products' [demonstrate] 'with 100% certainty the vaccine origin of the detected measles RNA'. It should be noted that few scientists consider abstracts to be reliable sources of information because the data are typically preliminary and abstracts are rarely subjected to rigorous peer review.

Dr Krigsman tries to bolster his argument for a persisting measles virus by citing Singh (Singh 2003) who found elevated anti-measles antibody levels in more than 80% of ASD children. Unless virtually all cases of autism are caused by measles virus (a position expressly excluded by the MRC, IOM and Cochrane reports)(MRC 2001, IOM 2001 & 2004, Demicheli 2005), then Singh's work must be in error or there must be an alternate explanation for this finding. We have recently tested anti-measles antibodies in children with ASD and found no differences with control children (D'Souza 2006).

Finally, Dr Krigsman argues that unsubstantiated comments from 'different pathologists' support his contention that 'the observed enterocolitis in ASD-GI children' is 'infectious' in nature. This seems like a remarkably weak level of evidence to be citing as one of the three relevant facts in support of his hypothesis. The substance and even existence of this type of evidence is not verifiable. If such comments were made, the scientific basis for them, if any exists, is unknown. His other relevant facts are the temporal association and the 'established association between ASD-GI and vaccine strain measles virus'. My analysis of his relevant facts:

- a temporal coincidence does not prove causality
- the detection of measles RNA in ASD children is based on flawed science
- the unsubstantiated comments of 'different pathologists' are irrelevant and do not represent verifiable scientific evidence

### ***C.3 Dr M Kinsbourne***

Dr Kinsbourne appears to believe that Michelle was in an 'encephalopathic state' following her MMR vaccine which 'led into a regression into severe autism' (pg 5). To my knowledge, there is no evidence that Michelle was encephalopathic at any time during the period immediately following her MMR. There is no mention of encephalopathy in any of the contemporaneous medical documentation and the consideration of such a state would certainly have prompted more intensive medical testing (eg: lumbar puncture, imaging, etc).

Dr. Kinsbourne includes measles on his list of 'Medical Concomitants of Autism' (pg 8) without any reference. He later cites an obscure German manuscript from 1948 that is not

included in his bibliography (Bosch 1948). He states categorically and without support that ‘none of the [other diseases listed] are associated with inflammation of the gut mucosa’. Although Dr Kinsbourne appears to be trying bolster his argument that the combination of ASD plus gut inflammation is a ‘smoking gun’ for a measles virus etiology, the actual evidence that even wild-type measles is a cause of autism is phenomenally weak. Bosch’s manuscript reports on two cases of possible association between natural measles and ‘infantile dementia’ but acknowledges that no other similar cases could be found in the literature. Furthermore, it can reasonably be assumed that almost every child born in the world between 1948 and the early 1970s acquired natural measles during the first years of life (measles vaccines were widely implemented only in the 1970s). Many hundreds of millions of infants acquired natural measles during this 20-30 year period. The WHO still estimates that up to 30-50 million infants and children suffer from natural measles every year despite the availability of a vaccine (WHO website). To my knowledge, no other cases of the purported measles-ASD association have been reported during this 60 year period.

It is curious that Dr Kinsbourne chooses to reference Richler in support of his statement that children with ‘regressive ASD’ have a higher rate of GI disturbance than other ASD children (Richler 2006). This paper studied 351 children with ASD and specifically addressed the question of regressive ASD and MMR. These authors concluded that ‘There was no evidence that onset of autistic symptoms or of regression was related to measles-mumps-rubella vaccination.’

Dr Kinsbourne tries to undermine the MRC, IOM and Cochrane Reports with his statement that ‘The epidemiological literature with respect to ASD is ... not applicable to Michelle Cedillo’s case.’ (Page 10). He argues that the specific combination of thimerosal, MMR and ASD has not been ‘examined in a controlled fashion’ (page 10). However, the epidemiologic studies of MMR and ASD that form the backbone of the negative reports have generally been performed in the setting of very high vaccination coverage rates (ie: broad population exposure to both thimerosal-containing vaccines and MMR). The ‘exposure’ of infants to vaccines is not really the same as ‘exposure’ to most bone fide toxins (eg: dioxins, lead). In the last decade, most infants in North America have received 3 doses of DPT, HBV vaccine, polio vaccine, and 1 dose of MMR (etc) in the first 15 months of life. The large majority of the children have therefore had essentially the same ‘exposure’ to vaccines, so the authoritative reports from the MRC, IOM and Cochrane groups cannot be dismissed out-of-hand. I am not aware of any convincing data showing that a lack of ‘exposure’ to vaccines protects children against the development of ASD.

Absent massive, population-based studies, it would be very difficult to detect a true association between thimerosal or MMR and ASD using epidemiologic tools if Dr Kinsbourne and colleagues were arguing that such an association occurred in 1 child out of 5 million exposed (ie: a very rare event). This is not their argument however. They claim evidence of a persisting measles infection in a large proportion of children with ASD (antibody or RNA). For example, Dr Kinsbourne cites Bradstreet’s communication to the IOM in which he reports finding MV genomic material in 19 of 28 CSF samples tested from ASD children (67%) as well as PBMC and gut tissues (Bradstreet IOM communication 2004). The simple frequency of these ‘positive’ results flies in the face of the mountain of epidemiologic evidence AGAINST such an association. Are we to believe that Dr Bradstreet has somehow collected large numbers of the one-in-a-million ASD children who just happen to have persisting MV in their guts and brains? The authoritative reviews are indeed relevant to the Cedillo case.

It is intriguing that Kinsbourne repeatedly cites work from Oldstone's group in support of his cascade of hypotheses. However, even though elements of the MMR-ASD-GI hypothesis should theoretically be of great interest to Dr Oldstone whose life's work focuses on viral persistence, the manuscripts of Uhlmann, Bradstreet, Wakefield (etc) are not cited in any of Dr Oldstone's cutting-edge work despite the publicity accompanying these manuscripts. The natural implication is that Dr. Oldstone sees little or no scientific basis for the persisting measles virus element of Dr Kinsbourne's hypothesis.

Dr Kinsbourne quotes Ashwood (Ashwood 2006) in support of his hypothesis, but neglects to mention that Ashwood's excellent review of the immune dysregulation in ASD contains no mention of the MMR-ASD hypothesis. Measles is mentioned in the context of congenital (wild-type) infection only (pg 8). The abstract for this article very logically states '*Recently, increasing research has focused on the connection between the immune system and the nervous system including its possible role in the development of ASD. These neuroimmune interactions begin early during embryogenesis and persist throughout an individual's lifetime ...*'. In the section dealing with inflammation associated with LNH, Ashwood states that '*This focused immune response [sic] direct to the epithelial may first be indicative of an autoimmune process directed against self-antigen contained within epithelial cells*' (pg 7). On page 9, Ashwood states '*the overwhelming majority of epidemiological, population studies indicate there is no established correlation between vaccinations and autism*'.

Kinsbourne uncritically refers to the Bradstreet manuscript (Bradstreet 2004) in support of his contention that MV genomic material would have been detected in Michelle's brain had either an LP or a brain biopsy been done. This report of 3 cases was published in a non-indexed journal. Non-indexed journals are either brand new (ie: no track record of scientific rigor) or are thought to be insufficiently rigorous to be included in the medical-scientific literature search engines (eg: PubMed). The Journal of American Physicians and Surgeons has been around for over 50 years, so its non-indexed status cannot be attributed to youth. Non-indexed journals are generally ignored by scientists as sources of reliable scientific information. The study itself has serious flaws that would likely have prevented its publication in an indexed journal. For example, there is no indication of ethical approval, no blinding, no antibody data for controls, etc. It is nonetheless interesting that the cerebrospinal antibody data from the three ASD children included in this manuscript actually argue powerfully AGAINST a persistent measles infection in the brains of these children (all had very high serum:CSF measles-specific antibody gradients in contrast to most SSPE cases). If Dr Kinsbourne's 'inference' (pg 15) is correct and vaccine-strain measles virus is, indeed, replicating in the brains of ASD children, then one would logically expect evidence of intrathecal IgG production. There was not.

Dr Kinsbourne states (pg 15) that he is 'aware of a number of children with ASD who have been found to harbour measles vaccine virus genomic material in lymphocytes and macrophages of the circulating blood' but provides no reference. He states categorically that Michelle had 'immune dysfunction' (pg 14) with no evidence other than Dr Byers's report. Dr Gupta's interpretation of the single immunologic evaluation of Michelle (conducted at approximately 3 years of age) was that her results were 'nearly normal'.

Dr Kinsbourne pulls very selectively from the SSPE and measles inclusion body encephalitis (MIBE) literature to try to make the point that measles virus can persist in the brain (pg15-16). However, both SSPE and MIBE are typically progressive and fatal illnesses that have very distinctive pathologic 'footprints'. To my knowledge, there is essentially no overlap between the pathology of SSPE and MIBE (in which measles virus is known to persist) and the limited pathological reports for ASD subjects. In SSPE, 'The

encephalitic process is characterized by perivascular cuffing consisting of lymphocytes and plasma cells with diffuse mononuclear infiltration of the grey and white matter. The most striking histological features ... are the enormous increase in hypertrophic astrocytes and proliferation of microglia cells as well as demyelination and the presence of intranuclear Cowdry type A and B inclusion bodies' (ter Meulen 1978). Measles virus proteins are readily detectable in the brains of children with SSPE by immunofluorescence (eg: Liebert 1986). Although I am not a trained pathologist, I am not aware of similar pathological findings in the brains of children who have died with ASD. Despite Dr Kinsbourne's characterization of Bailey's autopsy report (Bailey 1998b) as supplying 'dramatic support' for the MMR-ASD-GI hypothesis (pg 17), Bailey does not mention a possible viral etiology in the extensive discussion of the findings or the extensive review of the pathological literature in ASD. In both SSPE and MIBE, the causative viruses are heavily mutated and replication defective (Cattaneo 1989, Bitnun 1999, Rima 2006, Oldstone 2007). It takes time for these mutations to accumulate. As a result, the onset of MIBE is typically measured in months after exposure and the latent period for SSPE is measured in years (not days). Furthermore, individuals with MIBE are typically profoundly immunocompromised. Measles-containing vaccines have been used in hundreds of thousands of subjects with varying degrees of clinically-definable immunocompromise, including those with HIV, recovering transplant patients, etc (reviewed in Bitnun 1999), yet vaccine-associated MIBE and giant-cell pneumonitis cases are very rare (case reports). There is no evidence that Michelle had any significant degree of immunocompromise near the time she received her MMR vaccination.

Dr Kinsbourne cites Deykin to suggest that 'measles infection has ... been incriminated' in the development of autism (Deykin 1979). In this review, the authors state '*Yet the proportion of cases with histories of viral experience during the periods of interest was small; indicating that these four viruses [measles mumps, rubella, varicella] were unlikely to have played a major role in any substantial proportion of cases*'. It is worth noting that these authors found no statistically significant difference between ASD cases and controls for postnatal exposures or infections with wild-type measles virus.

Dr Kinsbourne's statement that, 'like measles virus, Bornavirus persists but does not expand to the extent that it causes global deficits and death' (pg 19) is entirely incorrect. When measles virus does persist in SSPE or MIBE in immunocompromised subjects, it is almost invariably progressive AND fatal (Griffin 1997, Bitnun 1999).

Dr Kinsbourne extrapolates wildly from the observation that some children with ASD have evidence of cytokine production peripherally and in their brains to state that 'Such findings explain the causative mechanism by which persisting virus infections, such as with residual measles vaccine virus, play a significant role in the cause of ASD' (pg 18). Croonenberghs correctly points out that '*Activation of the inflammatory response system has been observed in major depression and schizophrenia*' (references in Croonenberghs 2002). In Pardo's excellent review, he states that the first question raised by evidence of neuroinflammation in ASD is '*Whether the neuroglial and neuroimmune responses associated with autism are part of the primary reactions that contribute to CNS dysfunction in this disorder or are epiphenomena resulting from reactions to CNS dysfunction*' (Pardo 2005). In other words, it can be very difficult to sort out the cytokine 'chicken and egg' in subjects with chronic and serious CNS dysfunction. To state (as Kinsbourne does on pg 20) that 'It is not credible that concurrent presence of all three elements [gut disease, brain disease and measles virus infection] is mere coincidence.' is misleading. It is well-established that long-standing neuro-psychiatric conditions such as schizophrenia and depression are associated with profound alterations in bowel function as well as multiple alterations in immune system activation and function (eg: Pardo 2005). If any major psychological disturbance can elicit the same kind of local and

systemic cytokine response as occurs in ASD ... how can such responses be touted as a 'smoking gun' for a persisting measles infection?

It seems ludicrous to state (as Dr Kinsbourne does on page 20) that 'Direct examination of Michelle Cedillo's brain and cerebrospinal fluid has not been feasible'. If, as Dr Kinsbourne argues throughout his document, Michelle has a persisting vaccine-strain virus in her brain, it would be irresponsible not to investigate this possibility fully in order to consider therapy. Examination of cerebrospinal fluid (CSF) is a standard procedure in cases of suspected viral infection of the central nervous system (CNS). This is not to suggest that I believe that such a study should have been or should be conducted. All of the available evidence in Michelle's case (eg: repeated CT scans, MRI scan) show no sign of CNS inflammation and there is no convincing evidence that she either had or has a measles virus infection of her CNS.

In conclusion, Dr Kinsbourne is willing to ignore the fact that there is no evidence of clinically-relevant immune suppression in Michelle's case. He is also willing to ignore the fact that there is no evidence of a persisting measles virus infection or even inflammation in Michelle Cedillo's brain. Even if one were to take the evidence of virus persistence in Michelle's gut at face value (which I do not), all of his arguments about immunosuppression, neutropenia, anatomic distribution, neuroinflammation, etc are based on extrapolations from and questionable interpretations of limited data. His extended extrapolative argument also explicitly ignores intrinsic inconsistencies and large bodies of well-established, mainstream scientific literature. He argues that the court should pay attention to a 'trend' in ASD research in coming to its conclusion in the Cedillo case: that 'environmental factors, such as infections and toxins, [sic] is coming into fashion as a mechanism of causation' (pg 20). In Dally's excellent review of the medical community's struggle to find the etiology of Pink disease, there is a passage that seems particularly apt:

*The idea that disease of unknown origin was likely to be due to a specific 'infection' was prominent in medical thought at the time. The discovery, in the 1890s, of filterable viruses, invisible to the microscope, strengthened this hypothetical but 'scientific' explanation for mystery diseases.... This began a fashion that has lasted to this day, as can be seen, for example, in the literature on glandular fever, myalgic encephalomyelitis (ME) or chronic fatigue syndrome, and even depression. (Dally 1997).*

In light of the current proceedings, one could easily add Dr Kinsbourne's cascading MMR-ASD-GI hypothesis to this list.

#### **C.4 Dr Vera Byers**

Dr Byers' report is poorly referenced with many statements that appear to be entirely unsubstantiated. For example:

- She states that the high fevers that occurred in the days following Michelle's MMR immunization are evidence that her 'damaged immune system predated the MMR vaccination' (pg 4). Children with truly damaged immune systems and those in whom MV truly persists typically have very few symptoms around the time of immunization. Symptoms can be delayed for months and many of these individuals die without ever having developed a rash.
- Dr Byers states that 'the results of persistent measles [sic] has ranged from asymptomatic, to increased infection with pathogens' without references (pg 6). I am not aware of any literature demonstrating that SSPE or MIBE patients are unusually susceptible to other infections.
- Dr Byers states that Michelle's 'immunologic status prior to receiving the MMR was not abnormal' (pg 7) but provides no evidence. To my knowledge, Michelle had never had any immunological testing performed prior to August 1997.

- Dr Byers states that ‘several tests have shown [measles virus] to persist in [Michelle’s] body’ (pg 4). I believe that only a single test was performed.
- She states that Michelle’s ‘dysregulated immune system would be expected to secrete pro-inflammatory cytokines in the brain, as it [sic] is are in the gut’ (pg 6). She has no evidence from Michelle’s case for this statement.

#### **D. Principal Issues In The Cedillo Case**

##### **D.1 Is there any evidence to support the Thimerosal-Immune Deficiency Hypothesis?**

Simply stated – no. ‘Immune deficiency’ is a clinical state, not a laboratory observation and laboratory results do not necessarily correlate with clinical experience. One way to test the hypothesis that exposure to mercury causes clinically significant immune deficiency is to observe whether those exposed to high doses of mercury are more prone to infection.

To the best of my knowledge, none of the major methyl mercury exposure studies have demonstrated an increased incidence or prevalence of any infectious disease. The 300 page Minimata Disease Report contains no mention of increased susceptibility to or severity of infectious diseases. A Table dealing with ‘Other Diseases’ (pg 260) includes schizophrenia, depression, alcoholism etc, ... but no infectious diseases. (Tsubaki 1977). Similarly, Kjellstrom’s report of New Zealand children chronically exposed to methyl mercury (Kjellstrom 1989) contains no mention of unusual susceptibility to or severity of infectious conditions despite extensive health profiling. There is no mention of unusual infectious risk in Myers’s study of prenatal exposure with a 9 year follow up in the Seychelles (Myers 2003). A careful 22-year US family study following high dose methylmercury exposure revealed serious neurologic disease and persistence of high levels of mercury but did not mention any increased susceptibility to infectious agents (Davis 1994). In McRill’s study of subjects exposed to very high levels of mercury from a cosmetic powder (serum levels in excess of 20 µg/mL), there is no mention of increased susceptibility to infectious agents or greater severity of infections (Table 1, pg 6: McRill 2000). At the time, many physicians argued that Pink Disease might be caused by a neurotropic virus but none suggested that the children with Pink Disease were more susceptible to other infections (Dally 1997). Many of these children were seriously poisoned between 6 months and 3 years of age, a time when any increase in incidence or severity of infections should have been readily apparent. In Clarkson’s excellent review of the clinical manifestations of mercury exposures (including thimerosal) published in the New England Journal of Medicine in 2003, there is no mention of immunomodulation, immunosuppression or enhanced susceptibility to infectious diseases (Clarkson 2003).

Frankly, it is not particularly surprising that mercury-containing molecules such as thimerosal have effects on a variety of immune cells and cell lines *in vitro*. First, *in vitro* exposures are frequently massive compared to what occurs *in vivo* (See examples in Table 1). To emphasize the point that caution needs to be exercised in extrapolating from *in vitro* observations, it may be useful to consider the *in vitro* effects of several ‘natural products’ widely considered to be safe. For example, oil of ginger can cause *in vitro* suppression of T cell responses and cytokine production at doses in the 0.001-10 ng/mL range but suppression of cellular responses following oral administration only occur with doses in the 0.125-0.5 g/Kg range (Zhou 2006). *In vitro* effects on immune cell functions have been reported for green tea (Wilasrusmee 2002) and extract of ginseng at low doses (Larson 2003). *In vitro* exposure to very low doses of natural vitamin A and its metabolites (1 µM and lower) can have impressive effects on human immune cell activation, survival and function (Ludanyi 2005, Chabot 2007, B Ward, unpublished studies). The normal dietary intake of ascorbate (vitamin C) is in the range of 250-1000 mg/day yet sustained exposure of human T cells to low levels of ascorbate (10-12 µg/mL

range) can significantly decrease cell viability and lead to irreversible depression of mitogen responsiveness and IL-2 production (Eylar 1996). These kinds of effects are very similar to those reported following thimerosal exposure *in vitro*.

#### **D.2 Are Immunocompromised, Measles-Vaccinated Children at Increased ASD Risk?**

Since measles vaccination is essentially a ‘ubiquitous exposure’ in most of the world, it is worth asking if there are infant populations with well-defined immunocompromise that might shed some light on the hypotheses of the petitioners’ experts. Such populations exist in several parts of the world with high perinatal HIV rates (refs, Becker 2004) and/or high levels of intestinal parasites (Pit 2000). For example, my group has been working in Zimbabwe for almost 12 years studying mother-to-child-transmission of HIV. Many of the more than 16,000 children recruited to our studies and followed for 1-2 years have been infected by HIV perinatally (~30% maternal seroprevalence rate rising to ~40% by two years follow-up) (Humphrey 2006). This depressing scenario is repeated throughout much of sub-Saharan Africa and some regions of Brazil and South/Southeast Asia (Juneja 2005, Seth 2006). If we make the reasonable assumption that most of these children receive measles vaccine (as recommended by the WHO: Moss 2003), the cumulative exposure of HIV-infected children to vaccine-strain measles could be as high as 600,000 (Goulder 2001). Under the Expanded Program on Immunization and the Global Alliance for Vaccine Initiative (GAVI), virtually all of these children will also have received several doses of thimerosal-containing vaccines prior to their measles vaccination. Many of these HIV-infected children are immediately enrolled in a large range of studies (like ours in Zimbabwe) and followed closely. If persisting vaccine-strain measles virus is truly a cause of autism, there should be a massive burst of ASD in HIV-infected children throughout the world. To the best of my knowledge, there has been no such burst (our own experience in Zimbabwe plus personal communications with Pediatrics colleagues in Senegal, South Africa and the Sudan). Although the background rates of ASD are unknown in Africa as a whole, case series have certainly been reported (Lotter 1978, Dhadphale 1982, Khan 1996, Mankoski 2006) and high rates have been reported in some first-generation African populations (Gillberg 1995). It is noteworthy that none of the 14 ASD cases in Mankoski’s recent study in Tanzania were HIV positive. In 2005, Tanzania was estimated to have an overall HIV seroprevalence rate of 6.5% and at least 110,000 cases of pediatric HIV (World Bank 2007). In 2005, Brazil reported 600,000 people living with HIV and at least 12,000 cases of pediatric HIV (83% congenital transmission) (Matida 2005). This absence of any perceptible link between exposure to vaccine strain measles virus and the development of ASD in these genetically and geographically diverse populations with clear-cut Th2-deviated immunocompromise argues forcefully against the hypothesis advanced by petitioners’ experts.

#### **D.3 What Confidence Can One Have in the PCR Data Produced in this Case?**

The hypothesis of a persisting, vaccine-strain measles virus is at the heart of this case. The quality of the PCR data generated is therefore critical.

##### **D.3.1 The Early Days of the MMR-GI Hypothesis**

The MMR-ASD-GI hypothesis has been championed primarily by Dr Wakefield and colleagues. In the mid-1990s, these investigators used epidemiologic and basic science studies to implicate vaccine-strain measles virus in the development of IBD (among others Wakefield 1993, Smith 1993, Ekblom 1994, Wakefield 1995, Miyamoto 1995, Lewin 1995, Thompson 1995, Pardi 2000, Morris 2000, Kawashima 2000). However, the techniques used by Wakefield and colleagues were criticized (Ward 1997) and their hypothesis was largely dismissed following a series of methodologically sound epidemiologic and bench studies published by a number of groups towards the end of the 1990s (among others Hermon-Taylor 1995, Iizuka 1995, Haga 1996, Jones 1997, Feeney 1997, Nielsen 1998, Pebody 1998, Lawrenson et al 1998, Afzal 1999, Pardi 1999, Afzal

2000, Davis et al 2001, Iizuka 2001). Particularly damaging to the hypothesized MMR-IBD link was the discovery that a critical monoclonal antibody cross-reacted with a normal human protein (Iizuka 2000).

#### D.3.2 *Morphing of the MMR-GI Hypothesis into the MMR-ASD-GI Hypothesis*

In 1998, Wakefield and colleagues re-emerged with a small case series purporting to link MMR to ASD with gastrointestinal (GI) manifestations (Wakefield 1998). Although a few investigators attempted to use epidemiologic approaches to argue in support of the hypothesis (Geier 2005), a large body of negative laboratory and epidemiologic data accumulated rapidly in the years following the Lancet article (Peltola 1998, Chadwick 1998, Duclos 1998, DeStefano 1999, Taylor 1999, Afzal 2000, Kaye 2001, Smeeth 2001, Dales 2001, Afzal 2001, Ashraf 2001, Halsey 2001, Farrington 2001, Kastner 2001, Taylor 2002, later studies reviewed in Honda 2005, Fombonne 2006, Uchiyama 2007 among others). This hypothetical MMR-ASD-GI link has been subjected to rigorous review by the MRC ([www.mrc.ac.uk/pdf-autism-report.pdf](http://www.mrc.ac.uk/pdf-autism-report.pdf)), the Institute of Medicine (IOM 2001, IOM 2004) as well as the Cochrane group (Demicheli 2005): all concluded that the hypothesis had little scientific merit.

#### D.3.3 *PCR Support for the MMR-ASD-GI Hypothesis*

However, in the early 2000s, Wakefield recruited a small number of molecular biologists to apply molecular diagnostic techniques to the MMR-ASD-GI question. Using nested polymerase chain reaction (PCR) assays, Kawashima (2000) reported the presence of measles genomic material in peripheral blood mononuclear cells (PBMC) isolated from 3/9 ASD-GI children (Kawashima 2000). A short while later, O’Leary’s group applied *in situ* PCR and real-time PCR to ileal biopsies from 91 ASD-GI children and 70 non-ASD controls (Uhlmann 2002). They reported detection of measles virus genomic material in 75/91 ASD children but only 5/70 controls by real-time PCR. O’Leary also reported that 42/57 ileal biopsies from ASD children were positive by *in situ* RT-PCR compared to 1/5 from controls. They claimed that the PCR amplicons co-localized with a dendritic cell-specific monoclonal antibody in both control and ASD biopsies (Uhlmann 2002). A methodologically identical but less detailed manuscript with the same authors in different order appeared in a 2002 supplement of the same journal (Martin 2002). It is not clear if these two studies are distinct. Other data on the hypothesis were produced by Bradstreet who reported the identification of vaccine-strain measles genomic material in the cerebrospinal fluid (CSF) of 3 children with ASD and GI complaints (Bradstreet 2004).

There are many serious problems with these molecular data. Among others:

- Blinding and strategies for control of cross-contamination were not described in Kawashima’s paper. The latter is particularly important since this laboratory had previously claimed to identify measles virus genomic material in subjects with both intractable seizures and autoimmune hepatitis (Kawashima 1996, Kawashima 1996b). As a result, both wild-type and vaccine-strain measles virus amplicons had been generated in this laboratory prior to the MMR-ASD-GI study.
- In the Uhlmann paper, ‘case’ children are described simply as ‘affected’. Given the controversy surrounding the diagnosis of ASD, this lack of precision is inexcusable.
- Like the Kawashima paper, neither Uhlmann nor Martin provided details regarding the order in which specimens were analyzed or blinding of the specimens or operators. The lack of blinding is particularly problematic for *in situ* PCR and immunohistochemistry since these techniques are quite subjective. Important information is not provided (ie: how long were samples stored, no mention of RNA quality, which samples were ‘positive’ using specific primer pairs, no mention of concordance (or lack thereof) for the three measles genes targeted, only 5 control biopsies were tested by *in situ* RT-PCR without details). Uhlmann and colleagues use a sub-optimal concentration of UNG (an enzyme used to reduce the risk of cross-

contamination by previously amplified DNA: see D'Souza 2006) and failed to include an important reverse-transcriptase (minus) control (ie: leaving out the reverse-transcriptase step in the RT-PCR assay is a very sensitive way to reveal DNA contamination).

- Of the many technical problems with the Uhlmann manuscript, one of the most egregious is the absence of sequence data for the amplicons they claim to be of measles origin. To my knowledge, neither the O'Leary nor Unigenetics laboratories have ever published any sequence information for the amplification products they claim to be of measles origin. This type of information is critical to ascertain whether or not non-specific amplification products have been generated and to establish whether or not the material amplified is of vaccine-strain or wild-type origin.
- The Uhlmann study included 9 children with IBD as 'controls' and none of these biopsies were positive. This is very odd since Wakefield had previously published that most tissue specimens from Crohn's were positive for measles virus using various techniques much less sensitive than the techniques employed by O'Leary (Uhlmann 2002). This glaring contradiction was ignored.
- There is no evidence that the Unigenetics Laboratory either participated in a program of external quality assessment for its assays (EQA: a routine part of any diagnostic laboratory's existence and a key factor is assessing the reliability of results generated by laboratories). Quite the contrary, in fact; while in operation, Unigenetics consistently declined offers of EQA reagents made by the UK National Institute for Biological Standards and Control (NIBSC: personal communication M Afzal).
- Finally, the amount of measles virus genomic material that Dr O'Leary and his Unigenetics colleagues claim to have found in the gut biopsies of children with ASD are very high ( $1-3 \times 10^5$  copies/ng RNA). If measles virus genomic material was truly present at these concentrations in the gut tissues of ASD children, one would logically expect to see virtually every cell infected with massive disruption of tissue integrity. This criticism also applies to the test result included for Michelle Cedillo's intestinal biopsy (reported as F gene  $1.67 \times 10^5$  copies/ng RNA).

#### D.3.4 *PCR Evidence Against the MMR-ASD-GI Hypothesis*

Afzal and colleagues applied nested PCR and real-time PCR to PBMC samples from 15 children with ASD (10 with regression, 2 with GI complaints) (Afzal 2006). This methodologically rigorous study found no evidence of measles genomic material in any child. In collaboration with Dr E Fombonne, my own laboratory applied the Kawashima (nested PCR) and Uhlmann primer pairs (real-time PCR) as well as our own F gene primer pair (real-time PCR) to PBMC samples isolated from 54 children with ASD and 34 control children (D'Souza 2006). After rigorous application of melt-curve analysis, gel electrophoresis and sequencing, we found no evidence of persisting measles virus in any of samples. Some of the primer pairs used in the Kawashima and Uhlmann studies yielded non-specific products of human origin under our standard operating procedures (D'Souza 2006). Neither of these ASD-focused studies included analyses of intestinal biopsy material because the investigators did not believe that the procedure to obtain such material could be ethically justified. The absence of data from intestinal biopsies from ASD children in Afzal's study and our own cannot be considered a serious flaw since both Kawashima (Kawashima 2000) and Bradstreet (Bradstreet 2004) have reported the presence of measles genomic material in the PBMC of many children with ASD. Furthermore, in association with Dr E Seidman, my own laboratory has recently completed a study of the Kawashima and Uhlmann primer pairs in intestinal biopsy samples from children with IBD (24 IBD and 18 controls with GI complaints). Once again, we encountered extensive cross-reactivity using the published primers but no evidence of persisting measles virus in any of these samples after rigorous evaluation of the amplicons produced (D'Souza 2007).

*D.3.5 Competence of the O’Leary Lab and Unigenetics to Produce Reliable PCR Data*

I do not have direct access to the independent scientific review of the O’Leary laboratory that was mandated by the UK Legal Services Commission. However, it is widely believed that serious methodological concerns identified during this review contributed to the withdrawal of Legal Services funding for the MMR-ASD litigation in the UK (personal communications B Rima, <http://briandeer.com/mmr/lancet-lsc.htm>, <http://briandeer.com/mmr/oleary-pcr.htm>). The data that we have recently published (D’Souza 2006, D’Souza 2007) call into question all of the results reported using the Uhlmann and Kawashima primer pairs. This would include the reports by Kawashima 2000, Uhlmann 2002, Martin 2002 and Bradstreet 2004 as well as Bradstreet’s communication to the IOM (Bradstreet 2004) and the molecular studies included in the current case (Pet Ex 28-pg 179).

**E. Logical Inconsistencies in the Arguments Made by the Petitioner’s Experts**

**E.1 Where is the outcry for anti-virals or research into new anti-viral therapies?**

Bradstreet, Byers, Kinsbourne, Krigsman, Wakefield and others have argued that a persisting measles virus infection of the CNS causes autism, yet none has advocated for a treatment regimen that could directly address a viral infection. If there were solid evidence for their premise, treatment consistent with that premise would be the accepted standard of care.

**E.2 How can MMR be unsafe yet monovalent measles vaccine is OK?**

If persistent vaccine-strain measles is the real problem in ASD, then how can Wakefield and colleagues claim that monovalent measles vaccine is ‘safe and effective’? It is precisely the same virus at the same dose administered to the same children. I have never seen a scientifically credible argument for this position.

**E.3 Is it plausible that measles virus biology is so different in ASD and SSPE/MIBE?**

The Petitioner’s experts make selective use of the SSPE and MIBE literature but never address several important questions raised by the MMR-ASD-GI hypothesis:

- They fail to explain the different clinical outcomes in SSPE and MIBE patients and the MMR-ASD-GI patients.
- They fail to explain the differences in pathology between SSPE and MIBE.
- They fail to address the significance of the extensive mutations found in the viruses isolated from SSPE and MIBE patients: a phenomenon that has implications both for the time it takes for these infections to become clinically apparent and the actual sequences of the isolated viruses.

**E.4 Epidemiology is powerful for detecting common associations**

The petitioners’ experts appear to want to ‘have it both ways’. On the one hand, they respond to the reports of the MRC, the IOM and the Cochrane Group by arguing (as Dr Kinsbourne does) that epidemiology is irrelevant to the individual case (ie: Michelle Cedillo’s) because they have found measles virus genomic material in her gut biopsy. On the other hand, the colleagues whose work they reference have readily found measles virus in ASD children. Singh claims to have found elevated anti-measles IgG in more than 80% of ASD children (Singh 2003) and O’Leary’s laboratory (and subsequently Unigenetics Inc.) apparently had little trouble finding measles virus genomic material in many hundreds of ASD samples including gut biopsies, CSF and blood (33% in the Kawashima study, 82% in the Uhlmann study) (Kawahima 2000, Uhlmann 2002). These two arguments cannot scientifically coexist. If persisting measles virus is present in so many ASD children and it is responsible for their condition, then this association should have been detected in the epidemiological studies that have been performed.

E.5 Why just measles?

Measles virus belongs to a large virus family call the *Paramyxoviridae*. These viruses share a genetic organization and many biological characteristics including aspects of effective immunity (Crowe 2003, Rima 2006). Exposure to several members of this virus family is essentially universal among infants, including mumps virus (wild-type or vaccine-strain), respiratory syncytial virus, the four parainfluenza viruses and the newly-described metapneumovirus (Kahn 2006). In subjects with clinically-significant immunocompromise, infections with these viruses are often more severe and persistent (Couch 1997, Mendoza-Sanchez 2006, Debiaggi 2006 among others). We have not seen a change in the frequency, severity or manifestations of these ubiquitous viruses in the last 3 decades as would be expected were the petitioners' experts' hypothesis about immunodeficiency following thimerosal administration to be true. Further, if the MMR-ASD-GI hypothesis were correct, we should expect to see changes in the frequency, severity or manifestations of these closely-related infections in ASD children. We do not.

**In Summary**


There is no scientific support for the proposition that the administration of routine pediatric vaccines containing thimerosal has any clinically-relevant impact on immune system function in human infants. There is no convincing evidence that Michelle Cedillo had any degree of immunomodulation or immunosuppression (for any reason) at the time that she received her MMR vaccine.

The examples of SSPE and MIBE do not support the proposition that a persisting measles virus infection causes autism. The known features of these conditions contrast considerably with ASD and thus cast doubt on the proposition advanced.

There is no scientifically reliable evidence that a persisting, vaccine-strain measles virus is a cause of or a contributor to either inflammatory bowel disease or ASD. The epidemiologic and basic science data that have been published or presented in support of these associations are flawed and fundamentally at odds with the reports of several authoritative scientific committees. In several instances, these data have been outright discredited and disavowed.

**In Conclusion**

Based on my review of the medical records, expert opinions, literature and my own professional experience, I believe, to a reasonable degree of medical certainty that neither the thimerosal in the routine pediatric vaccines nor the live-attenuated MMR vaccine that Michelle received caused or contributed to the development of her autism.



Brian J Ward MSc (OXON), MDCM  
April 24, 2007

## **Brian J Ward**

### **Brief statement of background and qualifications**

I received medical training at McGill University (MDCM 1980) with subsequent training in international health (University of London DTM&H: 1984), Internal Medicine (Johns Hopkins School of Medicine: 1985 – 87), Infectious Diseases (Johns Hopkins: 1988-91) and Microbiology (McGill: 1991-92). En route, I received research training in neuroendocrinology as a Rhodes Scholar at Oxford (MSc with H Charlton: 1977-79) and as a post-doctoral fellow with Dr Diane Griffin in neurovirology (Johns Hopkins 1988-91). My studies in Dr Griffin's laboratory focused on the immunology of measles virus. I continued this interest at McGill where I have been on staff since 1992. My laboratory has been continuously funded to do measles-related studies since that time (NIH, CIHR, WHO, International Development and Research Council of Canada (IDRC) and the Crohns Colitis Foundation of Canada (CCFC) among others). These studies have included basic virology, development of nasal vaccines, examination of immune responses to vaccination and analysis of adverse events (eg: high-titer measles vaccines, the MMR-ASD-IBD hypothesis). Other areas of interest include mother-to-child-transmission of HIV and novel therapeutic and diagnostic strategies for parasitoses. I share responsibility for the direction of a vaccine evaluation site at McGill that specializes in early (Phase I/II) studies. My bibliography is attached.

Currently, I am past Chief of the Division of Infectious Diseases at McGill (2002-06) and Associate Director of the McGill Center for Tropical Diseases (1995-present). I am also the director of the National Reference Laboratory for Parasitology (Public Health Agency of Canada: 1996-present). I have served on advisory committees related to vaccine use including the National Advisory Committee on Immunization (NACI: 1994-2002), the Quebec Immunization Committee (CIQ: 1993-2001) and the Committee to Advise on Tropical Medicine and Travel (CATMAT: 1996-2006: chair 1998-2006). In 1994, I was a founding member of the Advisory Committee on Causality Assessment (ACCA: a national committee to assess vaccine injury causality: chair 1999-2002). I have also served on similar committees to evaluate injuries following anthrax (AVEC: 2000-03) and smallpox vaccination (CEIC: 2003-present) in the US. For our work with AVEC, committee members received the US Secretary of Defense Exceptional Public Service Award (2003). I am a founding member of the Canadian Alliance for Vaccine Evaluation and Research (CAIRE) and serve on the steering and management committees for this grouping of more than 90 vaccine investigators.

I regularly give lectures covering many aspects of virology, viral pathogenesis and vaccines to undergraduates, graduates, physicians and scientists. I have served as faculty or director for the National Vaccinology Course (co-sponsored by CAIRE and the Canadian Pediatric Society: 2001-07) and have served as an invited lecturer in vaccinology for the European TropEd Masters Program (2005). I have served on a range of peer-review committees for CIHR and other funding institutions and I am an associate editor for Human Vaccines (2004-present) and Stedman's Medical Dictionary (2004-08).

## REFERENCES

1. Afzal MA, Armitage E, Ghosh S, Williams LC, Minor PD. *Further evidence of the absence of measles virus genome sequence in full thickness intestinal specimens from patients with Crohn's disease.* J Med Virol. 2000 Nov; 62(3): 377-82.
2. Afzal MA, Minor PD, Armitage E, Ghosh S. *Measles virus and Crohn's disease.* Gut. 1999 Jun; 44(6): 896-7.
3. Afzal MA, Minor PD, Ghosh S, Jin L. *Measles virus persistence in specimens of inflammatory bowel disease and autism cases.* Dig Dis Sci. 2001 Mar; 46(3): 658-60.
4. Afzal MA, Ozoemena LC, O'Hare A, Kidger KA, Bentley ML, Minor PD. *Absence of detectable measles virus genome sequence in blood of autistic children who have had their MMR vaccination during the routine childhood immunization schedule of UK.* J Med Virol. 2006 May; 78(5): 623-30.
5. Ashraf H. *US expert group rejects link between MMR and autism.* Lancet. 2001 Apr 28; 357(9265): 1341.
6. Ashwood P, Wills S, Van de Water J. *The immune response in autism: a new frontier for autism research.* J Leukoc Biol. 2006 Jul; 80(1): 1-15.
7. Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. *A clinicopathological study of autism.* Brain. 1998 May; 121( Pt 5): 889-905.
8. Becker Y. *The changes in the T helper 1 (Th1) and T helper 2 (Th2) cytokine balance during HIV-1 infection are indicative of an allergic response to viral proteins that may be reversed by Th2 cytokine inhibitors and immune response modifiers--a review and hypothesis.* Virus Genes. 2004 Jan; 28(1): 5-18.
9. Bitnun A, Shannon P, Durward A, Rota PA, Bellini WJ, Graham C, Wang E, Ford-Jones EL, Cox P, Becker L, Fearon M, Petric M, Tellier R. *Measles inclusion-body encephalitis caused by the vaccine strain of measles virus.* Clin Infect Dis. 1999 Oct; 29(4): 855-61.
10. Bradstreet J. *Biological Evidence of Significant Vaccine Related Side-effects Resulting in Neurodevelopmental Disorders.* Presentation to the Vaccine Safety Committee of the Institute of Medicine. February 9, 2004.
11. Bradstreet JJ., El Dahr J., Anthony A., et al. *Detection of measles virus genomic RNA in cerebrospinal fluid of children with regressive autism: a report of three cases.* J Amer Physicians and Surgeons. 2004; 9: 38-45.
12. Cattaneo R, Schmid A, Spielhofer P, Kaelin K, Baczko K, ter Meulen V, Pardowitz J, Flanagan S, Rima BK, Udem SA, et al. *Mutated and hypermutated genes of persistent measles viruses which caused lethal human brain diseases.* Virology. 1989 Dec; 173(2): 415-25.
13. Chabot S, Trottier C, Mann C, Corley S, Chatterjee A, Miller W, Ward BJ. *Retinoic acid receptor-mediated signaling mediates anti-measles effect of vitamin A.* (revised and resubmitted to FASEB J – Mar 2007)

14. Clarkson TW, Magos L, Myers GJ. *The toxicology of mercury--current exposures and clinical manifestations*. N Engl J Med. 2003 Oct 30; 349(18): 1731-7.
15. Couch RB, Englund JA, Whimbey E. *Respiratory viral infections in immunocompetent and immunocompromised persons*. Am J Med. 1997 Mar 17; 102(3A): 2-9; discussion 25-6.
16. Croonenberghs J, Bosmans E, Deboutte D, Kenis G, Maes M. *Activation of the inflammatory response system in autism*. Neuropsychobiology. 2002; 45(1): 1-6.
17. Crowe JE Jr, Williams JV. *Immunology of viral respiratory tract infection in infancy*. Paediatr Respir Rev. 2003 Jun; 4(2): 112-9.
18. Dales L, Hammer SJ, Smith NJ. *Time trends in autism and in MMR immunization coverage in California*. JAMA. 2001 Mar 7;285(9):1183-5
19. Dally A. *The rise and fall of pink disease*. Soc Hist Med. 1997 Aug; 10(2): 291-304.
20. Davis LE, Kornfeld M, Mooney HS, Fiedler KJ, Haaland KY, Orrison WW, Cernichiari MS, Clarkson TW. *Methylmercury poisoning: Longterm clinical, radiological, toxicological, and pathological studies of an affected family*. Annals of Neurology 1994; 35: 680-688.
21. Davis RL, Bohlke K. *Measles vaccination and inflammatory bowel disease: controversy laid to rest?* Drug Saf. 2001; 24(13): 939-46.
22. Debiaggi M, Canducci F, Sampaolo M, Marinozzi MC, Parea M, Terulla C, Colombo AA, Alessandrino EP, Bragotti LZ, Arghittu M, Goglio A, Migliavacca R, Romero E, Clementi M. *Persistent symptomless human metapneumovirus infection in hematopoietic stem cell transplant recipients*. J Infect Dis. 2006 Aug 15; 194(4): 474-8.
23. Deer B. *Fresh Doubts Cast On MMR Study Data*; <http://briandeer.com/mmr/oleary-pcr.htm>
24. Deer B. *Taxpayer cash for MMR action is stopped after £15m that stoked fear was spent*; <http://briandeer.com/mmr/lancet-lsc.htm>
25. Demicheli V, Jefferson T, Rivetti A, Price D. *Vaccines for measles, mumps and rubella in children*. Cochrane Database Syst Rev. 2005 Oct 19; (4): CD004407.
26. DeStefano F, Chen RT. *Negative association between MMR and autism*. Lancet. 1999 Jun 12; 353(9169): 1987-8.
27. Deykin EY, MacMahon B. *The incidence of seizures among children with autistic symptoms*. Am J Psychiatry. 1979 Oct; 136(10): 1310-2.
28. Dhadphale M, Lukwago MG, Gajjar M. *Infantile autism in Kenya*. Indian J Pediatr. 1982 Jan-Feb; 49(396): 145-8.
29. D'Souza Y, Dionne S, Seidman E, Bitton A, Ward BJ. *No Evidence of Persisting Measles Virus in the Intestinal Tissues of Patients with Inflammatory Bowel Disease*. Gut 2007 (in press)

30. D'Souza Y, Fombonne E, Ward BJ. *No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder.* Pediatrics. 2006 Oct; 118(4): 1664-75.
31. Duarte CS, Bordin IA, de Oliveira A, Bird H. *The CBCL and the identification of children with autism and related conditions in Brazil: pilot findings.* J Autism Dev Disord. 2003 Dec; 33(6): 703-7.
32. Duclos P, Ward BJ. *Measles vaccines: a review of adverse events.* Drug Saf. 1998 Dec; 19(6): 435-54.
33. Ekblom A, Wakefield AJ, Zack M, Adami HO. *Perinatal measles infection and subsequent Crohn's disease.* Lancet. 1994 Aug 20; 344(8921): 508-10.
34. Eylar E, Baez I, Navas J, Mercado C. *Sustained levels of ascorbic acid are toxic and immunosuppressive for human T cells.* P R Health Sci J. 1996 Mar; 15(1): 21-6.
35. Farrington CP, Miller E, Taylor B. *MMR and autism: further evidence against a causal association.* Vaccine. 2001 Jun 14; 19(27): 3632-5.
36. Feeney M, Ciegg A, Winwood P, Snook J. *A case-control study of measles vaccination and inflammatory bowel disease. The East Dorset Gastroenterology Group.* Lancet. 1997 Sep 13; 350(9080): 764-6.
37. Geier DA, Geier MR. *A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis.* Med Sci Monit. 2005 Apr; 11(4): CR160-70.
38. Gillberg C, Schaumann H, Gillberg IC. *Autism in immigrants: children born in Sweden to mothers born in Uganda.* J Intellect Disabil Res. 1995 Apr; 39 ( Pt 2): 141-4.
39. Goulder PJ, Jeena P, Tudor-Williams G, Burchett S. *Paediatric HIV infection: correlates of protective immunity and global perspectives in prevention and management.* Br Med Bull. 2001;58:89-108. Review.
40. Griffin DE, Hardwick JM. *Regulators of apoptosis on the road to persistent alphavirus infection.* Annu Rev Microbiol. 1997; 51: 565-92.
41. Haga Y, Funakoshi O, Kuroe K, Kanazawa K, Nakajima H, Saito H, Murata Y, Munakata A, Yoshida Y. *Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction.* Gut. 1996 Feb; 38(2): 211-5.
42. Halsey NA, Hyman SL; Conference Writing Panel. *Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12-13, 2000.* Pediatrics. 2001 May; 107(5): E84.
43. Hermon-Taylor J, Ford J, Sumar N, Millar D, Doran T, Tizard M. *Measles virus and Crohn's disease.* Lancet. 1995 Apr 8; 345(8954): 922-3.

44. Humphrey JH, Hargrove JW, Malaba LC, Iliff PJ, Moulton LH, Mutasa K, Zvandasara P, Nathoo KJ, Mzengeza F, Chidawanyika H, Zijenah LS, Ward BJ; ZVITAMBO Study Group. *HIV incidence among post-partum women in Zimbabwe: risk factors and the effect of vitamin A supplementation*. *AIDS*. 2006 Jun 26; 20(10): 1437-46.
45. Iizuka M, Chiba M, Yukawa M, Nakagomi T, Fukushima T, Watanabe S, Nakagomi O. *Immunohistochemical analysis of the distribution of measles related antigen in the intestinal mucosa in inflammatory bowel disease*. *Gut*. 2000 Feb; 46(2): 163-9.
46. Iizuka M, Nakagomi O, Chiba M, Ueda S, Masamune O. *Absence of measles virus in Crohn's disease*. *Lancet*. 1995 Jan 21; 345(8943): 199.
47. Iizuka M, Saito H, Yukawa M, Itou H, Shirasaka T, Chiba M, Fukushima T, Watanabe S. *No evidence of persistent mumps virus infection in inflammatory bowel disease*. *Gut*. 2001 May; 48(5): 637-41.
48. Institute of Medicine (IOM). *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism*. 2001; Washington, D.C.: National Academies Press.
49. Institute of Medicine (IOM). *Immunization Safety Review: Vaccines and Autism*. 2004; Washington, D.C.: National Academies Press.
50. Jones P, Fine P, Piracha S. *Crohn's disease and measles*. *Lancet*. 1997 Feb 15; 349(9050): 473.
51. Juneja M, Mukherjee SB, Sharma S. *A descriptive hospital based study of children with autism*. *Indian Pediatr*. 2005 May; 42(5): 453-8.
52. Jyonouchi H, Sun S, Itokazu N. *Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder*. *Neuropsychobiology*. 2002; 46(2): 76-84.
53. Kastner JL, Gellin BG. *Measles-mumps-rubella vaccine and autism: the rise (and fall?) of a hypothesis*. *Pediatr Ann*. 2001 Jul; 30(7): 408-15.
54. Kawashima H, Miyajima T, Mori T, Yuan L, Ogihara M, Kinoue K, Takekuma K, Hoshika A. *A case of intractable epilepsy positive for the detection of measles virus genome in the cerebrospinal fluid and peripheral mononuclear cells using reverse transcriptase-polymerase chain reaction*. *Brain Dev*. 1996 May-Jun; 18(3): 220-3.
55. Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A. *Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism*. *Dig Dis Sci*. 2000 Apr; 45(4): 723-9.
56. Kawashima H, Mori T, Takekuma K, Hoshika A, Hata M, Nakayama T. *Polymerase chain reaction detection of the hemagglutinin gene from an attenuated measles vaccine strain in the peripheral mononuclear cells of children with autoimmune hepatitis*. *Arch Virol*. 1996; 141(5): 877-84.
57. Kaye JA, del Mar Melero-Montes M, Jick H. *Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis*. *BMJ*. 2001 Feb 24; 322(7284): 460-3.

58. Khan N, Hombarume J. *Levels of autistic behaviour among the mentally handicapped children in Zimbabwe*. Cent Afr J Med. 1996 Feb; 42(2): 36-9.
59. Kjellstrom T, Kennedy P, Wallis S, Stewart A, Friberg L, and Lind B. (1989) *Physical and mental development of children with prenatal exposure to mercury from fish. Stage II: Interviews and psychological tests at age 6*. Report 3642. Solna, Sweden: National Swedish Environmental Protection Board.
60. Larsen MW, Moser C, Hoiby N, Song Z, Kharazmi A. *Ginseng modulates the immune response by induction of interleukin-12 production*. APMIS. 2004 Jun; 112(6): 369-73.
61. Lawrenson R, Farmer R. *Measles, measles vaccination, and Crohn's disease. Age specific prevalences do not suggest association with in utero exposure*. BMJ. 1998 Jun 6; 316(7146): 1746.
62. Lewin J, Dhillon AP, Sim R, Mazure G, Pounder RE, Wakefield AJ. *Persistent measles virus infection of the intestine: confirmation by immunogold electron microscopy*. Gut. 1995 Apr; 36(4): 564-9.
63. Liebert UG, Baczko K, Budka H, ter Meulen V. *Restricted expression of measles virus proteins in brains from cases of subacute sclerosing panencephalitis*. J Gen Virol. 1986 Nov; 67 ( Pt 11): 2435-44.
64. Lotter V. *Childhood autism in Africa*. J Child Psychol Psychiatry. 1978 Jul; 19(3): 231-44.
65. Ludanyi K, Nagy ZS, Alexa M, Reichert U, Michel S, Fesus L, Szondy Z. *Ligation of RARgamma inhibits proliferation of phytohaemagglutinin-stimulated T-cells via down-regulating JAK3 protein levels*. Immunol Lett. 2005 Apr 15; 98(1): 103-13.
66. Mankoski RE, Collins M, Ndosi NK, Mgalla EH, Sarwatt VV, Folstein SE. *Etiologies of autism in a case-series from Tanzania*. J Autism Dev Disord. 2006 Nov; 36(8): 1039-51.
67. Martin CM, Uhlmann V, Killalea A, Sheils O, O'Leary JJ. *Detection of measles virus in children with ileo-colonic lymphoid nodular hyperplasia, enterocolitis and developmental disorder*. Mol Psychiatry. 2002; 7 Suppl 2: S47-8.
68. Matida LH, da Silva MH, Tayra A, Succi RC, Gianna MC, Goncalves A, de Carvalho HB, Hearst N. *Prevention of mother-to-child transmission of HIV in Sao Paulo State, Brazil: an update*. AIDS. 2005 Oct; 19 Suppl 4: S37-41.
69. McRill C, Boyer LV, Flood TJ, Ortega L. *Mercury toxicity due to use of a cosmetic cream*. J Occup Environ Med. 2000 Jan; 42(1): 4-7.
70. Medical Research Council. *Review of Autism Research: Epidemiology and Causes*. 2001; [www.mrc.ac.uk/pdf-autism-report.pdf](http://www.mrc.ac.uk/pdf-autism-report.pdf)
71. Mendoza Sanchez MC, Ruiz-Contreras J, Vivanco JL, Fernandez-Carrion F, Baro Fernandez M, Ramos JT, Otero JR, Folgueira D. *Respiratory virus infections in children with cancer or HIV infection*. J Pediatr Hematol Oncol. 2006 Mar; 28(3): 154-9.

72. Miyamoto H, Tanaka T, Kitamoto N, Fukuda Y, Shimoyama T. *Detection of immunoreactive antigen, with a monoclonal antibody to measles virus, in tissue from a patient with Crohn's disease.* J Gastroenterol. 1995 Feb; 30(1): 28-33.
73. Morris DL, Montgomery SM, Thompson NP, Ebrahim S, Pounder RE, Wakefield AJ. *Measles vaccination and inflammatory bowel disease: a national British Cohort Study.* Am J Gastroenterol. 2000 Dec; 95(12): 3507-12.
74. Moss WJ, Clements CJ, Halsey NA. *Immunization of children at risk of infection with human immunodeficiency virus.* Bull World Health Organ. 2003; 81(1): 61-70.
75. Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, Sloane-Reeves J, Wilding GE, Kost J, Huang LS, Clarkson TW. *Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study.* Lancet. 2003 May 17; 361(9370): 1686-92.
76. Nielsen LL, Nielsen NM, Melbye M, Sodermann M, Jacobsen M, Aaby P. *Exposure to measles in utero and Crohn's disease: Danish register study.* BMJ. 1998 Jan 17; 316(7126): 196-7.
77. Oldstone MB. *A suspenseful game of 'hide and seek' between virus and host.* Nat Immunol. 2007 Apr; 8(4): 325-7.
78. Pardi DS, Tremaine WJ, Sandborn WJ, Loftus EV Jr, Poland GA, Harmsen WS, Zinsmeister AR, Melton LJ 3rd. *Early measles virus infection is associated with the development of inflammatory bowel disease.* Am J Gastroenterol. 2000 Jun; 95(6): 1480-5.
79. Pardi DS, Tremaine WJ, Sandborn WJ, Loftus EV Jr, Poland GA, Melton LJ 3rd. *Perinatal exposure to measles virus is not associated with the development of inflammatory bowel disease.* Inflamm Bowel Dis. 1999 May; 5(2): 104-6.
80. Pardo CA, Vargas DL, Zimmerman AW. *Immunity, neuroglia and neuroinflammation in autism.* Int Rev Psychiatry. 2005 Dec; 17(6): 485-95.
81. Pebody RG, Paunio M, Ruutu P. *Measles, measles vaccination, and Crohn's disease. Crohn's disease has not increased in Finland.* BMJ. 1998 Jun 6; 316(7146): 1745-6.
82. Peltola H, Patja A, Leinikki P, Valle M, Davidkin I, Paunio M. *No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study.* Lancet. 1998 May 2; 351(9112): 1327-8.
83. Pit DS, Polderman AM, Schulz-Key H, Soboslay PT. *Prenatal immune priming with helminth infections: parasite-specific cellular reactivity and Th1 and Th2 cytokine responses in neonates.* Allergy. 2000 Aug; 55(8): 732-9.
84. Richler J, Luyster R, Risi S, Hsu WL, Dawson G, Bernier R, Dunn M, Hepburn S, Hyman SL, McMahon WM, Goudie-Nice J, Minshew N, Rogers S, Sigman M, Spence MA, Goldberg WA, Tager-Flusberg H, Volkmar FR, Lord C. *Is there a 'regressive phenotype' of Autism Spectrum Disorder associated with the measles-mumps-rubella vaccine? A CPEA Study.* J Autism Dev Disord. 2006 Apr; 36(3): 299-316.

85. Rima BK, Duprex WP. *Morbilliviruses and human disease*. J Pathol. 2006 Jan; 208(2): 199-214.
86. Seth R, Kalra V. *Autism in India*. Indian Pediatr. 2006 May; 43(5): 456.
87. Singh VK, Jensen RL. *Elevated levels of measles antibodies in children with autism*. Pediatr Neurol. 2003 Apr;28(4):292-4.
88. Smeeth L, Hall AJ, Rodrigues LC, Huang X, Smith PG, Fombonne E. *Measles, mumps, and rubella (MMR) vaccine and autism. Ecological studies cannot answer main question*. BMJ. 2001 Jul 21; 323(7305): 163.
89. Smith MS, Wakefield AJ. *Viral association with Crohn's disease*. Ann Med. 1993 Dec; 25(6): 557-61.
90. Taylor B, Miller E, Farrington CP, Petropoulos MC, Favot-Mayaud I, Li J, Waight PA. *Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association*. Lancet. 1999 Jun 12; 353(9169): 2026-9.
91. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. *Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study*. BMJ. 2002 Feb 16; 324(7334): 393-6.
92. ter Meulen V, Hall WW. *Slow virus infections of the nervous system: virological, immunological and pathogenetic considerations*. J Gen Virol. 1978 Oct; 41(1): 1-25.
93. Thompson NP, Pounder RE, Wakefield AJ. *Perinatal and childhood risk factors for inflammatory bowel disease: a case-control study*. Eur J Gastroenterol Hepatol. 1995 May; 7(5): 385-90.
94. Tsubaki T and Irukayama K (Eds.) (1977) *Minamata Disease: Methylmercury Poisoning in Minamata and Niigata, Japan*. Elsevier, New York.
95. Uhlmann V, Martin CM, Sheils O, Pilkington L, Silva I, Killalea A, Murch SB, Walker-Smith J, Thomson M, Wakefield AJ, O'Leary JJ. *Potential viral pathogenic mechanism for new variant inflammatory bowel disease*. Mol Pathol. 2002 Apr; 55(2): 84-90.
96. Wakefield AJ, Ekbom A, Dhillon AP, Pittilo RM, Pounder RE. *Crohn's disease: pathogenesis and persistent measles virus infection*. Gastroenterology. 1995 Mar; 108(3): 911-6.
97. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. *Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children*. Lancet. 1998 Feb 28; 351(9103): 637-41.
98. Wakefield AJ, Pittilo RM, Sim R, Cosby SL, Stephenson JR, Dhillon AP, Pounder RE. *Evidence of persistent measles virus infection in Crohn's disease*. J Med Virol. 1993 Apr; 39(4): 345-53
99. Ward B, DeWals P. *Association between measles infection and the occurrence of chronic inflammatory bowel disease*. Can Commun Dis Rep. 1997 Jan 1; 23(1): 1-5; discussion 5-6

100. Wilasrusmee C, Kittur S, Siddiqui J, Bruch D, Wilasrusmee S, Kittur DS. *In vitro immunomodulatory effects of ten commonly used herbs on murine lymphocytes*. J Altern Complement Med. 2002 Aug; 8(4): 467-75.
101. World Bank. *Tanzania HIV Status*.  
<http://web.worldbank.org/WBSITE/EXTERNAL/COUNTRIES/AFRICAEXT/EXTAFRHEANUTPOP/EXTAFRREGTOPHIVAIDS/0,,contentMDK:20450516~pagePK:34004173~piPK:34003707~theSitePK:717148,00.html> (site accessed Apr 17, 2007)
102. Zhou HL, Deng YM, Xie QM. *The modulatory effects of the volatile oil of ginger on the cellular immune response in vitro and in vivo in mice*. J Ethnopharmacol. 2006 Apr 21; 105(1-2): 301-5.
103. Chadwick N, Bruce IJ, Schepelmann S, Pounder RE, Wakefield AJ. *Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcription followed by the polymerase chain reaction*. J Med Virol. 1998 Aug; 55(4): 305-11.
104. Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D. *Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations*. Pediatrics. 2006 Jul; 118(1): e139-50.
105. Honda H, Shimizu Y, Rutter M. *No effect of MMR withdrawal on the incidence of autism: a total population study*. J Child Psychol Psychiatry. 2005 Jun; 46(6): 572-9.
106. Kahn JS. *Epidemiology of human metapneumovirus*. Clin Microbiol Rev. 2006 Jul; 19(3): 546-57.
107. Uchiyama T, Kurosawa M, Inaba Y. *MMR-vaccine and regression in autism spectrum disorders: negative results presented from Japan*. J Autism Dev Disord. 2007 Feb; 37(2): 210-7.