Title: **IMMUNIZATION AND CHILDREN AT RISK FOR AUTISM**

Introduction

Part One
The MMR Debate

Co-authors:

Roberts, Wendy, MD, FRCP(C)
Developmental Paediatrician
Associate Professor of Paediatrics
University of Toronto

Mary Harford, R.N.
Clinical Leader
Child Development Centre
Hospital for Sick Children

Address for Correspondence:

Wendy Roberts, MD, FRCP(C)
Developmental Paediatrician
Director, Child Development Centre
The Hospital for Sick Children
555 University Avenue
Toronto, Ontario
M5G 1X8
Telephone: 416-813-6333
Fax #: 416-813-7437
e-mail address: wendy.roberts@sickkids.ca

Acknowledgement: **Very special thanks go to Lee Steel, Parent Liaison in the Child Development Centre, for her invaluable advice from the parent perspective.**

IMMUNIZATION AND CHILDREN AT RISK FOR AUTISM

Recently, possible connections between immunization and developmental disorders, most notably autistic disorders, have been the subject of a great deal of debate and have caused much concern for parents who want to make the safest choices for their children.

Anxiety has risen steadily since the mid-1990's when a medical investigative team led by A. Wakefield postulated that Measles-Mumps-Rubella (MMR) vaccine might be a causative factor in the development of autism spectrum disorder. Since this initial publication, immunization remains controversial for some parents and uptake of MMR vaccine has fallen in some countries, despite much discussion regarding the safety of MMR, a lack of evidence for an association between MMR and autism, and the risks of insufficient protection against wild measles virus infection. Canadian uptake of MMR in 1998 was 95% but data does not exist to document any change in Canada since that time. Many clinicians are concerned that the uptake in younger siblings of children with autism is considerably lower.

Further anxiety for parents has been caused by the suggested association between developmental disorders and mercury toxicity due to thimerosal used as a preservative in some vaccines. Many Canadian parents, while continuing to seek chelation therapy in response to this suggestion, are not aware that, in Canada, thimerosal has never been added to MMR, and has not been present in DPTP or pentavalent vaccines since 1992. It is found only in Hepatitis B vaccine in some provinces.

This article is intended to be a guide for physicians as they counsel parents. It is accompanied by a handout for parents containing related references and websites where more information is available.

Part One

The MMR Debate

Focus on Autism

Autism is a more common neurological disorder than previously recognized and much is now appearing in the popular press about the devastating and lifelong nature of the condition. The unknown aetiology and lack of biological markers for autism not only limit discussion regarding the apparent increase in numbers of children receiving the diagnosis but also raise fear in prospective parents. Most experts agree that the increased prevalence, as high as 6 per 1000 for the spectrum disorder, reflects improved diagnostic methods as well as inclusion of higher functioning children who might not have received a diagnosis of autism in the past (1). Evidence is still being collected regarding whether there may be a true increase and, if so, whether any environmental factors such as heavy metals or pesticides may be involved in addition to the recognized genetic factors (2,3).

12 to 24 Months: The Crucial Stage

Typically, parents first note behavioural symptoms suggestive of autism at around 15 months of age, the time when MMR vaccine is first administered (4). Furthermore, at least one-third of children with autism have regression in language and social skills in the second year of life (5). Since neurological investigation reveals no organic aetiology**,** the temporal association with immunization suggests to some parents that vaccination must be causally linked. Although home video reviews and current studies of infants who have an older sibling with autism now suggest

that differences exist in the first year of life, most parents do not detect differences in their older child until the second year (6,7).

The recurrence risk for autism in subsequent siblings is at least 5 to 8% (1). When parents of one autistic child also worry about the vaccination connection, subsequent siblings are not only at risk for autism but also of not receiving timely vaccination.

The Debate is Launched!

Wakefield's first publication in 1998 (8) reported a consecutive series of 12 patients presenting with a loss of acquired language associated with diarrhea and abdominal pain. Thorough, multi-system investigation demonstrated no definitive abnormalities other than nonspecific colitis and ileal-lymphoid-nodular hyperplasia that was found in 9 of the children. Parents reported gastrointestinal (GI) symptoms for these children starting soon after their MMR vaccination. Wakefield suggested that these findings were likely initiated by an environmental trigger, although initially did not make the direct link with the vaccine. Instead, he merely commented on his theory of a link between GI inflammation and measles virus and the temporal association of MMR with autism.

In Wakefield's subsequent communication to the American Academy of Pediatrics (AAP) committee, (9) he proposed that associated changes in intestinal permeability and altered peptidase activity allow neurotoxic intestinal products (e.g., exorphins) to reach the brain, which is particularly susceptible to permanent damage during times of rapid cerebral development in infancy. He added, " In susceptible children (possibly for reasons of age, immune status, or genetic background) MMR vaccine is an atypical pattern of measles exposure that represents a significantly increased risk for intestinal infection and associated developmental regression

compared with the monovalent vaccine, or natural infection. Accordingly, the widespread use of MMR immunization is a major determinant of the apparent increase in rates of autism." The sentiment of this statement continues to be delivered by Dr. Wakefield to parents in autism meetings around the world. A survey at the Autism Society of America in 2000 indicated that more than 50% of parents present felt that vaccines were *the main causal factor* in their child's autism (9).

Wakefield's arguments focus on 3 areas that raise vaccination anxiety:

1) Abnormal GI tract

2) Impaired immune status

3) Monovalent vaccine use

1) Measles and "Leaky Gut"

Wakefield et al claim that autism is the result of GI abnormality, yet autistic symptoms predated reported GI disturbance. Since no control group existed, the reported ileonodular hyperplasia is considered a variant of normal. Leaky gut hypotheses (10,11,12,13) have suggested that differences in gut permeability lead to opioid excess and thus neuropsychiatric abnormalities, as well as causing malabsorption and metabolic abnormalities such as methylmalonic aciduria. Although D'Eufemia has also discussed leaky guts in autism (14), there is as yet no further data to support the impact of leaky gut on behavioural abnormalities. Neither is there evidence for Wakefield's previous claims about measles link to Inflammatory Bowel Disease (IBD) (15) that caused years of concern for that population until failure of replication refuted his claims (16). There are conflicting reports of measles virus nucleocapsid RNA being present in intestinal tissue in individuals with autism and IBD. Measles nucleocapsid RNA has also been found in

individuals with neither autism nor IBD (17). It may be that a human tissue antigen cross-reacting with measles antigen results from inflammation with a variety of causes, not just an atypical response to measles (9). The presence of virus in affected tissue does not imply a causal association with a disorder, and Wakefield has not produced convincing evidence that MMR vs monovalent vaccine strains of measles induced intestinal pathology (18).

There is, on the other hand, some evidence that gastrointestinal problems exist in autism. Horvath (19) has described chronic inflammation in the esophagus, stomach and duodenum of children with chronic diarrhea, reflux and autism. Kagan-Kushnir (20) found an increased incidence of reflux and diarrhea in children with autism compared to non-affected siblings. Taylor et al (21) in his recent report in the British Medical Journal (BMJ) reported significant gastrointestinal problems in children with autism, apparently more likely in the regressive type. These gastrointestinal problems were not more frequent in the group who received MMR compared to the group who did not receive MMR before its introduction in 1988. The connection between these gastrointestinal abnormalities and behavioural symptoms needs more exploration but does not appear to be related to immunization.

2) Is immune function in autism conferring vulnerability to vaccine?

A number of studies have suggested underlying immunologic abnormalities in autism ranging from decreased cellular immune function, increased immunoglobulin E and increased autoantibody production (9). Singh and Fudenberg (22) as well as Gupta (23) suggested that immune abnormalities in autism could cause vulnerability to MMR vaccine and precipitate autistic regression. They described a genetic association with autism linked to a null allele of the complementC4b gene in the Class III region of the Major Histocompatibility Complex. Evidence

supporting differing vulnerability to any type of infection or specifically measles infection due to different immune status in families with a history of autism (24) has not been found.

3) Monovalent vs.Trivalent Vaccines

Wakefield suggested that monovalent vaccines may pose less challenge to the vulnerable immune system (9) although no data exist to support this hypothesis. Since the majority of vaccine safety data relates to MMR, it is difficult to find evidence relating to the questions: Is it physiologically more natural to spread out exposure to antigens? If there is a qualitative difference in immune status, is there increased risk from more than one antigen exposure at a time?

In fact, children are often exposed in nature to more than one wild virus in a short period of time in winter and spring. An early study comparing reactions to monovalent measles vaccine vs. MMR reported fewer side effects from MMR than from univalent measles (25). Since MMR was introduced so soon after the measles vaccines became available, little safety data exists for the monovalent vaccines. In addition, some may not be as effective (26). Although not available in Canada, some parents are getting the monovalent measles vaccine from the United States. Precise Canadian numbers do not exist, but the Medicines Control Agency in Britain reports importing 8,000 monovalent measles vaccine doses in 2001 compared to 900 in 2000.

The biggest risk in the use of monovalent measles vaccine is the delay in protection for rubella and mumps, since 6 needles will be required over an unspecified period of time. Some parents do proceed with MMR after children have passed 2 or 3 years of age when their fear of autistic regression has diminished.

Evidence to Refute Wakefield's Claims about Autism and MMR

The strong evidence for the lack of association of MMR and autism is contained in the very comprehensive AAP Report (9) and in the Canadian Paediatric Society (CPS) Statement, August 2001 (27). Taylor and Kaye (21,28,29) in England have some of the most convincing evidence:

- The increased rate of reporting of autism to the General Practice Research database was not effected by MMR.
- A nearly 4-fold increase in the incidence of autism occurred in 2-5 year old boys born between 1988-93, while the uptake of MMR stayed constant at 95%.
- Incidence and age of diagnosis of autism was the same in vaccinated and unvaccinated children.

The rate of regressive autism in the U.K. was similar pre- and post-MMR introduction in 1988. Fombonne published a similar review of pre- and post-MMR data in which he found no change in regression rate or age of onset of parental concerns (30). Similarly, in California, Dales (31) reported that the increase in reports of children receiving services for ASD occurred in the late 1980's and 1990's long after the MMR vaccine was introduced in the United States. In Sweden, ecological data of Gillberg and Hejbell (32) showed rates of autism that did not change with MMR introduction in the 80's.

Side Effect Data

Peltola in Finland (33,34) documented 31 children with transient gastrointestinal symptoms in the first 4 weeks after MMR, five of whom also had febrile seizures. Most symptoms resolved in one week, and all in 6 weeks. Peltola reported no cases of autism in a 14-year prospective follow-up of 3 million vaccinations through hospital, health centre and public health nurse

records. While Peltola has strong short-term safety data, it is unclear why no cases of autism were reported in 14 years. Conservative estimates based on population incidence would suggest several hundred children would have autism in over one million children being followed. Nonetheless, this study contains the best evidence of overall safety of MMR.

Physician's Role

As covered in the handout for parents included with this article, there are key discussion points that may help concerned parents:

- Autism is thought primarily to originate from prenatal injury.
- Evidence is increasing that infants have signs of autism, well before the usual age of diagnosis.
- Data does not exist to support the use of monovalent vaccine.
- There is a 1/1000 risk of a wild measles virus infection causing encephalitis and/or death compared to 1/100,000 risk of severe adverse reaction to immunization (35).
- There are dozens of reported cases of wild measles infections every year in Canada (36,37) and the numbers in England are rising as immunization uptake decreases.
- Data collected in Colorado between 1987 and 1998 clearly shows that unimmunized children between 3 and 5 years of age are 66 times more likely to acquire measles infection than are their immunized peers (38). This number will increase if more parents fail to immunize their children.
- There is no evidence that the younger sibling of an affected child (even one with regressive autism) is more likely to regress if the first sibling regressed.
- The percentage of regressive autism has not changed pre- and post-MMR use (30).

- There is no evidence that children with autism have more severe reactions to wild measles infections.
- If immune status is different in autism, wild virus infection will pose a much greater threat to a young child than will a vaccination.

The traditional medical world is perceived as unwilling to listen to questions from parents, therefore when physicians such as Wakefield raise controversial hypotheses to the general public they can become very popular and bring dangerous credence to unproven hypotheses. Once claims are made about vaccinations, as with therapies such as secretin three years ago (39), the inevitable delay in collecting evidence to refute the claims creates periods of time during which worried parents feel they do not have the information needed to make informed decisions. Caution from physicians in the interim (e.g. “You must immunize!”), may be seen as typical of the conservative and defensive medical system and may antagonize rather than convince some members of the general public. Listening to parents and presenting the evidence for safety as well as the risks of delay in vaccinating are still the most effective strategies.

Title: **IMMUNIZATION AND CHILDREN AT RISK FOR AUTISM**

Part Two
If MMR is not causing autism, is it Mercury?

Co-authors:

Roberts, Wendy, MD, FRCP(C)
Developmental Paediatrician
Associate Professor of Paediatrics
University of Toronto

Mary Harford, R.N.
Clinical Leader
Child Development Centre
Hospital for Sick Children

Address for Correspondence:

Wendy Roberts, MD, FRCP(C)
Developmental Paediatrician
Director, Child Development Centre
The Hospital for Sick Children
555 University Avenue
Toronto, Ontario
M5G 1X8
Telephone: 416-813-6333
Fax #: 416-813-7437
e-mail address: wendy.roberts@sickkids.ca

Acknowledgement: **Very special thanks go to Lee Steel, Parent Liaison in the Child Development Centre, for her invaluable advice from the parent perspective.**

Part Two

If MMR is not causing autism, is it Mercury?

Mercury derived from thimerosal (used as a preservative) has also received a great deal of attention on the Internet and through litigation proceedings against companies producing vaccines in the U.S. This has served to heighten parents' concerns regarding vaccine safety, particularly for children seen as particularly vulnerable.

Media coverage of published reports such as Bernard's article "Autism, A Novel Form of Mercury Poisoning" (40) has had a big impact on the general public. Bernard claims that the cumulative effects of mercury from a series of immunizations in the first 2 years of life may represent an unrecognized mercurial syndrome leading to autism in susceptible children. This has led to a trend to use chelators, most often oral DMSA, in American and Canadian children with autism. Many parents feel guilty if they do not take a chance with chelation treatment despite possible side effects or risks, and physicians who will prescribe chelators become very popular and very much in demand with parent groups.

Since the Internet contains primarily American information, many Canadian parents and some physicians do not know that Canadian DPTP, Pentacel and MMR vaccines *do not contain thimerosal*. Unlike the situation in the U.S., common childhood vaccines, including DPTP and MMR, have been free of thimerosal/mercury in Canada since 1992. The only exception is the infant Hepatitis B vaccine used in some provinces and containing an amount of mercury that is well below the most conservative safety estimates (12.5 microgram Hg) (41). Despite the differences in Canadian and U.S. vaccines, many Canadian parents have sought chelator therapy because of their anxiety about mercury in vaccines.

If, as suggested, mercury in vaccines contributes to autism, one would then expect Canadian incidence figures for autism to be lower than international figures. In fact, Nova Scotia data from the 1980's and anecdotal data from physicians' practices in Canada are quite comparable to that reported in other countries (1,42).

What is known about mercury and developmental disorders?

Thimerosal is metabolized to ethylmercury that is felt to have similar effects to methylmercury. Apart from recognized delayed sensitivity reactions, high dose exposure is known to include neurotoxicity and nephrotoxicity. Chronic low dose exposure may cause subtle neurologic abnormalities. Weir (43) and Chance (3) have reviewed the data on pollution from environmental mercury and the measures taken to minimize exposure of Canadians. Ball (44) has reviewed the few human studies evaluating thimerosal. None of these investigations have found evidence of toxicity after low dose exposure. Health Canada has recently published a thorough review of all of the data and has concluded that thimerosal-free vaccines are now available for all children in Canada for routine immunizations (41). A certain number of special vaccines containing thimerosal are still used (such as Hepatitis B) in some Canadian jurisdictions. Influenza vaccine still contains a very low concentration of thimerosal but is not used in infants. These should still be offered in all instances where no thimerosal-free alternative is available because the balance of benefit is clearly in favour of preventing infection.

Conflicting information exists regarding low dose exposure to methylmercury. Animal studies have shown abnormal regulation of mercury, copper, zinc and other heavy metals having an effect on neuronal development (45). Studies with children have been done with populations whose diet consists primarily of fish, a potential source of heavy metal toxins. Davidson (46) in

the Seychelles study reported no correlation between mercury levels and developmental problems, whereas Grandjean (47) in the Faroe Islands suggested detectable neuropsychologic abnormality in 7-year-olds whose mothers consumed pilot whale meat, by measuring mercury levels in maternal hair samples and cord blood. Dysfunction in language, attention and memory was suggested but no symptom specifically resembled autism. Further analysis is ongoing since all the effects were small, but maternal ingestion of mercury appears to be the most significant factor for young children.

As a result of Ball's review and an independent review by the Institute of Medicine (IOM) (48), the following conclusions regarding mercury and vaccines have been reached:

- Low dose thimerosal exposure in humans has *not* been demonstrated to be associated with effects on the nervous system.
- Thimerosal exposure from vaccines has *not* been proven to result in mercury levels associated with toxic response.
- Signs and symptoms of mercury poisoning are *not* identical to autism, ADHD, or speech / language delay.
- There is no evidence that ethylmercury causes any of the pathophysiological changes known to be associated with autism (e.g., genetic defects).

Unique Concerns for Parents with Children at Risk for Autism:

Metallothionein and Chelator Use Because of Mercury in Vaccines

Walsh from the Pfeiffer institute presented a study to the American Psychiatric Association (APA) in May 2001 (49) suggesting that an inborn error in metallothionein proteins in autism may interfere with clearing toxic metals as well as interfere with immune function. In fact,

parents need to know that Walsh has not measured metallothionein in autism but merely makes inferences from treatment responses recorded in his Centre, which has a proprietary interest in zinc products marketed for people with autism. Dr. Amy Holmes has considerable credibility as a concerned pediatrician. She presented data at the International Meeting for Autism Research (IMFAR) in November 2001 (50) suggesting that children with autism have a positive response to chelation, usually with DMSA, in combination with dietary lipoic acid supplements (supposedly allowing the chelation effect of DMSA to cross the blood brain barrier). In open label use of chelation, Holmes reported that younger children show most benefit when treated for 2 to 3 months. Side effects included transient increases in hyperactivity, self-stimulatory behavior, and loose stools. Excretion of heavy metals was suggested as proof of a heavy metal problem in children with autism. Although no one has, as yet, replicated these findings, parents continue to feel that mercury and other heavy metals may pose a threat and seek chelation therapy.

The AAP News in August 2001 presented a good review of the facts that parents need about chelators (51):

- Mercury stays in the body for a brief time: 12 weeks. This is unlike lead, arsenic and other metals.
- DMSA does not cross the blood-brain barrier.
- Chelation is an invasive treatment that may effect liver, bone marrow and renal function and may cause allergy and loss of essential nutrients (such as zinc and others) that may not be replaced by taking food supplements.
- Apart from directly causing adverse behavioral effects, chelation (depending on the chelator, the dose and the metal being chelated) can result in changes in the toxicokinetics that can

lead to increased concentrations of the toxin in the central nervous system causing greater neurodevelopmental injury.

- Chelation has minimal effect on methylmercury and has not been shown to reverse neurologic injury from any type of metal poisoning.

Current Research

Although it is too late for parents making current decisions about siblings' vaccinations, the NIH is now responding to parents' concerns. Their internet website (www.nichd.nih.gov) contains excellent information for parents and outlines initiatives underway:

- Research is being done to compare classic autism (since birth) versus autism after regression. Vaccination records are being studied to see if autism onset was related to MMR or other vaccines; signs of persistent infection related to MMR will be sought.
- Environmental effects (pollutants and vaccines) on child health will be studied by following 100,000 children.

Conclusions

Definite evidence exists for the safety of vaccinations currently being given to Canadian children. All possible efforts must be made to protect children from devastating infectious diseases.

Listening to parents, understanding their concerns, and helping them to evaluate the evidence regarding the rapid media presentation of "quick fixes" is a time-consuming and sometimes difficult process for the physician. Too rapid denunciation of parental concerns leads to loss of trust in the public health system. Everyone may suffer as a result.

Scientists need to be encouraged to undertake controversial research without fear of vilification by colleagues; at the same time, caution is needed to avoid raising the profile of questionable hypotheses while studies are being conducted.

It is essential to have ongoing studies into vaccination risks for special subgroups of children (such as siblings of children with autism) whose potentially unique responses may be lost in large group data. While reassuring data exists, vulnerability to measles or heavy metals for children genetically susceptible to autism has not yet been unequivocally ruled out. Evidence that early signs of autism present in infancy before obvious regression noted by parents may change the perception of onset being related to vaccines, and reinforce the genetic bases of the disorder.

Failing to immunize constitutes a well-known and extremely high risk for all children. This is particularly the case for families with a history of autism if there is any increased vulnerability to infection or toxins. As parents wait for results of studies currently underway, physicians need to keep reinforcing the evidence and the known risks from overwhelming infectious diseases. They must encourage parents to protect all their children through vaccination.

Title: **IMMUNIZATION AND CHILDREN AT RISK FOR AUTISM**

Part Three
Vaccination and Autism Spectrum Disorder (ASD):
A Guide for Parents

Co-authors:

Roberts, Wendy, MD, FRCP(C)
Developmental Paediatrician
Associate Professor of Paediatrics
University of Toronto

Mary Harford, R.N.
Clinical Leader
Child Development Centre
Hospital for Sick Children

Address for Correspondence:

Wendy Roberts, MD, FRCP(C)
Developmental Paediatrician
Director, Child Development Centre
The Hospital for Sick Children
555 University Avenue
Toronto, Ontario
M5G 1X8
Telephone: 416-813-6333
Fax #: 416-813-7437
e-mail address: wendy.roberts@sickkids.ca

Acknowledgement: **Very special thanks go to Lee Steel, Parent Liaison in the Child Development Centre, for her invaluable advice from the parent perspective.**

VACCINATION AND AUTISM SPECTRUM DISORDER (ASD):

A GUIDE FOR PARENTS

Possible connections between autistic disorders and immunizations have recently been the subject of a great deal of debate, and have understandably caused much concern for parents who want to make the safest choices for their children. This guide is intended to help parents understand the controversy and make informed choices.

Medical science has not yet solved the mystery of autism. There is still no blood test or procedure that can identify children on the autism spectrum. We believe the cause is genetic and that autism starts soon after conception, in the first three months of fetal life. Studying videos of children in their first year of life who later received a diagnosis of autism has helped us to see some early signs of the disorder that had not been noticed before. For example, babies who may eventually be diagnosed with autism tend to be less interactive, more interested in objects than in people, and are either more passive or more irritable than other babies of the same age. Ongoing research continues to increase our understanding of the complexities of ASD.

Is the number of children with autism increasing?

No good evidence exists to show us that more children have autism now than in years past.

Experts agree that what seems to be a higher number of children with autism are actually more children being identified and receiving a diagnosis of autism spectrum disorder. Why?

- More professionals are being trained to recognize early symptoms of ASD.
- In the past, autism was narrowly defined, with only the most severely affected children receiving the diagnosis.
- We now know that autism exists on a broad spectrum that includes children who are mildly affected, children with severe symptoms, and many levels of autism symptoms affecting

children in between. This is why the name "Autism Spectrum Disorder" has become widely accepted as a more descriptive term.

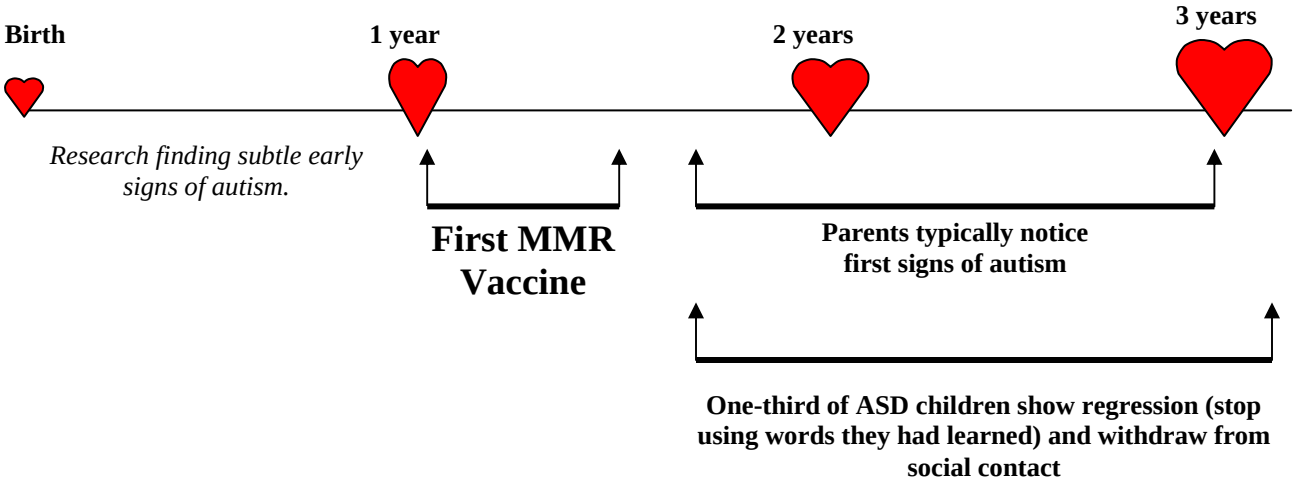
- Children with autism who may previously have been misdiagnosed with another disorder are now being correctly identified.
- *In short, a larger number of knowledgeable professionals are identifying autism spectrum disorder in more children and at an earlier age.*

Of course, other factors that may influence the number of children diagnosed with autism have not been entirely ruled out. For example, research continues into the possibility that environmental toxins (e.g., pesticides, heavy metals) may cause genetic changes that affect the development of the immature fetal brain, leading to a variety of neurological problems. We do not have all the answers yet.

Part 1: MEASLES-MUMPS-RUBELLA (MMR) VACCINATIONS

Why was MMR vaccine ever linked to autism?

Some people have assumed that there are links among autism, changes in child behaviour, and MMR vaccination because the first MMR shot is given very close to the time that we commonly begin to identify autistic symptoms.



The scientific debate began in 1998 with the release of results from a British research study that raised the question of a link between autism and MMR vaccine because of a gastrointestinal problem described as “leaky gut”.

Suggestions of a Connection

Dr. Andrew Wakefield, England, 1998:

- studied 12 children (8 with autism; 4 with other developmental delays)
- 9 of the 12 showed mild intestinal inflammation, reported by parents to have started soon after their MMR vaccination
- Wakefield suggested an environmental/ external cause, but did not immediately make a direct link to the MMR vaccine
- Wakefield later reported to the American Academy of Pediatrics, suggesting that:
  - ➔ measles virus in MMR vaccine is different from other forms of the virus
  - ➔ the MMR measles virus causes damage to the intestine or “leaky gut”
  - ➔ damaged intestine leaks toxic intestinal products from gastrointestinal system which can then reach the developing brain, resulting in neurological damage and autism

What We Know

England, 1998:

- 90% of British children received MMR
- vast majority do not have autism
- *some autistic children have been shown to have intestinal inflammation with unknown cause, but this problem has occurred whether the children received MMR vaccine or not*
- *no other scientific study has found any evidence of measles causing intestinal damage or “leaky gut”*
- Wakefield earlier claimed that measles was linked to Inflammatory Bowel Disease (IBD) but further studies by others have found no link between the virus and IBD

What do we know for sure?

- There is *no reliable evidence* that measles causes a "leaky gut" which can release toxins that reach the brain to cause neurological disorders.
- The increase in reported cases of autism spectrum disorder has *not* been proven to be associated with MMR vaccination.
- The rate of autistic regression since MMR vaccine was introduced is similar to the rate of regression before the vaccine was available.
- Rates of reported autism have risen while the number of children receiving MMR has not changed from an average of 95%.
- The percentage of children with autism is the same in vaccinated and unvaccinated populations.
- Some studies have suggested that autistic children have abnormalities in their immune systems, however, there is no evidence that ASD children get sick more often, or that they do not fight infection as well as other children.

I already have one autistic child. My second child seems normal at 12 months – how likely is it that he will show signs of autism in the next year?

- The overall risk of having a second child with ASD is between 5 and 8%.
- There is no current evidence that siblings are more likely to have autistic regression because their older brother or sister lost language and social skills around age two.

Should I wait before vaccinating my second child? My Paediatrician says its okay to wait until he is over 2 years old.

Since there is no evidence that the introduction of MMR vaccine increased the number of children with autism, it is unlikely that delaying MMR will make any difference to the risk of your second child developing ASD.

What evidence is there that MMR vaccine is safe?

There is strong short-term safety data relating to the study of 3 million vaccinations in Finland:

- Only thirty-one children had transient gastrointestinal symptoms during the first four weeks after MMR; five of them also had fever-related seizures.
- Most symptoms resolved in one week, and all resolved in six weeks.
- No cases of subsequent autism were reported in the study's 14-year follow-up.

Monovalent versus Trivalent vaccines

MMR is described as a "trivalent" vaccine, since three viruses are targeted (measles, mumps and rubella). "Monovalent" vaccine targets only one virus, such as measles.

- Wakefield suggested that monovalent vaccines might offer less risk of negative effects, although no evidence exists to support this theory.
- There is evidence that some monovalents may not be as effective as the trivalent vaccines and, in fact, may cause more adverse reactions.

Isn't it more "natural" to spread out exposure to viruses over a period of time – not to expose a child to several viruses at once?

In fact, children are commonly exposed to many different viral illnesses in everyday life, often several within a very short period of time.

- Surprisingly, an early study comparing reactions to monovalent measles vaccine with MMR showed that children receiving MMR had *fewer* side effects and *less* respiratory infections in the weeks following vaccination than children receiving monovalent measles immunization. This suggests that MMR made children more resistant to other infections in the short-term.

Where can I get a monovalent vaccine?

- Monovalent vaccines are no longer available in Canada.

- They are only available in the United States.

Are there risks in using monovalent vaccine?

Monovalent vaccines are not as well studied as is MMR therefore there is not much safety data.

- The biggest known risk in the use of monovalent measles vaccine is the delay in protection for rubella and mumps, since 6 needles will be required over an unspecified period of time to vaccinate for all three diseases. Children may be over 3 years old before all of these vaccinations are received, making them vulnerable to serious infection in the meantime.

What should parents know about the potentially serious nature of viral infections?

North Americans do not often worry about viruses like measles, mumps and rubella because we feel these diseases are under control. It is through vaccination, however, that developed nations have been able to minimize the effects of these infections. The risk of contagious and potentially dangerous disease increases dramatically when large numbers of children are not vaccinated.

- For example, the World Health Organization (WHO) states that "Measles ranks as one of the leading causes of childhood mortality in the world...it is estimated that in 1997 nearly one million deaths from measles still occurred (in developing countries). Outbreaks of measles continue to occur even in highly vaccinated populations" (WHO Guidelines for Epidemic Preparedness and Response to Measles Outbreaks, May 1999, available on the Internet at www.WHO/CDS/CSR/ISR/99.1).
- Data collected in Colorado between 1987 and 1998 shows that unimmunized children between 3 and 5 years of age are 66 times more likely to acquire measles infection than are children who receive immunization by vaccine. This number will increase if more parents fail to immunize their children. (Ref: Dr. Daniel Feikin et al in the Journal of the American Medical Association (JAMA), December 27, 2000; Vol. 284, No. 24; pp. 3145-50.)

- Health Canada has set a goal of eliminating measles through vaccination by the year 2005, but during the past ten years even Canada has struggled with rising numbers of confirmed measles cases. Measles is known to be a persistent and very contagious virus.

What is being done to reassure parents of children with autism?

The National Institutes for Health (NIH) in Washington, D.C. is responding to parents' concerns with a lot of research.

- The NIH Internet website contains excellent information for parents, including ongoing research project information and results.

Conclusions and Recommendations for Parents

There are many answers still to be found, but we do know that:

- There is definite evidence that the vaccinations currently given to Canadian children are safe.
- Evidence that early signs of autism are present during infancy, before obvious symptoms are noticed, indicates that the onset of autism occurs well before vaccination.
- The risk that autism is triggered by MMR vaccine is not currently well supported by sound scientific data.
- Failure to immunize constitutes a well-known and extremely high risk for all children.
- All possible efforts must be made to protect children from devastating infectious diseases. Crucial to this process is ensuring that children receive vaccinations promptly.

Part 2: MERCURY POISONING

If MMR doesn't cause autism, is it Mercury?

Mercury can be derived from thimerosal, which is used in some vaccines as a preservative. In the past few years, it has been claimed that cumulative mercury poisoning from the usual series of childhood immunizations may be an unidentified cause for autism in susceptible children.

This theory has caused further anxiety about vaccines as well as a trend for parents to seek chelation therapy aimed at removing heavy metals like mercury from their child's body, despite the risks and expense of this treatment.

Important Facts about Mercury and Thimerosal

- *Canadian DPTP and MMR vaccines do not contain thimerosal.* The mercury alarm was raised in the United States, where thimerosal is used in DPTP and other vaccines. If thimerosal/mercury causes autism, it would be reasonable to expect a difference between the number of autism cases in Canada and the U.S., since one population is exposed to cumulative mercury while the other is not. Such a difference has not been seen.
- *In Canada, only one vaccine commonly used for infants under 6 months of age contains thimerosal – a Hepatitis B (HBV) vaccine (not used in British Columbia).* The amount of mercury in infant HBV vaccine is well below the most conservative safety estimate. No significant difference has been noted in the occurrence of autism in provinces that do and do not use the thimerosal-containing HBV.

What is Chelation Therapy?

Chelation involves injecting a chemical into the bloodstream that is intended to attach its molecules to particles of toxic substances in the body (e.g., heavy metals). The toxins are then "piggybacked" out of the body when the chemical is excreted in the urine.

Unique Concerns for Parents of Autistic Children

There is a great deal of information available about the relationship between heavy metal poisoning and autism. Chelation therapy is the most frequently recommended treatment. Here is what current evidence tells us:

- Canadian children are *not* at risk from mercury in vaccines.

- The facts do not support chelation to get rid of mercury. The August 2001 issue of the American Academy of Pediatrics News presented a good review of the facts about Chelators:
    - Some chelation therapies can actually *increase* the concentrations of a toxin in the brain, causing more brain damage, not less.
    - Unlike lead, arsenic and other metals that stay in human tissue much longer, mercury stays in the body for only about 12 weeks, making mercury chelation unnecessary.
    - The most common mercury chelator, DMSA, does not cross the blood-brain barrier despite claims by chelation practitioners to the contrary.
    - Chelation is an invasive treatment that can affect liver, bone marrow and kidney function, and may cause allergy.
    - Chelation therapy can cause significant loss of essential nutrients (such as zinc) that may not be replaced easily through the diet or by taking oral supplements.
    - Chelation may cause transient changes in behaviours such as increases in hyperactivity and self-stimulatory behaviour.
    - Chelation has minimal effect on mercury, and has *not* been shown to reverse neurological injury from any type of metal poisoning.

What is known about the effects of mercury exposure on a child's development?

Health Canada has recently reviewed the available information about thimerosal/mercury:

- There is no evidence that thimerosal exposure from vaccine results in toxic mercury levels in humans.
- Symptoms of mercury poisoning are not the same as symptoms of autism, attention deficit-hyperactivity disorder (ADHD), or speech-language delay.
- There is no evidence that thimerosal leads to any of the physical differences that are associated with autism, such as genetic abnormalities.
- Autism is thought primarily to begin before birth, rather than being acquired during the first years of life.

- A study of children whose diet consisted primarily of mercury-containing fish showed no relationship between the mercury levels in their bodies and developmental problems.

What is being done to reassure parents of children with autism?

As with the MMR controversy, the National Institutes of Health is responding to parents' concerns. Among the research initiatives underway is a study of the effects of the environment (including pollutants and vaccinations) on the health of 100,000 children.

Conclusions

- Good evidence exists showing that Canadian vaccines are safe.
- Common childhood vaccines, including DPTP and MMR, have been free of thimerosal/mercury in Canada since 1992. The only exception is the infant Hepatitis B vaccine used in some provinces and known to pose extremely low risk of mercury toxicity.
- Environmental sources are much more likely to cause the presence of heavy metals in human tissue than exposure to substances like vaccines.
- Ongoing research is needed to find definitive answers about the origins of autism.

FOR MORE INFORMATION ABOUT AUTISM, VACCINATIONS AND HEAVY METAL TOXICITY, the following web addresses may be helpful:

National Institutes for Health: **www.nichd.nih.gov**

Health Canada: **www.hc-sc.gc.ca/pphb-dgspsp/publicat/codr-rmtc/02vol28-09**

Institute of Medicine: **www.iom.edu/ImSafety**

National Academy Press: **www.nap.edu**

Centre for Disease Control: **www.CDC.gov/nip/**

World Health Organization: **www.who.int/vaccines-diseases/safety/index.html**

REFERENCES

1. Bryson, SE, Smith, IM. Epidemiology of Autism: Prevalence, Associated Characteristics and Implications for Research and Service Delivery. Mental Retard and Dev Disab Research Reviews, 1998; 000: 1-7.
2. Jones, MB, Szatmari, PA. Risk Factor Model of Epistatic Interaction, Focusing on Autism Amer. J of Medical Genetics, 2002. 114: 558-565.
3. Chance, GW. Environmental contaminants and children's health: Cause for concern, time for action. Ped and Ch Health, 2001; 6, #10: 731-43.
4. Howlin, P, Moor, A. Diagnosis in Autism. A Survey of over 1200 Patients in the U.K., Autism, 1997; 1: 135-172.
5. Tuchman, RF, Rapin, I, Shinnar, S. Autistic and Dysphasic Children. #1. Clinical Characteristics. Pediatrics, 1991; 88: 1211-1218.
6. Zwaigenbaum, L, Rombough, V, Adams, B, Roberts, W, Szatmari, P, McDermott, C, Brian, J, Bryson, S (2001, November). Prospective study of infant siblings of children with autism: Preliminary findings. Poster presented at International Meeting for Autism Research, San Diego, CA.
7. Mars, AE, Mauk, JE, Dowrick, PW. Symptoms of Pervasive Developmental Disorders as observed in prediagnostic home videos of infants and toddlers. J Peds 1998 132: 500-504.
8. Wakefield, AJ, Murch, SH, Anthony, A, et al. Ileal-lymphoid nodular hyperplasia, Non-Specific Colitis, and Pervasive Developmental Disorder in Children. Lancet, 1998; 351: 637-41.
9. Halsey, N, Hyman, S, and the Conference Writing Panel. Measles, Mumps and Rubella Vaccine and Autism Spectrum Disorder. Report from the New Challenges in Childhood

Immunization Conference convened at Oak Brook, Illinois, June 12-13, 2000. Pediatrics, 2001; 107, #5: 1-23.

10. Sahley, T, Panksepp, I. Brain Opioids and Autism: An updated analysis of possible linkages. J Aut and Dev Disord, 1987; 17: #2: 201-211.
11. Reichelt, KL, Hale, K, Hambeiger, A, et al. Biologically Active Peptide-Containing Fractions in Schizophrenia and Childhood Autism. Acto Biochem Psychopharmacol, 1981; 28:627-643.
12. Shattock, P, Kennedy, A, Rowell, F, Berney, TP. Role of Neuropeptides in Autism and their Relationships with Classical Neurotransmitters. J Brain Dysf, 1999; 3: 328-345.
13. Megson, M. Is Autism G-Alpha Protein Defect Reversible with Natural Vitamin A? J Med Hypotheses, 2000; 54: 979-983.
14. D'Eufemia, P, Celli, M, Finocchiaro, R, et al. Abnormal Intestinal Permeability in Children With Autism, Acta Paediatr, 1996; 85: 1076-1079.
15. Wakefield, AJ, Peltola, RM, Sim, R, et al. Evidence of Persistent Measles virus infection in Crohn's disease. J Med Virol, 1993; 39: 345-353.
16. Afzal, MH, Armitage, E, Begley, J, et al. Absence of detectable measles virus genome sequence in inflammatory bowel disease and peripheral blood lymphocytes. J Med Virol, 1998; 55:243-249.
17. Katayama, Y, Kohso, K, Nishimura, A, et al. Detection of measles virus mRNA from autopsied human tissues. J Can Microbiol, 1998; 36: 299-301.
18. Wakefield , AJ. The gut-brain axis in childhood developmental disorders. J Ped. Gastroent. Nutr, 2002 May-June;34 Suppl 1:S14-17.

19. Horvath, K, Papademitrion, JC, et al. Gastrointestinal Abnormalities in Children with Autistic Disorder. J Ped, 1999; 136: 559-563.

20. Kagan-Kushnir, T, Griffiths, A, Roberts, W. Gastrointestinal Symptoms in Autism Spectrum Disorders. (Submitted for publication 2002)

21. Taylor, B, Mellor, E, et al. Measles, Mumps and Rubella Vaccination and bowel problems or Developmental Regression in Children with Autism: Population Study. BMJ, February 2002; 324: 393-396.

22. Singh, VK, Fudenberg, HH, Emerson, D, Coleman, M. Immunodiagnosis and Immunotherapy in Autistic Children. Annals NY Acad Sci, 1988; 540: 602-604.

23. Gupta,S, Aggarwal, S, Heads, C. Dysregulated Immune System in Children with Autism: Beneficial Effects of Intravenous Immune Globulin on Autistic Characteristics. J Aut and Dev Dis, 1996. 26(4): 439-52.

24. Comi, AM, Zimmerman, AW, Frye, VH, et al. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Ch Neuro, 1999; 14: 388-94.

25. Miller, E, Goldacre, MA, Pugh, S. Risk of Aseptic Meningitis after Measles, Mumps and Rubella Vaccine in UK Children. Lancet, 1993; 341: 979-982.

26. Plotkin, SA. Rubella vaccine. In: Plotkin, SA, Orenstein, WA, Eds. Vaccines. 3rd Ed. Philadelphia, PA, WB Saunders Co, 1999; 409-440

27. Measles/Mumps/Rubella Vaccine and Autistic Spectrum Disorder: A Hypothesis Only. Canadian Pediatric Society Statement Infectious Diseases and Immunization Committee. Embree, J, Chair. Ped and Ch Health, July/August 2001, 6; 387-391

28. Taylor, B, Miller, E, Farrington, P, et al. Autism and Measles, Mumps and Rubella Vaccine: No epidemiological evidence for a causal association. Lancet, 1999, 353: 2026-29.

29. Kaye, JA, DelMarMelro-Montes, M, Jick, H. Mumps, Measles and Rubella Vaccine and the Incidence of Autism Recorded by General Practitioners: A Time Trend Analysis. BMJ, 2001; 322: 460-463

30. Fombonne, E, Chakrabarti, S. No Evidence for a New Variant of Measles-Mumps-Rubella-Induced Autism. Pediatrics, 2001, 108, #4: e58

31. Dales, L, Hammer, S, Smith, NJ. Time Trends in Autism and in MMR Immunization coverage in California. JAMA, 2001, June 13; 285(232): 2832-2833.

32. Gillberg, C, Heijbel, H. MMR and Autism. J Aut, 1998; 2: 423-4.

33. Peltola, H, Patja, A, et al. No Evidence of Measles, Mumps and Rubella Vaccine Associated Inflammatory Bowel Disease or Autism in a Fourteen Year Prospective Study. Lancet, 1998; 351:1327-8.

34. Peltola, H, Heinonen, OP. Frequency of True Adverse Reactions to MMR Vaccine. A Double Blind Placebo Controlled Trial in Twins. Lancet, April 26, 1986; 939-942.

35. The National Institute of Allergy and Infectious Diseases at the NIH and the National Immunization Program at the CDC reports (electronic). Available: www.nichd.nih.gov

36. Health Canada, Government of Canada. Report of Wild Measles Infection (electronic). Available: www.hc-sc.gc.ca

37. Health Canada, Government of Canada. Notifable Diseases Summary (electronic). Available: www.hc-sc.gc.ca

38. Feikin, D, Lezotte, D, Hamman, R, Salmon, D, Chen, R, Hoffman, R. Individual and Community Risks of Measles and Pertussis Associated with Personal Exemptions to Immunization. JAMA, 2000, December 27; 284 (24); 3145-3150.

39. Roberts, W, Weaver, L, Brian, J, Bryson, S, Emelianova, S, Griffiths, A, MacKinnon, B, Yim, C, Wolpin, J, Koren, G. Repeated Doses of Porcine Secretin in the Treatment of Autism: A randomized placebo-controlled trial. Pediatrics, 2001; 107, #5: e71.

40. Bernard, S, et al. Autism: A Novel Form of Mercury Poisoning. Med Hypotheses, 2001; 56 (No 4): 462-471.

41. Health Canada. Exposure to Thimerosal in Vaccines used in Canadian Infant Immunization Programs with respect to risk of neurodevelopmental disorders. Canada Communicable Disease Report, Vol 28-09, 1 May 2002.

42. Fombonne, E. Is There An Epidemic of Autism? Pediatrics, 2001; 107, #2: 411-412.

43. Weir, E. Methylmercury exposure: Fishing for answers. CMAJ, 2001; 165: 205-6.

44. Ball, LK, Ball, R, Pratt, RD. An Assessment of Thimerosal Use in Childhood Vaccines. Pediatrics, 2001; 107, #5: 1147-1154.

45. Magos, L, Brown, AW, Sparrow, S, Bailey, E, Snowden, RT, Skipp, WR. The Comparative Toxicology of Ethyl and Methyl Mercury. Archives Toxicol, 1985; 57: 260-267.

46. Davidson, PW, Myers, GJ, Cox, C. Effective Prenatal and Postnatal Methyl Mercury Exposure from Fish Consumption On Neurodevelopment: Outcomes At 66 Months of Age in the Seychelles Child Development Study. JAMA, 1998; 280: 701-707.

47. Grandjean, P, Yeihe, P, White, RF. Cognitive Deficit In Seven Year Old Children With Prenatal Exposure to Methyl Mercury, Neurotoxicol Teratol, 1997; 6: 417-428.

48. Institute Of Medicine Report (electronic). Available: www.iom.edu/imsafety

49. Walsh, WJ, Usman, A, Tarpey, J. "Disordered Metal Metabolism in a Large Autism Population". American Psychiatric Association, May 2001.

50. Holmes, A, Cave, S, El-Dahr, JM. “Open Trial of Chelation With Mes0-2,3-Dimercapto Succinic Acid (Dmsa) and Lipoic Acid (LA) in Children with Autism”. International Meeting for Autism Research (IMFAR), 10 November 2001 (electronic). Available: www.imfar.org

51. Shannon, M, Levy, S, Sandler, A. Chelation therapy neither safe nor effective as autism treatment. AAP News, August 2001: 63.