Bandolier Extra

Independent evidence-based thinking about health care

MMR VACCINATION AND AUTISM

Bottom line

The evidence is that MMR is not associated with autism in children. The quality, validity, and size of that evidence is overwhelming. There is no temporal relationship between MMR vaccination and autism, nor any different sort of autism associated with MMR, nor bowel problems. Autism rates began to rise before MMR, and continue to rise even if MMR is withdrawn. Autism rates tend to be lower in children vaccinated with MMR, though not significantly so.

What is autism?

Infantile autism was originally characterised in the 1940s as delayed development. While autistic children look normal, they have severe language disorder, lack of emotional rapport or eye contact, and there are major barriers to communication. Many are abnormal from birth, but in some behavioural regression occurs in the second year after an initial normal period of development. Autistic children are solitary and orderly and often distressed by changes in routine. They treat people as objects, and words as meaningless sound. Half may develop useful speech by the age of five years, but usually not conversation. Many have low IQ, a quarter develop epilepsy, usually in adolescence, and about 1 in 10 become partially independent as adults.

The cause of autism is not known, and it is possible that autism, of itself, is not a condition, but rather a non-specific manifestation of other conditions. No consistent changes are found, though some metabolic abnormalities are found in some cases. Boys are affected more than girls, and the incidence of autism has been rising, in part because of improved diagnosis, but also possibly because of environmental or other factors that are not understood.

There are related conditions called autism spectrum disorders. One is Asperger's syndrome, with mildly impaired or normal intelligence, again affecting mostly boys, who tend to be late to walk and talk and remain rather clumsy. Typically they tend to be socially aloof, unaware of others and their feelings, literal, and often pedantic in manner. They often have narrow but intense interests involving memory rather than comprehension.

Risk factors for autism

These are not well understood. It has been claimed, for instance, that autism occurs more often in families of scientists or professionals [1]. A recent study indicated that risk of autism was associated with smoking in early pregnancy, maternal birth outside Europe or North America, Caesarian delivery, small for dates, low Apgar and congenital malformations. The implications are that intrauterine and neonatal factors are important factors for autism.

This was a comprehensive study of the medical birth register of the whole of Sweden, in which information had been prospectively entered since 1973, and where all pregnancies have a high degree of support, with up to nine ante-natal visits. All infants born in Sweden from 1987 to 1994 with a discharge diagnosis of infantile autism by age nine years were the cases. Controls were individually matched by sex, year and hospital of birth, with five controls per case. Controls were alive and had no diagnosis of autism at the time of case-subject diagnosis. Analysis included associations with maternal characteristics (age, smoking, place of birth), pregnancy and delivery complications (hypertension during pregnancy, diabetes, vacuum or Caesarian delivery), and infant characteristics (gestational age, birth weight, season of birth).

The mean age at first diagnosis of autism was 4.4 years for boys and 4.6 years for girls, for a case-sample of 408 children (321 boys and 87 girls). Out of many associations examined, those with a statistically significant odds ratio are shown in Table 1.

Clearly intrauterine environmental factors are playing a part in the development of autism. It seems unlikely that there will be a single cause, genetic or environmental, but adverse intrauterine and neonatal conditions are likely to result in more frequent autism in infants.

Cost of autism

A study from the Institute of Psychiatry [3] indicates that the cost of autism in Britain is of the order of £1 billion.

The authors performed systematic searches of literature, of various electronic databases, and contacted authors and experts to assemble the package of information on the disorder, its impact on individuals, families and society, and on the costs involved. At each stage of the cost calculations the evidence is outlined in detail.

Table 1: Significant associations with diagnosis of infantile autism

Maternal, delivery or infant characteristic	Odds ratio (95% CI)
Apgar below 7 at five minutes	3.2 (1.2 to 8.2)
Maternal birth outside Europe or N America	3.0 (1.7 to 5.2)
Small for gestational age	2.1 (1.1 to 3.9)
Presence of congenital malformation	1.8 (1.1 to 3.1)
Caesarean delivery	1.6 (1.1 to 2.3)
Daily smoking during pregnancy	1.4 (1.1 to 1.8)

The main results are shown in Table 2. For a person with autism and additional learning disability the average lifetime costs was £2.94 million. For someone with higher functioning autism the average lifetime cost is £785,000. With an assumed prevalence of autism of five per 10,000 and with 75% of persons with autism having additional learning disability, the annual social cost of autism in Britain is £957 million.

Autism incidence has been rising

Rising autism rates have been documented in many countries in recent decades. An example for the UK [4] comes from north east London where there was a computerised record of children with autistic spectrum disorders. Community paediatricians, special needs schools, and local child psychiatry teams were approached for additional cases. The latest review included records identified in 2000.

Diagnosis used was that made by the principal clinician, using the first mention of autism in any clinical record or letter for the date of provisional diagnosis. Records were also examined for any mention of regression, parental concern, and final diagnosis, and the dates of all these events related to immunisation with MMR.

There were 567 children with autistic spectrum disorder born between 1979 and 1998. Using a denominator of the children aged 5-14 years in the area, at the end of 2000 the prevalence of autistic spectrum disorder in children aged 5-14 was 19 per 10,000 children.

The median age of regression, parental concern and both provisional and final diagnosis were much higher in those with Asperger's syndrome than those with childhood or atypical autism (Table 3). There was some evidence of a reduction in age of diagnosis over time. Provisional diagnosis was made at 3.5 years in 1985 but 3.0 years by 1995 for childhood and atypical autism. For Asperger's syndrome, provisional diagnosis was made at 6.0 years in 1985 but 4.9 years by 1995.

In 44 of 106 children with childhood or atypical autism a specific trigger was mentioned as a possible cause. These were:

- 13: household or social change (like birth of a sibling)
- 12: vaccination (MMR in 8 of the 12)
- 7: viral or bacterial infection
- 7: seizures
- 2: after surgery
- 3: other causes

After excluding unvaccinated cases and those vaccinated when aged over 24 months, MMR was mentioned as a trigger in 6/30 (20%) after August 1997 when the MMR theory of a link with autism was first publicised, and in 2/46 (4%) before August 1997.

Table 2: Costs of autism in Britain for individuals (lifetime) and society (annual)

Cost category	Individual with learning disability (£)	Individual with higher functioning autism (£)	UK total (£ million)
Hospital services	26,600	30,700	11
Medication	3,400	8,300	2
Other health and social	71,600	31,200	25
Living support	2,134,000	312,500	669
Voluntary support	18,800	----	5
Special education	179,100	108,300	64
Sheltered work	16,200	67,800	12
Day activities	422,400	74,500	134
Lost productivity	---	137,100	14
Family members time	39,600	14,400	13
Family expenses	30,800	---	9
Total	**2,940,500**	**784,800**	**957**

Table 3: Major events

	Diagnosis		
	Childhood autism	**Atypical autism**	**Asperger's syndrome**
Number	278	195	94
Male (%)	83	81	86
Regression (%)	27	23	2
Bowel problems (%)	18	16	10
Median age (months) at:			
Regression	18	20	40
Parental concern	18	22	28
Provisional diagnosis	35	44	74
Final diagnosis	40	51	97

The trend in diagnosis flattened after about 1991 (Figure 1), at about 2.6 per 1000 live births for childhood and atypical autism.

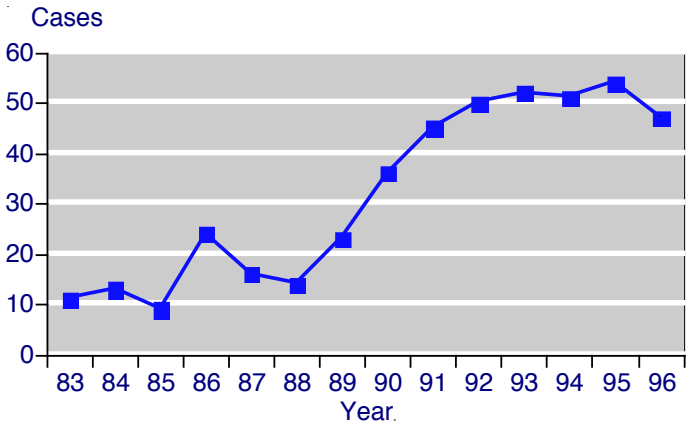
There was a levelling off in the number of autism cases during the early 1990s. Neither this, nor the previous increase was related to any change in the rate of MMR vaccination. MMR vaccination was mentioned by a small proportion of all parents (less than 2%) as a possible trigger, but that increased after the 1997 MMR scare. Age at diagnosis had decreased, suggesting changes in diagnostic practice.

Autism and MMR

Publication of a study of 12 selected children with autism and bowel disorders, and the association of these with previous MMR vaccination [5] was at the heart of the controversy linking use of the triple MMR vaccine to autism. The study itself has proved to be highly contentious, with all but one of the authors and the journal in which it was published subsequently repudiating the article and its conclusions.

Although the article itself seemed to make no connection, publicity surrounding it made the connection that because measles virus was present, and because measles virus might have come from the vaccine, and because the children had autism and bowel disorder, then the vaccine caused the problem. There is about as intelligent as saying that because the lights are on and it is dark outside, putting the lights on made it dark outside.

Figure 1: Annual cases in a population



Without dwelling on the problems of the study itself or the concerns that have been expressed over events that may or may not have surrounded it, it is worthwhile noting the features, at least in the popular and media mind, that associated MMR with autism. They included:

- Autism rates had increased flowing introduction of MMR.
- MMR vaccination led to regression; meaning that children who were developing normally regressed in their development after MMR vaccination.
- MMR vaccination caused a form of autism associated with bowel disorders.
- MMR, but not single vaccines, overwhelmed the immune system.

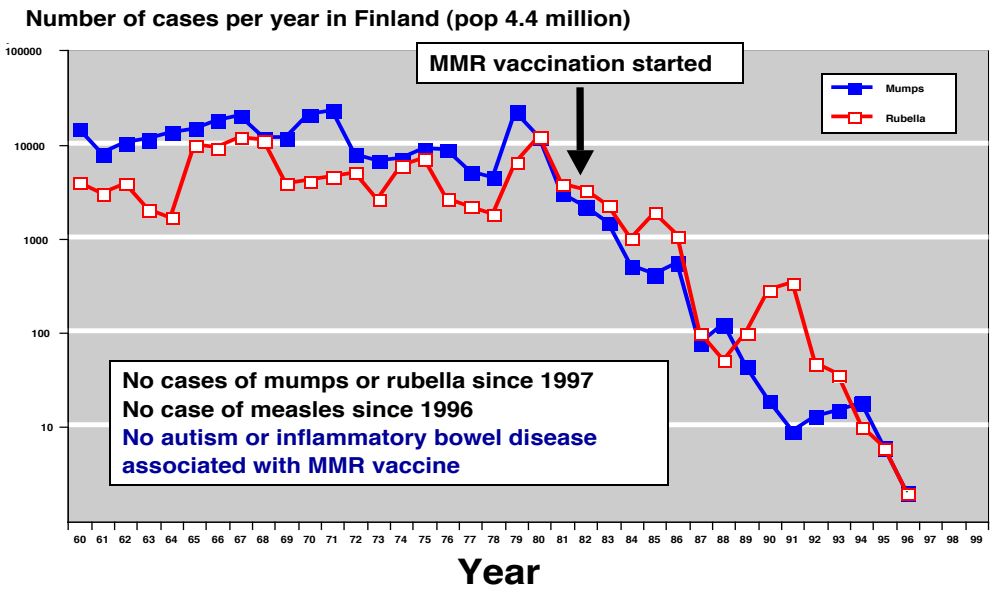
A huge amount of research of high quality and validity has been assembled subsequently, none of which supports any of these contentions.

Finnish experience

In Finland, much of the push for immunisation came from the large number of recruits or conscript soldiers who fell ill. Before immunisation more than a quarter of them had clinical mumps. A third of them had orchitis (inflammation of the testicle), a quarter of those (1 in 12 of the total) had bilateral orchitis, and a quarter of them (1 in 50 of the total) were rendered sterile. Mumps contracted during military service was a major cause of infertility in the general population, and a major cause of hearing impairment in children, as well as later deafness.

Rubella was also common, with about 1 case per 1000 people a year. Again there was an association with hearing impairment in children, and congenital rubella syndrome (CRS) was a problem. As a reminder to those of us who forget that infectious diseases are not merely inconvenient, when rubella infection occurs during pregnancy, especially during the first trimester, foetal infection is likely and often causes CRS, resulting in abortions, miscarriages, stillbirths, and severe birth defects. Up to 20% of the infants born to mothers infected during the first half of pregnancy have CRS. The most common congenital defects are cataracts, heart disease, deafness, and mental retardation.

Figure 2: Mumps and rubella in Finland after MMR



In 1982 a major effort was put into vaccinations using a triple MMR vaccine. The programme involved 1000 child health centres, catch up programmes, and military recruits. Two million people (40% of the population) received 3.5 million doses, and coverage was over 95%. A national reporting system for mumps, measles and rubella is in force, policed by the National Public Health Institute. Serological confirmation of reported cases has been a requirement since 1987.

The number of cases of measles ran at 5,000-15,000 in the decades before the introduction of a vaccination programme. Since 1985 the number of cases was tiny, and in 1996 fell to zero [6]. For mumps and rubella, the number of cases was a few thousands to a few tens of thousands a year, but fell sharply after the introduction of MMR to a few hundreds or tens (Figure 2), and since 1997 there have been no cases except cases imported from outside Finland [7].

Table 4: MMR vaccination in Finland - all potentially serious adverse events in 1.8 million people given 3 million doses of vaccine.

Event	Total number of events	Number with possible MMR association	Incidence per 100,000 doses of vaccine
Death	1	0	0.00
Allergic disorders			
Anaphylaxis	30	14	0.50
Urticaria	30	25	0.80
Asthma	10	5	0.20
Henoch-Schönlein purpura	2	1	0.03
Stevens-Johnson syndrome	1	1	0.03
Neurologic disorders			
Febrile seizure	52	28	0.90
Epilepsy	3	1	0.03
Undefined seizure	4	2	0.07
Encephalitis	4	3	0.10
Meningitis	4	0	0.00
Guillain-Barré syndrome	2	2	0.07
Transient gait disturbance	5	5	0.30
Confusion during fever	3	2	0.07
Miscellaneous			
Pneumonia	12	5	0.20
Orchitis	7	1	0.03
Diabetes	3	0	0.00

Table 5: Autism and MMR vaccination in Denmark

	Vaccinated	Unvaccinated
Total number of children	440,655	96,648
Number with autism	263	53
Percent with autism	0.06	0.055
Number with autistic spectrum disorder	345	77
Percent with autistic spectrum disorder	0.078	0.08

Harm from vaccines

Measuring the elimination of disease by using vaccination programmes is one epidemiological problem. A harder one, and where the heat is generated, comes from the epidemiological challenge of showing that the vaccines themselves cause no serious harm. Common minor and reversible harm (fever, malaise) is one facet of the problem. Rare major and irreversible harm (autism, inflammatory bowel disease) is another.

In order to tackle both in an effective way, the Finnish National Board of Health and Public Health started a long-term country-wide surveillance system to detect serious adverse events associated with MMR [8]. A series of seminars was held for public health and other involved professionals before the project started, and materials were made available in both official languages (Finnish and Swedish). There was also public information.

In the event of a possible serious adverse event (defined as any temporal association without limit of time between MMR and a life-threatening disorder, triggering of a chronic disease or hospital admission), a form was completed and forwarded to a central office with a serum sample. A second form and second sample followed two weeks later. Forms, envelopes and collection tubes were available at child health centres and hospitals.The total number of reported vaccine-associated events in 1.8 million people having 3 million vaccinations was 437. Of these, potentially serious adverse events occurred in 169 people, 79 of whom went to hospital. These 169 people were subject to serious scrutiny.

Details of all the potentially serious adverse events are shown in Table 4. About half the reported adverse events could be ascribed to other factors (like other vaccinations given with MMR) on clinical, serological and epidemiological analyses. No event had an incidence of more than 1 case per 100,000 doses of vaccine.

There were no cases of autism, and no cases of ulcerative colitis, Crohn's disease or any chronic disorder affecting the gastrointestinal tract.

California experience

A California study [9] used data from 21 regional centres covering all of California for the years 1980 to 1994. MMR immunisation rates by two years of age were about 72% before 1988 and about 82% afterwards, with the same preparation used since 1979. During this time the number of cases of autism, about 200 in 1980, increased inexorably to about 1200 by 1994. The trend for increasing autism in California persisted long after the introduction of MMR vaccination, and was not affected by a modest increase in immunisation rates in the mid 1980s.

Danish experience

A retrospective study of all children born in Denmark between January 1991 to December 1998 provided an insight into the effects of MMR vaccination in a complete population [10]. The national Danish vaccination programme recommends first MMR vaccination at 15 months and again at 12 years. In Denmark, a system of unique personal identification numbers, linked to vaccination registers and linked information about the diagnosis of autism, makes almost complete follow up possible. A record review of 40 children with autism by a consultant in child psychiatry confirmed that 92% of children met operational criteria for autism.

There were 440,655 children vaccinated, and 96,648 children who were unvaccinated. The mean age of vaccination was 17 months, and 99% of children vaccinated had their first vaccination before they were three years of age. The proportion of vaccinated boys and girls was the same, at 82%. Table 5 shows the number and percent of children who developed autism or autistic spectrum disorders.

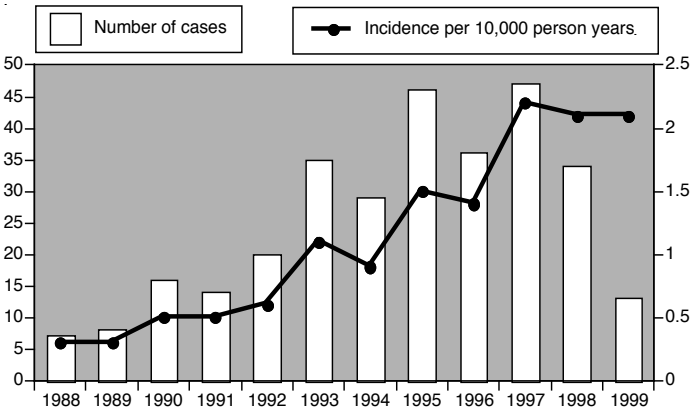
Using person-years of exposure, there was no statistically significant difference between vaccinated and unvaccinated children for autism (relative risk 0.9, 95% confidence interval 0.7 to 1.2) or autistic spectrum disorders (relative risk 0.8, 0.7 to 1.1). There was no association between development of autism and age at vaccination (95% before two years of age) or the interval between vaccination and development of autism, with no clustering at any particular time.

This study provides additional information confirming the lack of any association between MMR vaccination and development of autism. About 1 in 1,700 children developed autism and 1 in 1250 autistic spectrum disorder whether they were vaccinated or not.

British experience

A study [11] based on the UK General Practice Research Database identified 305 children (254 boys) aged 12 or younger whose diagnosis of autism was first recorded between 1988 and 1999. The peak age of first diagnosis was at years three and four, but with a substantial number being diagnosed at six years or older. The number of cases and incidence of autism increased substantially and constantly over the period (Figure 3).

Figure 3: Total number of cases of autism and incidence per 10,000 person years in UK



The study included a detailed analysis of 114 boys born in 1988-1993 who had a first recorded diagnosis of autism at ages 2-5 years. For them the four-year risk of diagnosed autism rose from 8 per 10,000 for boys born in 1988 to 29 per 10,000 for boys born in 1993 while the MMR vaccination rate was constant at about 97%.

A second study also used the UK General Practice Database [12]. It included cases of children with a first recorded pervasive developmental disorder (PDD) in the study period (1987 to 2001), and for each case planned five controls. Controls were individually matched by year of birth, sex, and general practice. Details of vaccination were extracted, together with diagnoses of autism, Asperger's syndrome, or other PDD. The date of provisional diagnosis of PDD was taken as the date of the diagnosis (because final diagnosis could take several months). Duplicate records were excluded, and practices provided anonymised data to help with characterisation of diagnosis in some cases.

There were 1,294 cases and 4,469 controls, of which 83% were male. For cases, 78% had MMR vaccination at any age, similar to the 82% for controls. For cases 70% had MMR vaccination before their third birthday and 62% before 18 months. The median age at first MMR vaccination was 1.2 years for cases and controls.

The mean age at diagnosis was 5.4 years, with 77% of diagnoses being for autism and 23% for other PDDs. The

Figure 4: Age of first diagnosis of PPD for vaccinated and unvaccinated children

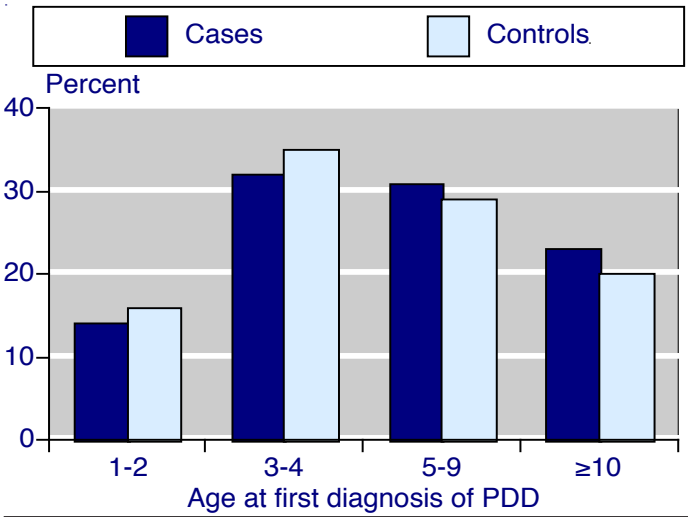
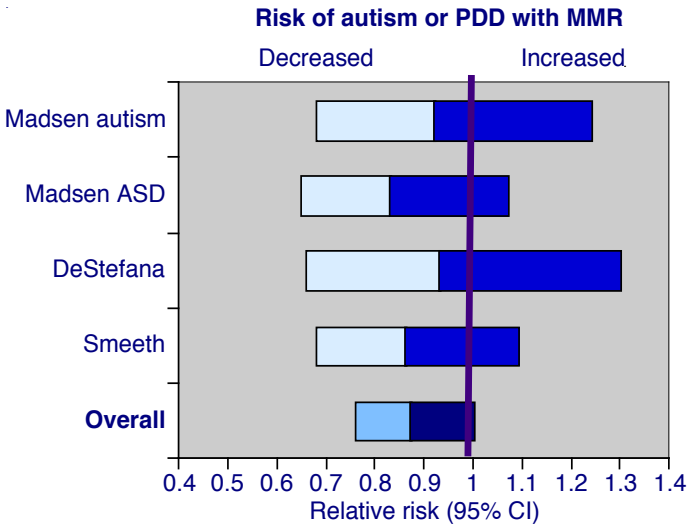


Figure 5: Meta analysis of risk of developing PDD with MMR vaccination (bars show 95% confidence interval of the relative risk, with junction between shades as the point estimate) in three studies identified by first author



age at which a PDD was diagnosed was the same in both groups (Figure 4). Most children were diagnosed after their fifth year.

The odds ratio for the association between MMR vaccination before the index date and a diagnosis of PDD was 0.73 (95% CI 0.59 to 0.91). After adjustment for age at which children joined the database it was 0.86 (0.68 to 1.09). Analyses based on age of children when first vaccinated (cut offs of three years and 18 months) produced similar results, as did separate analysis for autism and other PDDs.

Systematic review and meta-analysis

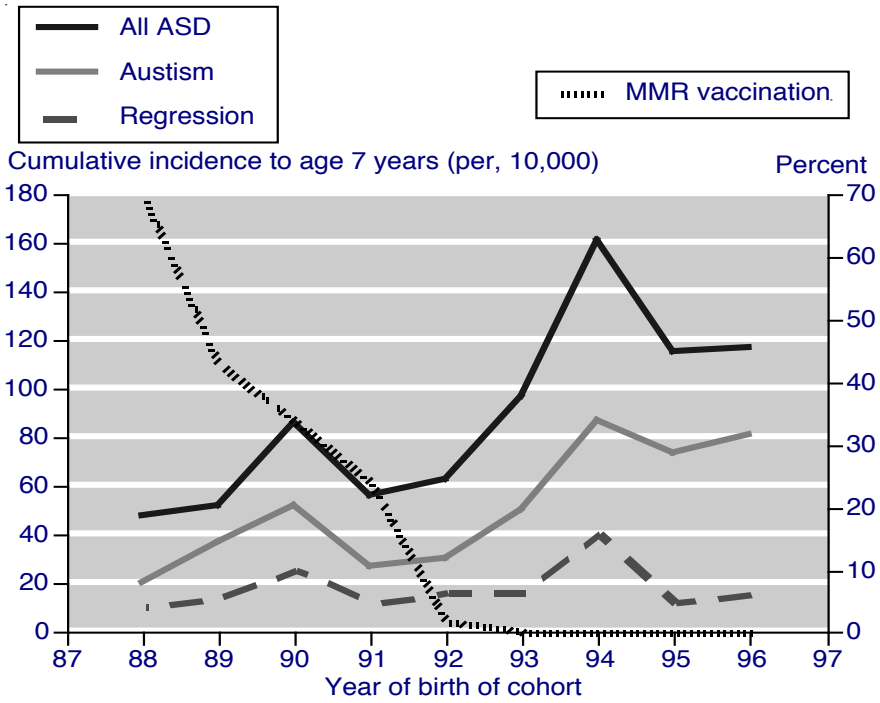
The paper also sought other studies that assessed the risk of PDD in those who had MMR vaccine and those who did not. Eligible studies were those from which an overall effect measure could be obtained. There were three such studies, including the one reported above. The previous study [11] study using the UK GP database had to be excluded because it would have used the same sample. The results (Figure 5) showed that risk of a PDD for a child having MMR vaccination was not significantly different from that from a child not having the vaccination. The combined relative risk of 0.87 (0.76 to 1.001), if anything, pointed to a lower risk with vaccination.

Japanese experience

In Japan, MMR vaccine was introduced in 1989, but the programme was terminated in 1993 and only single vaccines used thereafter. The experience of Japan therefore constitutes a real-world experiment of replacing triple MMR vaccine with single vaccines because of problems with production. If the proponents of a link between MMR and autism are correct, the result should be that cases of autism fall after withdrawal of MMR.

The study [13] was conducted in a part of Yokohama with a population of about 300,000, which was stable, or reflected

Figure 6: Autistic conditions in birth cohorts to age seven years, and MMR vaccination rate in Japan: autism, all autistic spectrum disorders (ASD), and autism with regression



changes typical for Japanese society as a whole, over the period of the study. The population was served by a special centre (Yokohama Rehabilitation Centre) that included a developmental psychiatry unit with early intervention services for developmental disorders. There was in place an early detection and intervention system that included specific routine checkups at four, 18 and 36 months, working to defined diagnostic criteria. At 18 months, about 90% of children participated in the programme, but those who did not, or those who were missed by the programme, could be referred by nurseries, paediatric clinics, or other services. These services began in 1987, two years before introduction of MMR.

The study had not only specific diagnostic criteria, but also complete and consistent coverage of a defined population over the time covering the introduction and withdrawal of triple MMR vaccine.

Over the whole period, and with full follow up to age seven years in birth cohorts from 1988 to 1996, 278 children developed autistic spectrum disorder, 158 autism, and 120 other autistic spectrum disorders. Of those with autism, 60 had definite regression and another 12 probable regression, according to defined tests. In the 1988 birth cohort, 70% of children had the MMR triple vaccine, falling to 1.8% in the 1992 birth cohort. Thereafter no children had the MMR triple vaccine (Figure 6).

The incidence of all autistic spectrum disorders, and of autism, continued to rise after MMR vaccine was discontinued. The incidence of autism was higher in children born after 1992 who were not vaccinated with MMR than in children born before 1992 who were vaccinated. The incidence of autism associated with regression was the same during the use of MMR and after it was discontinued. The increase of autistic spectrum disorders was evident in children with higher IQ.

The increase in autism and autistic spectrum disorders in this part of Yokohama displays the same increase over time seen in other parts of the world. Here, though, the increase occurred even when the MMR vaccine was withdrawn. This destroys any possible causative link between use of the vaccine and autism.

Perhaps the most important features of the study were that it comprehensively covered a population, and that the population was served by a special service testing children for developmental disorders, using standard methods over the whole period. The quality and validity of the study is superlative, and the size good.

Gastrointestinal disease and autism

Another examination of the UK General Practice Database [14] included all children born after 1987 and registered within six months of birth. Children with a diagnosis of autism in the 12 years to the end of 1999 were identified, and records obtained to demonstrate the correct diagnosis. Also identified were children with inflammatory bowel disease (ulcerative colitis, regional enteritis), chronic gastroenteritis, food intolerance and recurrent gastrointestinal symptoms at any time before the first recorded diagnosis of autism.

For each case of autism, five controls were selected, matched by birth date, sex, and doctor's practice. They were given an imaginary date of diagnosis of autism that was the same as for the case with which they were matched, and then treated in exactly the same way for ascertaining any prior gastrointestinal symptoms.

There were 211,000 children, and 96 cases of autism (crudely 1 case in every 2,200). There were 449 controls. No child had Crohn's disease or ulcerative colitis. Gastrointestinal disorders before the date of diagnosis were found in 9% of the children with autism, and 9% of the children who acted as controls. There was no statistical difference. Most of the

gastrointestinal disorders were cases of symptoms of diarrhoea, colic, or vomiting within six months of one another, or food intolerance.

The link between bowel disease and autism has been that gastrointestinal disorders were evident before the diagnosis of autism. This appears not to be true. A further claim was that first the gastrointestinal disorders, and then the autism, were caused by vaccination (either with measles vaccine, or MMR). This paper does not address that issue, but it effectively demolishes the theory on which the original claims of a link were made.

New variant of MMR-induced autism

It has been suggested by parents and others that there is a new type of autism caused specifically by the MMR vaccine. The suggested new variant is a combination of developmental regression and gastrointestinal symptoms occurring shortly after immunisation. There are three separate claims:

1. That there is a new phenotype of autism involving regression and gastrointestinal symptoms.
2. That this new variant is responsible for increases in autism rates.
3. That this new phenotype is associated with biological findings suggestive of persistent measles infection.

The first of these claims has been tested using information on three sets of children [15]. The main sample was 97 children with pervasive developmental disorders from Staffordshire born between 1992 and 1995. Autistic disorder was present in 26 children, atypical autism in 56, Asperger syndrome in 13 and childhood disintegrative disorder in one (one child with Rett syndrome was excluded). All had been vaccinated with MMR.

Two clinical samples for comparison were from the Maudsley Hospital. The first sample (MFS) included 99 patients with a diagnosis of autism and born between 1954 and 1979, and therefore not exposed to MMR. The second sample (MHC) was 68 children born between 1987 and 1996 with a confirmed diagnosis of pervasive developmental disorders, and exposed to MMR. For all three samples detailed information was available on the children, from medical notes and parents.

Age at first parental concern has not changed. There was no difference in the mean age of first parental concern in the three study samples, which was about 19 months in each sample (Table 6).

Rate of regressive autism has not increased. In two samples for which information on regressive autism was available, there was no difference in the proportion with any form of regressive autism (or definite, or probable) in children exposed or not exposed to MMR (Table 1). Parents with children with regression did not become concerned at an earlier age than parents of children without regression.

There was no association between regression and gastrointestinal symptoms. Gastrointestinal symptoms were reported for 19 children, with constipation being the most common, followed by abdominal pain, bloody stools, and diarrhoea. Bloody stools were mostly transient and associated with constipation. No child had inflammatory bowel disorder, or medical investigations for bowel syndromes. No association was found between gastrointestinal symptoms and regression. Only two children in the whole sample (2%) had both gastrointestinal symptoms and regression, lower than what could be expected by chance.

This is a lovely study from the Institute of Psychiatry. It set out to test whether there was a new variant of autism caused by MMR and associated with regression and gastrointestinal symptoms. Using three well worked up samples of children both exposed and not exposed to MMR, it could find absolutely no evidence for any effect. Indeed, one might even turn this round and say that if there was no evidence from this sample, there was no evidence at all.

The authors go on to point out that regression in autism is not a new phenomenon. In a review of the literature they demonstrate regression rates of 22% to 50% in studies between 1963 and 1998 (Table 7). The variation between studies is what might be expected by chance given the small numbers of some of the studies, but it is clear that regression occurred in children with autism long before MMR. In this study regression occurred in 18% of autistic children in a pre-MMR sample and in 16% of autistic children in a post-MMR sample.

Whatever way you look at it, there is no evidence here for any increase in regression, nor any association between gastrointestinal symptoms and regression, nor any change in the descriptions of autism before or after MMR was introduced.

Table 6: Characteristics of three samples of autistic children over time

	MFS sample	MHC sample	Stafford sample
Number of children	98	68	96
Birth period	1954-1979	1987-1996	1992-1995
MMR status	pre-MMR	Post-MMR	Post MMR
Age at first parental concern (mean, months)	19.5	19.2	19.2
Regression probable (%)	14	--	7
Regression definite (%)	4	--	8
Any regression (%)	18	--	16

Table 7: Review of studies examining regression in autism

Year of publication	Number of children	Regression definition	Regression rate (%)
1963	100	Setback in development	25
1964	14	Setback in development	50
1966	32	Setback in development including speech loss	31
1974	116	Retrogressive shift with speech disappearance	22
1985	261	Speech/gesture loss lasting over six months	37
1998 (children born before 1975)	179	Normal development followed by loss of words for minimum of three months	30

MMR and febrile seizures

MMR is generally well tolerated and associated with few adverse effects. It is, however, associated with an increased risk of febrile seizures, probably due to vaccine-induced fever. A study [16] quantified the short and long term risks.

The study population was all children born in Denmark in the years 1991-1998. As all people born in Denmark have a unique personal identity number, and because this number can be used to link national registries, it allows for the possibility of evaluating rare events in a whole population. MMR vaccination status was obtained, together with information on febrile seizures or epilepsy in patients discharged from hospital, or seen in outpatients or emergency departments.

The population studied was 540,000 children, with 1.9 million years of follow up. Of these, 440,000 (82%) had MMR vaccination. There were 17,986 children with at least one febrile seizure, of which 973 occurred within two weeks of vaccination.

The rate of first febrile seizure was higher in vaccinated than unvaccinated children, by 10% (relative risk 1.1; 95% CI 1.05 to 1.15). Febrile seizures occurred more frequently in the first and second week after MMR vaccination (relative risk 2.8; 2.6 to 3.0), but not at any time thereafter, up to five years. None of the following factors was associated with higher risk than this: siblings with febrile seizures or epilepsy, sex, birth order, gestational age at birth, birth weight, socioeconomic status or maternal levels of education. There was an additional risk in children with a previous history of febrile seizures.

Compared with children who were not vaccinated, the additional risk of febrile seizures within 14 days of MMR vaccination was one or two cases per 1,000 doses of vaccine, so the risk increased from 1 per 1,000 to 2-3 per 1,000. For children with a history of febrile seizures the additional risk was 19 per 1,000 doses, so it increased from 12 to 31 cases per 1,000.

Recurrent seizures

Compared with children who were not vaccinated, recurrent febrile seizures were very slightly increased in children who has one episode of febrile seizure within 14 days of vaccination (relative risk 1.2; 1.01 to 1.4), but there was no increased risk in those who experienced a seizure after 14 days.

Epilepsy

Compared with children who were not vaccinated, there was no increased risk of epilepsy in children who had a febrile seizure with 14 days of MMR vaccination, or in those who had a febrile seizure after 14 days.

This is an enormous study from a very important database. MMR vaccination can produce a fever, and therefore increases the risk of a febrile seizure. The absolute risk is one or two per 1,000 doses of vaccine. Children with a personal history of febrile seizures have a higher risk, of an additional 20 per 1,000 doses of vaccine. There was no association between febrile seizure and later development of epilepsy.

Vaccine preservatives not linked to autism

Thiomersal (UK spelling) or thimerosal (US spelling) is an organic compound that contains ethylmercury, and which is frequently used as a preservative in chemistry and biochemistry. It has also been used as a preservative in vaccines.

There has been concern that giving organic mercury compounds to children might adversely affect their development, because high doses of mercuric compounds affect kidneys and nerves. Methylmercury has particularly been associated with environmental contamination and major human health problems. A study that examines the relationship between use of thiomersal and autism [17] is particularly welcome if it is sufficiently large and of high enough quality to answer the question with some authority.

The study was conducted in Denmark, where, since 1968, people have had a unique identification number. This, together with the use of other specialist registries was used to construct a database of a comprehensive cohort of children born between 1990 and 1996. Information on vaccination could be linked to diagnosis of autism or autistic spectrum disorders, and potential confounders. Autism was diagnosed according to strict diagnostic criteria. All diagnoses up to the end of 2000 were recorded.

From 1970, the only thiomersal-containing vaccine used in Denmark was a whole-cell pertussis vaccine. This was used until March 1992 when the last batch was released and used. The vaccine was reformulated without thiomersal, and used until January 1997. The vaccine was administered at five weeks, nine weeks, and 10 months, irrespective of thiomersal content, and had the equivalent of 25 μg ethylmercury in the first dose and 50 μg in succeeding doses, for a maximum dose of 125 μg for each child.

This therefore constituted a population based cohort study of thiomersal use in childhood vaccination.

In the cohort were 467,450 children with just under three million person-years of follow up. There were 440 cases of autism where the mean age at diagnosis was 4.7 years and 878 cases of other autistic spectrum disorders where the mean age at diagnosis was 6.0 years. Information was lost on 5,770 children (1.2%), mainly because of emigration.

Of the cohort, 95.6% were vaccinated at least once, 89% twice, and 63% received all three doses of the whole-cell pertussis vaccine. Only 4.4% did not receive any whole-cell pertussis vaccine.

There was no association between use of thiomersal and the risk of developing autism or autistic spectrum disorder (Table 8). For neither autism nor autistic spectrum disorders was there any increased diagnosis associated with use of thiomersal-containing vaccine. Neither was there any dose-response with increasing exposure to ethylmercury. The relative risks were adjusted for a range of possible confounders, but crude rates were no higher, and even lower, in children exposed to ethylmercury compared with those not exposed.

What we have here is a superb study of what was, in effect, a real world before-after experiment. The study was huge, and comprehensive, covering almost 99% of children born in Denmark during a period during which a switch was made from use of a vaccine containing thiomersal to one that did not. It was the only vaccine given to children that did contain thiomersal. Moreover, diagnosis of autism or autistic spectrum disorder was according to strict criteria, and comprehensively applied. Follow up was for a minimum of four years, ensuring that almost all cases likely to occur should have occurred during that time.

Of course, Denmark changed to having thiomersal-free vaccines. Even with good evidence of lack of association, that is a good thing. What we have, though, is powerful evidence that autism and autistic spectrum disorders do not arise from use of thiomersal in vaccines.

Are we sure that MMR does not cause autism?

Whatever causes autism, it is not the MMR vaccine. On every single point raised to suggest some sort of link, the high quality, valid evidence, using large numbers of children, demonstrate that there is no link. The only suggestion of a link came from a discredited and flawed study.

Actually, the scientific community has reacted incredibly well to public concerns, even if those concerns were misplaced. It took the concerns seriously, and went and performed rigorous studies to rapidly demonstrate that any concerns were groundless. It may have taken some time, but that is in the nature of science. Good studies do not grow on trees, and resources are stretched at the best of times.

Table 8: Potenetial associations between use of thiomersal and autism or autistic spectrum disorders

Autism				
Vaccination	**Person-years at risk**	**Cases**	**Cases/10,000**	**Relative risk (95% CI)**
All thiomersal-free	1,660,159	303	1.8	1.0
Any containing thiomersal	1,220,006	104	0.9	0.9 (0.6 to 1.2)
Dose of thiomersal				
None	1,660,159	303	1.8	1.0
25 μg ethylmercury	169,920	18	1.1	1.0 (0.6 to 1.7)
75 μg ethylmercury	447,973	33	0.7	0.7 (0.5 to 1.1)
125 μg ethylmercury	602,113	53	0.9	1.0 (0.6 to 1.5)
Autistic spectrum disorders				
Vaccination	**Person-years at risk**	**Cases**	**Cases/10,000**	**Relative risk (95% CI)**
All thiomersal-free	1,660,159	430	2.6	1.0
Any containing thiomersal	1,220,006	321	2.6	1.1 (0.9 to 1.4)
Dose of thiomersal				
None	1,660,159	430	2.6	1.0
25 μg ethylmercury	169,920	40	2.4	1.0 (0.7 to 1.4)
75 μg ethylmercury	447,973	130	2.9	1.2 (0.9 to 1.6)
125 μg ethylmercury	602,113	151	2.5	1.1 (0.8 to 1.5)

The media has behaved less well, because it appears to have wanted to keep the rumpus going, with an approach that tried to balance one view in favour with another against. But there never was a balanced view. Right from the beginning, the overwhelming mass of scientists were aware of the flawed nature of any tentative link between MMR and autism. It was probably right for the media initially to ask the hard questions, but it was wrong not to have weighted the poor quality, validity, and size of the evidence against the link. It should also have emphasised much earlier that the balance of evidence was massively against any link between MMR triple vaccine and autism. The media failed to spot that the real issue was that we don't know what causes autism.

In June 2000, sponsored by the Centres for Disease Control and Prevention, the American Academy of Pediatrics convened a conference on "New challenges in childhood immunizations". The conference was attended by representatives from various paediatric committees, parents, practitioners and scientists, with a multidisciplinary panel of experts to review the evidence on what was known about the pathogenesis, epidemiology and genetics of autistic spectrum disorders, and what was known about the supposed link between inflammatory bowel disease, measles and MMR vaccine.

The report [18] can be downloaded from the Pediatrics website, and the URL is given below. It is 23 pages long, but worth every word. It is comprehensive and authoritative, yet humble and sensitive at the same time. Some of the results and conclusions are in Table 9. The paper looks at every aspect of autism and measles vaccination, and especially the link with MMR. The application of causality criteria is particularly useful, and there is a voluminous reference list.

In particular, it called for more and better research to understand and prevent autistic spectrum disorders and identifies areas for further study, including:

- Factors associated with autistic spectrum disorders, including genetics and environmental exposures in utero and during the first months of life.
- The nature and incidence of regression in autistic spectrum disorders.
- Epidemiological studies to determine whether there are changes in the incidence and prevalence of autism, and to identify risk factors.
- Whether measles or other viruses persist after infection or immunisation.
- Factors responsible for differences in immunologic parameters in people with autistic spectrum disorders and those unaffected.
- Whether there is evidence for previously unrecognised infectious agents affecting the central nervous system of persons with autistic spectrum disorders.

Reading and understanding this paper would greatly benefit healthcare professionals dealing with childhood vaccinations. Its language is accessible for parents as well. It may not be the easiest of reads for any of us, but all of us can benefit from it. There's also more on the CDC Internet site at http://www.cdc.gov/nip/vacsafe/concerns/autism/.

Perhaps the most important lesson from the conference is that it is less about proving the lack of a link between MMR and autism, and more about finding the cause of autism and doing something about it.

What does cause autism? There is no clear answer to that, and it is likely that there won't be one for a considerable time. A 2005 review [19] shows that autism is associated with conditions with developmental errors in early embryogenesis. Autism is possibly related to environmental factors, possibly as early as four to six weeks after conception. It makes the point that a healthy pregnancy and healthy baby need planning, and planning of the mother's health (including diet, smoking, alcohol, and medicines) from well before conception.

Table 9: Conclusions of the US conference on MMR and autism

Main results of US conference on MMR and autism
Autism is a complex disorder of uncertain and probably multiple aetiologies.
Abnormal brain development in autism may occur before 30 weeks' gestation.
In utero, rubella is a known cause of autism.
Animal data support the biological plausibility that exposure to unrecognised infectious or environmental agents could cause autistic spectrum disorders.
Increased reporting of autistic spectrum disorders occurred long after the introduction of widespread use of MMR vaccine in the USA in 1971.
Some children with autistic spectrum disorders have gastrointestinal symptoms, but an increased rate has not been established.
Separate administration of measles mumps and rubella vaccines provides no benefit over MMR and would result in delayed or missed immunisations.
Continued scientific efforts need to be directed to the identification of causes of autistic spectrum disorders.

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