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Viewpoint

MMR Autism Controversy: Could Both Sides be Right?

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Rates of autism are rising, and MMR and toxic metals have been blamed. Some parents insist that vaccination provoked their child's autism; researchers have disputed such claims. But could both sides be right? Perhaps MMR and toxic metals do cause disease, but only in a subgroup of susceptible children.

5 years ago a report in *The Lancet* produced a storm of controversy. Andrew Wakefield, working in London, reported on autistic children who regressed after vaccination with measles, mumps and rubella (MMR) vaccine. The inference was that live vaccine viruses, in these children, contributed to the development of autistic symptoms.

But researchers have been unable to find any evidence to support the link between MMR and autism.

Even so, protests have widened to include the thimerosal vaccine supplement - a mercury-based preservative – some vigorously blaming mercury for their child's autism. The fact that MMR vaccine does not contain thimerosal has not quietened anxieties.

Diverging views have resulted in a stand-off, with many parents refusing to vaccinate despite reassurances from medical authorities. Uptake of MMR vaccine has fallen. Coverage in London declined from 87% in 1995 to 73% in 2002, according to a report of the London Assembly Health Committee.

In a 7 August 2003 report in the journal *Science* by Vincent Jansen and colleagues suggest that the dropping level of vaccine protection could soon reach the point where isolated outbreaks of measles will become established in the population - the once rare disease measles may be set to return to haunt families who refuse vaccination.

And a recent BBC drama has inflamed opinion further.

But who is right? Could childhood vaccines contribute to autism? The facts are as follows:

One, that autism is increasing.

Second, some parents, no-one knows exactly how many, insist that their child's autism developed just after receiving a scheduled childhood vaccine, notably the measles/mumps/rubella (MMR) triple vaccine.

Third, some vaccines contain traces of mercury, a toxic metal that can cause brain dysfunction.

Last, across hundreds of children studied, no statistically significant link has been found between vaccination and autism. No change in autism rates was observed following the introduction of MMR vaccine in 1988, according to a large London study reported by Brent Taylor and colleagues in 2002.

And, reinforcing the point, exactly the same percentage of parents (26%) expressed worries about their child's development before MMR as after vaccination. And autism was seen in children who were never vaccinated. Other studies confirm this pattern.

Is it really plausible to suggest that vaccines, with or without heavy metals, could cause autism? Perhaps both the parents and the researchers are right – MMR does not cause autism in ordinary children, but suggestions are emerging that a subgroup of children might be especially susceptible.

Autism - a modern disease

In the 1940s Leo Kanner in Baltimore and Hans Asperger working independently in Vienna encountered a condition different from anything encountered previously. Mostly boys, affected individuals had little interest in communicating with others, pursuing solitary activities.

The children reported by Kanner had the classic triad of impairments - delayed speech, lack of social communication and eye contact, and repetitive self-stimulatory activities such as spinning and hand-flapping. And often accompanied by anxiety and epilepsy.

Asperger's syndrome is a somewhat less common, though milder version of autism, also characterised by social withdrawal, but sometimes with specific performance elevation in areas of delimited interest.

Though cases of autism go back more than 50 years, they were rare. Many teachers and doctors have never seen a case until recently.

A former doctor, in *The Scotsman* last year, writes: "I was in general medical practice for 30 years. I never encountered autism until my last year, when a young lad, severely affected, came to my practice".

A majority of teachers canvassed by the UK National Autistic Society feel that the increase is real.

In California, over a 10-year period the number of children newly diagnosed with autism rose almost 3-fold, according to a report by the California

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Department of Health Services. The rise in a single year (2001-2) was 21%. Similar increases have been seen in other parts of the US.

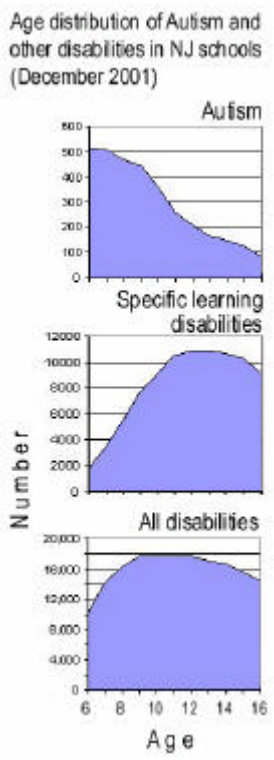
A 2001 estimate by the UK Medical Research Council put the incidence as high as 1 in 166 children under 8. But a 2002 survey in England and Wales organized by the National Autistic Society of the UK suggests a strikingly higher figure - 1 in 80 - in primary school children, three fold higher than in secondary education. This points to an ongoing increase.

The excess of younger children with autism is reiterated in New Jersey, according to a 2002 report by the Office of Special Education Programs at the New Jersey State Department of Education. When all disabilities are considered (6 to 16 years old) the peak is at age 11, reflecting overall progress of diagnosis and therapy. Specific learning disability peaked at 13-14 years of age (Figure).

But, in this state, autism has a strikingly different age distribution, with a 6-fold higher prevalence at age 6 than at age 16.

And the peak New Jersey incidence rate for autism, around 0.8%, is comparable to the recent 1% estimate in the UK.

Better diagnosis could be responsible for the apparent increase. But the unique and distinctive signs of autism - repetitive behaviours and lack of communication - are not easily missed. Even so, other milder forms of autism are less easy to spot, and figures could plausibly be an underestimate.



Though parents protest a huge rise, and researchers remain unconvinced, a fair view would be of a steady increase, with autism indeed becoming more and more common.

That is a worrying development. According to a 2001 UK study the cost of caring for an autistic individual can amount to over £40,000 per annum, and with incidence reaching 1% the expenditure for this one condition could be immense.

A December 2003 report from Inverness, UK, now points to an even higher figure – 1 in 49 children.

Viruses and vaccines

Are the live viruses in childhood vaccines plausible suspects?

The answer is yes - virus infection of the brain can sometimes cause autism. Reports in the medical literature describe rare cases of autism following congenital cytomegalovirus or rubella. Herpes encephalitis has been specifically implicated as the trigger for the development of autism in two adolescents aged 11 and 14. A male who contracted temporal lobe herpes encephalitis at 31 yrs went on to develop symptoms diagnostic of autism.

Could this then point to vaccines? There are three threads to the following discussion. One looks at potential culprits, another at prevalence. The third looks at age of onset.

The MMR vaccine has been vocally challenged. Measles (rubeola) and mumps are normally minor diseases of childhood, but can sometimes produce severe disease or death – different reports place measles hospitalisation at 1 per thousand with death at anything between 1 in 3,000 and 1 in 18,000.

Rubella (german measles) is also a minor disease, but during pregnancy is dangerously associated with spontaneous abortion and mental retardation, and sometimes autism, in 20% of infants, but though specific cases have been associated with this condition the frequency of the diagnosis is not known.

Following the tradition of Edward Jenner (cowpox vaccine against smallpox), the vaccine protecting against these three diseases contains weakened live viruses. These cause only low-grade infection and produce robust immunity. Because they are so similar to the parent viruses, this immunity protects against infection with virulent strains.

Other childhood vaccines, such as Diphtheria, Tetanus, Pertussis (DTP) are killed vaccines with no potential to cause infection.

Oral poliovirus vaccine stands out because it contains, like MMR, live attenuated virus. Though the vaccine itself has been found innocuous, new cases of polio have been attributed to revertant viruses sometimes found in the vaccine.

Looking wider, chicken pox is caused by the varicella zoster virus. Here the attenuated vaccine virus is not entirely innocuous: it can persist to erupt later in life as shingles (herpes zoster). The vaccine causes seizures in approximately 1/1000 children, but to be contrasted with hospitalisation needed in 3 per 1000 infections and death at around 3 per 100,000 infections with disease virus.

Of all these vaccines, the attenuated herpes (chicken pox) vaccine is the most credible suspect given the reports of autism onset in two adolescents

following herpes encephalitis. And congenital herpes-related cytomegalovirus can cause autism.

But UK children do not presently receive chicken pox vaccine, though there are proposals to introduce such vaccination, and a causal link with vaccination is ruled out.

Even so, one cannot exclude the possibility that attenuated live viruses in MMR and polio vaccines could produce disease in especially susceptible children.

There is a precedent. A 1987 report described life-threatening systemic vaccinia infection of a US serviceman following smallpox vaccination; but it turned out that this individual was immunologically compromised through HIV infection.

Thus vaccine viruses can cause disease if the host is especially susceptible. Could this apply to MMR? This not ruled out, for the frequency of adverse reactions to MMR and vaccinia virus are not dissimilar.

In the case of vaccinia, mild adverse reactions are seen in one of every 1000 to 10,000 patients, sometimes requiring hospitalisation (one in 100,000) but causing death only rarely (one in 1 million).

MMR is not very different. According to a so-far unconfirmed 2002 study by Mark and David Geier of Maryland, the rate of serious side-effects - cerebellar ataxia, autism, mental retardation and permanent brain damage - was 2.63 per 100,000 MMR vaccines. Other studies confirm serious encephalitis at a rate of 1 per million.

Rates were apparently a lower, but only a little (~4 fold), with the killed diphtheria, tetanus and whooping cough vaccine, arguing that some of the suspected MMR side-effects are coincidental and not causal.

On the one hand, in a population like the UK where up to 1 million MMR vaccines are issued per year, one could expect a large handful of cases where the vaccine is the cause of brain disease, with autism in a fraction.

On the other hand, if autism is now affecting 1% of primary age children, one can calculate that the large majority of cases are not caused by childhood vaccines – but little solace to the rare children where vaccines are likely to be responsible.

Age of onset

Autism is first diagnosed in pre-school years, often at age 2-3. According to current UK guidelines, MMR vaccine is first administered at 12-15 months. So recognition of autism in the months following vaccination could be coincidence.

Behavioural idiosyncrasies are seen on family videotapes taken during the first year of life, and support the idea that autism was present earlier in at least some children.

Minor physical anomalies are more common in autism. Males generally have a long fourth finger compared to the second, while this is inverted in females. According to some recent but probably reliable studies, autistic children are biased towards male-type.

Because skeletal dimensions are laid down early in pregnancy, this bias points to perturbations during gestation rather than to early childhood.

Other data too point to pregnancy. Maternal age and smoking during pregnancy are risk factors. 4% of Swedish thalidomide victims meet the diagnostic criteria for autism. Maternal anticonvulsant medication is associated with autistic behaviour in offspring.

Therefore, early toxicological insult is likely to be at the heart of later-life autism.

Toxic metals

Another suspect is the heavy metal preservative Thimerosal (also Thiomersal), ethyl mercury, used to prevent bacterial contamination of vaccines. This has raised fears that the mercury might cause brain disease.

The toxicity of heavy metals has been known for centuries. Neurologic and psychiatric complications are common. Lead in children is known to cause developmental delay, lack of coordination, forgetfulness, lethargy and sometimes convulsions.

Some have even attributed the demise of Roman civilisation to the habitual use of lead containers for water, food and wine, but that could be fanciful thinking or, who knows, it might be true.

Mercury used in the manufacture of hats gave rise to the expression 'mad as a hatter' while, last century, Pink disease in infants due to mercury-containing teething powder was associated with lethargy and proneness to emotional and psychiatric disorders. Some attribute Sir Isaac Newton's remarkable moodiness to mercury exposure during his metallurgical researches.

But levels of mercury in childhood vaccines are low. Even so, the preservative is based on ethyl mercury, rather than the metallic or methyl mercury: data on uptake, metabolism and toxicity are limited. However, a large Danish study recently reported that autism incidence continued to increase following withdrawal of all thimerosal from childhood vaccines in 1992.

Could metals cause autism?

At the beginning of the 1990s, in Canada, a surprising discovery was made. When Nancy Hallaway's three-year-old twin boys were diagnosed, she discovered that she was not alone - there were at least 6 new cases - and all the children lived around the same street.

A likely cause of this cluster was the toxic metal lead. In her 1995 book 'Turning Lead into Gold', co-written with her physician, Dr. Ziburts Strauts, she describes how these children had elevated blood levels of lead and other heavy metals. Hallaway reported marked improvement when lead removal therapy was applied, using metal-binding compounds such as EDTA (ethylene diamine tetraacetic acid) or penicillamine.

Increased blood lead in autism was first reported in the 1970s but was ascribed to unusual eating habits of autistic children who often nibble on non-food

items, and risk ingesting lead paint for instance. But this odd nibbling behavior, termed 'pica', is a well-known feature of trace metal deficiency that accompanies metal poisoning - and a powerful indication that toxic metals are at play.

Mercury is also implicated. The symptoms of mercury poisoning can be superficially similar to those of autism - repetitive behaviours, mental impairment, predisposition to epileptic seizures, according to a 2001 report from Sallie Bernard in New Jersey, published in *Medical Hypotheses*.

And some autistic children have markedly increased blood mercury - unpublished data from a Louisiana MD, Amy Holmes, suggest that up to 50% of autistic children benefit from chelation with DMSA (dimercapto succinic acid), some being cured.

The rise in autism could be following a hike in toxic metals in the environment. Though increasingly released into the atmosphere by industrial processes, the extent of release is not precisely known - it is not possible to assess a direct parallel with autism.

Environmental metals are reaching worrying levels. A 1999 study by the US National Wildlife Federation reported that rainfall mercury was up to 65 times in excess of the recommended safe level.

Atmospheric toxic metals pass to the sea, where they are taken up by marine life, particularly at the end of the food chain. In a 2003 study from Japan, all tested samples of whale meat exceeded the provisional safety limit on the maximum density of mercury (0.4 parts per million), with an average content of 11.6 ppm. One sample was recorded at 23.1 ppm.

Researchers specifically looking at methyl mercury recorded values of up to 10.6 ppm, more than 35 times the safe limit of 0.3 ppm.

In the UK, the Food Standards Agency recommended in 2002 that pregnant mothers and infants should avoid consuming more than one meal per week of shark, swordfish or marlin.

Such warnings are not issued lightly, and one must suspect that some individuals are already affected.

But is there any specific link between toxic metals and autism? A potential pitfall is that toxic metals are increasingly widespread in the environment, but few children develop autism. That could point to a genetic susceptibility factor.

Toxic metal susceptibility

Twin studies confirm a genetic factor. The risk of autism is sharply elevated in identical twin brothers and sisters of affected individuals, and to a lesser but significant extent in their siblings.

New data now suggest that autistic children differ in the way they handle toxic metals. This insight comes from a paper by Amy Holmes and colleagues published in the *International Journal of Toxicology*.

These researchers analysed first baby haircuts from autistic children. Hair samples generally contain measurable levels of mercury and other metals, reflecting ongoing exposure from fish-rich diets, dental amalgams and so forth. But, to their surprise, mercury was almost entirely absent from the baby-hair of children later becoming autistic, even though metal exposure was typical.

Moreover, as the severity of the disease increased, the level of hair mercury went down.

And, in the same study, when they normalised for maternal mercury exposure, chiefly from fish meals, dental amalgams, and mercury-containing RhoD immunoglobulin, mercury levels in hair from normal children went up exactly in line with exposure. But in those infants later becoming autistic it stayed at baseline, irrespective of exposure.

Whatever is ailing these children, part of the syndrome includes failure to export mercury into hair. And, while excretion into hair is only a minor route for removing toxic metals from the body, this could perhaps be a sign of a more generalised deficit - it is quite plausible that autistic children are unable to get rid of heavy metals like mercury.

Elevated hair mercury levels in control children could then be a sign of resistance to toxicity: in a study on mercury poisoning in the Seychelles some years ago it was found that boys with *higher* levels in their hair performed better on several cognitive tests.

And, in subjects unable to mobilise mercury, one suspects that it must stay in the body.

Toxic excess or deficiency

Two-fold effects of heavy metals are probable. First, they interfere with brain function. Heavy metals accumulate in central brain regions such as the hippocampus and amygdala - and dysfunction of just these regions could partly explain the behavioural signs of autism.

Second, they compete with natural heavy metals essential for normal brain function. In rats, supply of one metal in excess can cause deficiencies for other metals. Deficiency in copper and zinc is known to produce overt brain disease: in rats, copper deprivation causes degenerative changes in the hippocampus.

Both excess and deficiency could operate in autism. A 1985 study reported abnormally low levels of copper and chromium in autism.

Postmortem studies on autistic individuals have revealed abnormalities of nerve cell packing density in the hippocampus, highly reminiscent of the effects of copper deprivation.

Effects of toxic metals: depressed immunity

Immune system deficiency, gut dysfunction, and epilepsy are all seen in toxic metal excess. These are also common features of autism. And depressed immunity could permit proliferation of otherwise innocuous agents.

Live vaccine viruses can be extremely dangerous for children whose immunity is compromised, for instance by HIV infection. Disease has been observed in a small number of cases of HIV-infected children receiving MMR, and current guidelines in North America and Europe stipulate that live MMR vaccine should not be given to HIV-positive children; the restriction extends to oral poliovirus and chicken-pox vaccines. Nevertheless, the number of adverse

reactions to MMR in HIV-positive children has been surprisingly few, and many now recommend that these children should receive the vaccine.

The gut has its own localised immune system that can be damaged by heavy metals. This could lead to localised proliferation of vaccine viruses, contributing to the dispersed gut inflammation seen in many children with autism, as first reported by Wakefield and now independently confirmed.

It could also predispose to gut infections by toxic bacteria. A 2002 report by Sydney Finegold and colleagues in San Francisco described hugely elevated levels of Clostridia in the gut of autistic individuals. Toxins released by overgrowth of abnormal bacteria in the gut could reach the brain via the bloodstream.

Therefore, depressed immunity due to metal poisoning could contribute to the proliferation of pathogens and the development of brain disease including autism.

Why no autism in overt mercury poisoning?

When large numbers of people were poisoned with mercury in Minamata, Japan, autism was not reported, or only rarely. The same holds for regions like the Faroes and the Seychelles where dietary mercury is reaching worrying levels.

But three factors were not considered in these studies.

First is that the levels of exposure, particularly in Minamata, were so high that susceptible children, instead of developing a milder disorder, were likely to have been massively debilitated.

Second, these children did not receive attenuated viruses as in MMR.

Third, metals are not the only environmental toxin today - other agents like dioxins and bisphenols are increasingly widespread. And a combination of toxins can cause damage even at levels where each element is within safety limits.

Perspective - To vaccinate or not to vaccinate

As the MMR debate continues, it seems likely that neither vaccines nor toxic metals alone cause autism. But heavy metals may play the larger role – and toxic metal sensitivity combined with childhood vaccines could, at least potentially, contribute to the rise in autism.

Both the researchers and the vocal parents could be right. The data from Holmes and colleagues do argue strongly that some children have a deficit in getting rid of metals. In just these children, most particularly if exposed during early life, metal poisoning could weaken their immune systems to a point that innocuous vaccines cause brain damage.

While the Holmes data need to be reproduced, there are immediate implications for vaccination policy.

It would seem unwise to compound the heavy metal load by including mercury in childhood vaccines. Other countries have removed all mercury-based preservatives from vaccines.

Even so, according to Amy Holmes, maternal dental amalgams account for 60% of infant mercury exposure at birth, and the relative contribution of vaccine mercury is not known, but may be minor.

Then, a decision must be taken on the (mercury-free) MMR triple vaccine. One could argue that sensitive children should not receive the vaccine. Unfortunately, this subgroup cannot be identified at present.

But, importantly, it could be calamitous for sensitive children to encounter virulent disease viruses. It would seem doubly imperative that the population is vaccinated.

Three hundred years ago, worried mothers threatened with smallpox epidemics inoculated their children with raw smallpox lesions. This was not madness. Though this procedure killed perhaps 1 in 100, the other 99 were protected from a disease capable of destroying entire communities.

Parents worried about the risks of MMR vaccine should consider whether the risk of autism is a small price to pay in return for protection against the far more serious consequences of full-blown disease.

The fatality rate from measles in patients immunocompromised by AIDS can be up to 40%, while adverse effects with MMR vaccine are extremely rare. The World Health Organisation has concluded: the benefits of measles and poliovirus vaccines far outweigh the potential risks in HIV-infected children'.

In the longer term the pressure will be on to confirm that some children are especially susceptible to the vaccine viruses. A quick way of identifying them will be needed. For the future, a killed vaccine for use in these children could be justified; the Government of Ireland has recently funded research in this direction.

Time will tell if there really is a link between metals and autism. And, if so, this might prompt re-evaluation of other increasingly prevalent diseases including asthma and ME (myalgic encephalomyelitis), and of measures to control industrial emissions containing toxic metals.

Unfortunately, one of the largest emitters of atmospheric mercury, the USA, now seems determined to relax controls on industrial release, with a December 3rd report in the Washington Post stating 'The Bush administration is working to undo regulations that would force power plants to sharply reduce mercury emissions and other toxic pollutants.'

Given increasing evidence for a causal link between heavy-metal exposure and autism, the wisdom of this development must be challenged.