

# Vaccines and the changing epidemiology of autism

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## Abstract

**Background** The epidemiology of autism has been rather confusing, with very variable published prevalence figures and no clear incidence data. The cause of autism is unclear; vaccines have been incriminated.

**Methods** Literature review and interpretation.

**Results** The recorded prevalence of autism has increased considerably in recent years. This reflects greater recognition, with changes in diagnostic practice associated with more trained diagnosticians; broadening of diagnostic criteria to include a spectrum of disorder; a greater willingness by parents and educationalists to accept the label (in part because of entitlement to services); and better recording systems, among other factors. The cause(s) of autism remains unclear. There is a strong genetic component which, along with prenatally determined neuro-anatomical/biochemical changes, makes any post-natal 'cause' unlikely.

**Conclusions** There has (probably) been no real increase in the incidence of autism. There is no scientific evidence that the measles, mumps and rubella (MMR) vaccine or the mercury preservative used in some vaccines plays any part in the aetiology or triggering of autism, even in a subgroup of children with the condition.

## Keywords

autism, epidemiology, immunization, pervasive developmental disorders, prevalence data

## Introduction

The epidemiology of autism is difficult. Over the years, diagnostic criteria have changed and broadened to encompass a spectrum of autistic disorder including many children with normal or near-normal intelligence. Some diagnostic transference from other conditions to autism has occurred. Service provision has improved, in part stimulated by new legislation: this has increased professional and parental acceptance of the label 'autism'.

A broad summary of the epidemiology suggests that across the autistic spectrum, men are affected more frequently than women – about 4:1 (but less so where there is severe cognitive impairments, and

increasing to 10 : 1 in some surveys for Asperger's syndrome); there are learning difficulties (mental retardation) in about 70% of cases; and rarely (no more than 5% or 6%), autism is associated with medical conditions such as tuberose sclerosis or fragile X syndrome.

Epidemiological surveys in autism have been of varying quality and type, especially regarding case definitions and case finding, so comparisons are difficult. The terms used vary (including autism, core autism, childhood autism, atypical autism, autistic spectrum disorder, autistic condition, pervasive developmental disorder – not otherwise specified, high functioning autism and Asperger's syndrome). Different age groups have been

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assessed, which is likely to affect the completeness and adequacy of ascertainment (at younger ages the condition might not yet be recognized and diagnostic tools are less reliable; in adolescents, manifestations change and involvement with services may decline. The preferred age for study is between 6 and 12 years).

Early epidemiological studies suggested a prevalence of 4–10 affected individuals per 10 000 children; recent population-based surveys, however, have shown a much higher prevalence, 40–60 cases per 10 000 children (Fombonne 1998, 2003). Valid estimates require a defined total population of large enough size to identify sufficient cases for close confidence intervals, systematic standardized screening of the mid-childhood section of that population, with diagnosis confirmed using quality assessments.

### Prevalence vs. incidence

There has been much publicity about the increased prevalence of autism recorded in the past 20 or 30 years. However, there is little evidence that the incidence of autism has increased over this period. Prevalence reflects the number of individuals in a given population who have a 'defined' disorder – being a function of disease incidence, disease ascertainment, disease duration and population dynamics. The prevalence of autism will also be affected by changing diagnostic fashions, changing diagnostic criteria and other influences such as more trained diagnosticians, a willingness to accept a particular diagnosis, earlier age at diagnosis, and better recording systems.

Incidence on the other hand is the number of new cases of the condition occurring in a population over a defined period of time (often 1 year). Incidence may provide clues to causation. Prevalence is unlikely to do so although it is useful to estimate needs and plan services. Most prevalence studies are based on administrative registers. Large increases have been documented; for example, the California Department of Developmental Services reports (1999, 2003) have shown a marked increase in recorded cases of autism since the early 1980s. Such registers have marked limitations for epidemiological studies including: not having a clear

denominator, i.e. only giving numbers of cases, not rates for a population (population numbers, and sub-populations, e.g. children, within a total population, can vary markedly over time); not adjusting for diagnostic changes; not adjusting for age characteristics; not adjusting for age at diagnosis; and increases may not be specific to autism.

### Different populations, different rates of autism

Comparison of children with autism in the periods 1983–1985 and 1993–1995 using California register data (MIND study 2002) showed an unexplained halving of the rate of associated mental retardation in the autism groups. Response rates in the study were very low, especially in the mental retardation control group. The 1983–1985 population was thus a different population of children with autism compared with the 1993–1995 cohort. Diagnostic procedures for determining special educational disability such as autism, are not standardized even within districts, much less wider areas, nor have they been uniform over time.

### Diagnostic transfer: not a major reason for the increased prevalence

Changes in diagnostic practice have been suggested as a reason for the recorded increased rates of autism. Croen and colleagues (2002) studied the same Californian population and documented an increase in the number of children diagnosed with autism and a decrease in the number of children diagnosed with mental retardation. This suggested a change in diagnosis from mental retardation to autism, although the effect may not be as large as originally suggested (Croen *et al.* 2003). Jick and Kaye (2003) used the UK General Practice Research database to assess changes in the diagnosis of autism compared with developmental disorder where autism was not mentioned (including speech and language developmental delay, other delays in development and other specific learning difficulties); the recorded incidence of autism by year of birth increased over the period of study. There was a corresponding decrease in other developmental disorders. This also suggested some diagnostic substitution.

### Changes in definitions and entitlement to services

Diagnostic transfer is not the major explanation for the increased prevalence of autism. Diagnostic substitution did not explain the marked increase seen in Minnesota (Gurney *et al.* 2003). The US disability category classifications were compared for US cohorts from 1975 to 1995; no matching decreases were seen for mental retardation or speech/language impairment to explain the marked increase in the prevalence of autism. This increase was higher for the younger than older cohorts, but the rate of increase was lessening for the most recent. A recent levelling of previously rising autism prevalence has also been reported in London (Lingam *et al.* 2003).

### Previous under-diagnosis of autism

The recent increase in autism might just reflect under-diagnosis in the past. There have been new requirements and improved funding/services which would encourage diagnosis. In the USA, states must report children receiving special educational services; autistic spectrum disorder was introduced as a disability category in the special education laws in 1991; all federal funding especially for children was consolidated under the Individuals Education Act from 1994. Other factors contributing to an increased rate of diagnosis were the introduction of revised diagnostic criteria – Diagnostic and Statistical Manual (DSM) 111-R in 1987 and DMS-1 V in 1994. These Minnesota researchers also documented a marked increase in the number of educational staff trained to use autism diagnostic tools and so ascertain more cases in their area. They considered that these factors taken together would easily explain a substantial underestimate of autism in the past. Autism prevalence in the UK may have been seriously underestimated in the early 1970s (Heussler *et al.* 2001).

### Is the incidence of autism increasing?

Time trends, comparing prevalence rates over time, have been used as a proxy for changes in

incidence. As outlined above, time trends can be misleading.

Five approaches to investigate possible changes in incidence have been described (Fombonne 2003). These have proved of varying effectiveness:

#### 1. Repeat surveys in defined geographical areas

A circumscribed population in Staffordshire, the UK, has been studied and restudied using the same methodology, which included standardized health professional screening, a second-stage review by a developmental paediatrician, then multidisciplinary assessment which included the Autism Diagnostic Interview. Childhood autism prevalence for children born 1992–1995 was found to be 16.8 per 10 000 children; with total autistic spectrum disorder, 62.6 per 10 000 (Chakrabarti & Fombonne 2001). The repeat study showed 22 per 10 000 with childhood autism and a total pervasive developmental disorder rate of 58.7 per 10 000 (Chakrabarti & Fombonne 2005). These studies strongly suggest that the incidence of autism has not increased. Other evidence suggesting that there has been no real increase in the incidence of autism was the demonstration in repeat studies of a levelling in the rate of autism from 1992 in north-east London – where previously prevalence rates had been rising (Lingam *et al.* 2003). Earlier repeat studies, e.g. in Sweden (Gillberg 1984; Gillberg *et al.* 1991), demonstrated an increase from 4 cases per 10 000 in 1980 to 6.6 in 1984 to 9.5 in 1988. These changes were thought not to be a real increase but to reflect service developments and broadening of definitions.

#### 2. Incidence studies

There have been so far no completely satisfactory studies because of changing criteria and definitions; the Staffordshire studies outlined above come closest, but their numbers were small.

#### 3. Successive birth cohorts

Fombonne reported autism in successive birth cohorts across France. Rates of autism remained steady over the years 1972, 1976, 1981 and 1991 at

5.1, 4.1, 3.1, and 5.4 cases per 10 000 (Fombonne 2003).

#### 4. Comparison of cross-sectional epidemiological surveys

Comparing different rates from different studies each with unique design features has not proved a sound basis to determine time trends or changes in the incidence because of methodological differences. Wide variations were reported in different prevalence studies undertaken in the UK over the period 1999–2001 (ranging from 10.1 to 62.6 cases of pervasive developmental disorder per 10 000 population). Over the same period, rates reported in US studies also varied widely, from 4.8 to 67.0 (Fombonne 2003).

#### 5. Referral statistics

These include reports like those from California, with varying referral patterns and varying availability of services, as well as changes in diagnostic concepts, diagnostic practice and population changes over time. These factors, together with associated increased public and professional awareness of the condition, make comparisons using such data meaningless for incidence determination.

#### Causes of autism

Autism has a high genetic loading: there is high concordance in identical twins and an increased risk for sibs; with a family loading for affective disorder. There is an extended phenotype in the families – with subtle social and language defects, and circumscribed interests. However, the genetic details have proved heterogeneous and polygenic. A large number of candidate genes are being investigated.

Autism is also a biological disorder, associated with a number of medical conditions. Changes have been described in the brains of some children with autism that could only have occurred during the first 3 months of pregnancy. Inflammatory changes in the blood have been demonstrated at birth in children subsequently diagnosed with

autism or other pervasive developmental problems, but not in children subsequently diagnosed with cerebral palsy or controls (using neonatal blood spots: Nelson *et al.* 2001). There is an IQ-related increased risk of epilepsy, and increased head size has been described in some (but not all) studies. Some imaging studies have shown a probable increase in white matter and a possible myelin abnormality together with other abnormalities from the early embryogenic stage of development.

Despite this strong evidence of prenatal abnormality, various post-natal environmental agents, such as vaccines, have been incriminated as causes of autism, postulated as mediated through dysfunction of the immune system and/or interacting with a genetic susceptibility at a critical phase of development. However, no definite post-natal causes have been identified.

#### Vaccines and autism

Falsehood flies and the truth comes limping after; so when men come to be undeceived, it is too late: the jest is over and the tale has had its effect. (Jonathan Swift, *The Examiner* 1711)

Immunization and vaccination against infectious diseases has been one of the great success stories, perhaps the greatest, in modern medicine. However, because immunization and vaccination has succeeded, people have forgotten the diseases, side effects from vaccines loom larger, and cranks get more of a hearing.

Most concern about the possible role of vaccines in autism has concentrated on MMR vaccine (against measles, mumps and rubella) and on thiomersal – the mercury-based preservative used in some vaccines. The main celebrity in the MMR/autism controversy is Andrew Wakefield. He was the first author of a paper with the unprepossessing title ‘Ileal-lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children’ published in *The Lancet* in February 1998 (Wakefield *et al.* 1998), which reported 12 children who had autistic spectrum disorder and bowel symptoms. In eight of cases, the parents or

the child's physician associated MMR vaccination with the onset of behavioural symptoms, after a mean interval of 6.3 days (range 1–14). This paper was seized on by the media and various pressure groups, creating a furore that led to a calamitous fall in MMR vaccine uptake in the UK – from more than 90% nationally in 1995 to 70% in some parts of the country 6 years later. There has been an unwelcome return of mumps, outbreaks of measles and the likelihood of epidemics of these conditions, together with a return of congenital rubella.

*The Lancet* case-series was a highly biased sample (referrals to a tertiary paediatric gastroenterology unit), and there were no controls and no case validation. The quality of *The Lancet* paper, and other output from the research group, has been widely criticized, being described by the Chief Medical Officer of the UK as poor science. The reported associations have not been confirmed by anyone, anywhere in the world.

Subsequently, various other concerns about the study have emerged – described in detail by an investigative journalist, Brian Deer (see <http://www.briandeer.com>). Most of the children in the study were litigants against MMR vaccine manufacturers. The research leading to *The Lancet* paper was at least partly funded by the Legal Aid Board (now the Legal Services Commission), which subsequently taking into account this prestige publication in *The Lancet*, authorized large amounts of further research funding. More than £15 000 000 of taxpayers' money (including at least £5 000 000 to the MMR lawyers) was spent. Funding was withdrawn in 2003; the Legal Services Commission commented then '... this was the first case in which research had been funded by legal aid. In retrospect, it was not effective or appropriate for the LSC to fund research. The courts are not the place to prove new medical truths'. Ten of the 13 original authors have retracted the implication in the paper that MMR vaccine might cause autism (Murch *et al.* 2004).

### Evolution of a hypothesis

The hypothesis that MMR might cause autism 'evolved' as other studies that refuted the initial hypothesis were published. Evolution included: the

possibility that MMR might only cause autism if co-factors are present; or following the administration of antibiotics, or if given during intercurrent infections; or if there was a personal history of atopy or a family history of autoimmunity; or if the mother had received MMR or rubella vaccination shortly before, during or after pregnancy; and/or that the child might already be sensitized by early exposure to thiomersal from vaccines given during the first year of life (Wakefield 2000). This expanded hypothesis, which covered a high proportion of the child population, meant that there was no necessary correspondence between the MMR injection and the onset of autism, which could occur anytime afterwards.

### Initial 'evidence' cited implicating MMR as the cause of autism (and refutation)

- 1 *Parental testimonies* described the onset of 'regressive autism' in previously normal children shortly after MMR. [Some parents, however, are now seeking compensation for cases with onset years after MMR. Parents are usually very reliable historians regarding their child's early life. Sometimes, however, there is the possibility of recall bias, in some instances reflecting changing beliefs about causal relationships. An expert group convened by the Medicines Control Agency (Committee on Safety of Medicines 1999) reviewed the records of 92 children with autism whose parents thought that MMR had caused or triggered their child's condition. In 36 (39%) of these children, there was evidence in the medical record that there had been concerns about the child's behaviour before the MMR vaccination. However, in only 1 (1%) of these cases did the parent recall this early concern.]
- 2 The (apparent) *rise in autism* in the UK and California which coincided with the introduction of MMR vaccine (Wakefield 1999). (Time-event associations are notoriously unlikely to reflect cause-effect relationships, and Wakefield has disassociated himself from this 'evidence'.)
- 3 *Onset of 'new autistic enterocolitis'* syndrome shortly after MMR. [Now, however, 'any' induction interval is thought possible. The postulated

but heavily disputed bowel problem, autistic enterocolitis, has been a central plank of the MMR-causes-autism belief. It is hypothesized that MMR vaccine damages the bowel; this allows dietary 'opioid peptides' to leak into the system, which leads to brain damage, regression of development and autism. However, this leaky bowel hypothesis is not plausible (Gershon 2002); if the gut leaks opioid peptides as a result of persistent measles infection, then leakage would occur both ways, but protein-losing enteropathy is not a feature of 'autistic enterocolitis'. As well, liver metabolism would remove peptides, which cannot penetrate the blood-brain barrier, and there is no evidence for the existence of 'opioid peptides' anyway.]

### Other evidence against a causal relationship between MMR vaccine and autism

- 1 *Population studies* from Sweden (Gillberg & Heijbel 1998), the UK (Taylor *et al.* 1999; Farrington *et al.* 2001; Kaye *et al.* 2001; Smeeth *et al.* 2004), Finland (Peltola *et al.* 1998), the USA (Dale *et al.* 2001) and Denmark (Madsen *et al.* 2002) have shown no relationship. Critics of these epidemiological studies have suggested that there could still be subgroups 'at-risk' where there was a real link between MMR and autism/bowel conditions. It is impossible to prove a negative in science; however, the multiple epidemiological studies have been individually robust and collectively completely consistent. Application of the 'rule of three' (Eypasch *et al.* 1995) suggests that if there is any direct relationship between MMR and autism, it could not occur more frequently than 3 cases per 1 million vaccinations. Thus MMR could not be the cause of any 'epidemic' of autism. MMR vaccine was withdrawn in Japan from the early 1990s because of concern about the mumps component; recorded prevalence of autism continued to rise – MMR could not be responsible (Honda *et al.* 2005). Recorded cases of autism rose in the UK from 1959, while measles infections fell; no step changes were seen in the increasing rates of autism when measles vaccine was introduced, then MMR, or when the Urabe strain of mumps was removed from the vaccine.
- 2 *Observational studies*: No increase was seen in visits to British general practitioners by children subsequently diagnosed with autism compared with controls, in periods of 2 and 6 months after MMR vaccination.
- 3 *No evidence for 'new variant' autism* – a postulated but unconfirmed condition following MMR vaccination and associated with regression of development and bowel problems. The Wakefield hypothesis (including the evolved versions) absolutely requires that there should be an increase of regression and bowel problems in children with autism after MMR vaccination. MMR was introduced to the UK in October 1988. There was no associated increase in bowel problems or regression among children with autism (Fombonne & Chakrabarti 2001; Taylor *et al.* 2002). Regression of development has been a recognized feature of autism since first description, reported in 20–40% of cases. No increase has been seen in recent cohorts.
- 4 *No 'autistic enterocolitis'*: A possible specific bowel problem has been described in autism, but this remains controversial. Measles particles have been reported in samples taken from some children with putative autistic enterocolitis. However, the techniques used are unreliable, and comparator controls have been inadequate. Even if measles particles were present, they might be a normal finding. These studies need validation and independent replication.

### Thiomersal

The mercury preservative in vaccine has been hypothesized as causing or 'priming' for autism and related developmental disorders. If this were the case, it would be expected that higher doses given earlier would cause more problems, and that infants born preterm – smaller and exposed to a higher dose comparatively early – would be most at risk. No such relationship has been found in prospective or retrospective UK studies (Andrews *et al.* 2004; Heron *et al.* 2004). A systematic review

(Parker *et al.* 2004) of 10 epidemiological and two pharmacokinetic papers concluded that the studies did not demonstrate a link between thiomersal-containing vaccines and autistic spectrum disorder, and the pharmacokinetics of ethyl-mercury make such an association less likely. They observed that those epidemiologic studies that purported to demonstrate a link had significant design flaws that invalidated their conclusions. The US Institute of Medicine (McCormick *et al.* 2004) has also recently reviewed and rejected any causal relationship between MMR vaccine and autism, and between thiomersal-containing vaccines and autism.

### Lessons to be learned from the MMR–autism scare

There are various general concerns regarding MMR–autism and other vaccine scares.

These include:

#### 1. Robust vs. junk science

Strict adherence to the scientific method and robust methodology must underpin investigations/reports, especially those that might adversely affect the public health.

#### 2. Medical journalism and the peer review process

*The Lancet*, which published the original early report, has been criticized for doing so. The editor has robustly defended his decision, but concerns remain about the appropriateness of a major journal giving credence through publication to a hypothesis with such limited scientific underpinning. Blame might also be attributed to the choice of paper's reviewers, who apparently were all gastroenterologists with no paediatric, public health, epidemiological or vaccine expertise.

#### 3. The role of the media

Media frenzy certainly contributed to public concern and decreased MMR uptake. There is evidence

of a co-ordinated anti-MMR campaign among some sections of the press. Some newspapers and magazines could be considered a toxic influence on autism and on vaccine uptake. Coverage of the controversy has been disproportionately anti-vaccine. This is not too surprising. Journalists and editors want a good story; they often do not care about the public health. Only bad news is good news. Good news is no news.

#### 4. The legal profession

'Ambulance-chasing' lawyers have been criticized for falsely raising families the hopes of finding a 'reason' for their child's condition, but mainly making them feel guilty for allowing their child to be vaccinated.

#### 5. Information

The need for reliable information is made difficult by the plethora of opinion and often actively misleading statements on the Internet. The public's low esteem of politicians and 'government' has not helped, with (inappropriate) comparisons made between MMR–autism and 'mad cow disease'. Some members of the medical profession, often financially motivated, have supported single-dose vaccination (separate measles, mumps and rubella injections) under the spurious banner of patient choice (but what child would choose six injections when he/she would be better protected with two?) There has been widespread uncertainty regarding the exact science – particularly when the media insist on providing a 'balanced' view, giving at least equal space/time to anti-vaccinationists, even though more than 99% of informed medical and health-related professionals fully support the MMR vaccination.

#### Final comment

All is not gloom. The raised profile of autism resulting from the vaccine scares has benefited many children with autism and their families; better services are now being provided, and money is being spent on autism research, including more definitive epidemiological studies.

## References

- Andrews, N., Miller, E., Grant, A., Stowe, J., Osborne, V. & Taylor, B. (2004) Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association. *Pediatrics*, **114**, 584–591.
- Chakrabarti, S. & Fombonne, E. (2001) Pervasive developmental disorders in preschool children. *Journal of the American Medical Association*, **285**, 3093–3099.
- Chakrabarti, S. & Fombonne, E. (2005) Pervasive developmental disorders in preschool children: confirmation of high prevalence. *American Journal of Psychiatry*, **162**, 1133–1141.
- Committee on Safety of Medicines (1999) Report of the Working Party on MMR Vaccine. *Current Problems in Pharmacovigilance*, **25**, 9–10. Available at: <http://www.mca.gov.uk/ourwork/monitorsafequalmed/currentproblems/volume25jun.htm> (checked August 2005).
- Croen, L. A. & Grether, J. K. (2003) Response: a response to Blaxill, Baskin, and Spitzer on Croen *et al.* 2002 'The changing prevalence of autism in California'. *Journal of Autism and Developmental Disorders*, **33**, 227–229.
- Croen, L. A., Grether, J. K., Hoogstrate, J. & Selvin, S. (2002) The changing prevalence of autism in California. *Journal of Autism and Developmental Disorders*, **32**, 207–215.
- Dales, L., Hammer, S. J. & Smith, N. J. (2001) Time trends in autism and in MMR immunization coverage in California. *Journal of the American Medical Association*, **285**, 1183–1185.
- Department of Developmental Services (1999) *Changes in Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998: A Report to the Legislature March 1, 1999*. California Health and Human Services Agency, Sacramento, CA, USA.
- Department of Developmental Services (2003) *Autism Spectrum Disorders: Changes in the California Caseload an Update: 1999 through 2002*. Department of Developmental Services, California Health and Human Services Agency, Sacramento, CA, USA.
- Eypasch, E., Lefering, R., Kum, C. K. & Troidl, H. (1995) Probability of adverse events that have not yet occurred: a statistical reminder. *British Medical Journal*, **311**, 619–620.
- Farrington, C. P., Miller, E. & Taylor, B. (2001) MMR and autism: further evidence against a causal association. *Vaccine*, **19**, 3632–3635.
- Fombonne, E. (1998) The epidemiology of autism: a review. *Psychological Medicine*, **29**, 769–786.
- Fombonne, E. (2003) Epidemiological surveys of autism and other pervasive developmental disorders: an update. *Journal of Autism and Developmental Disorders*, **33**, 365–382.
- Fombonne, E. & Chakrabarti, S. (2001) No evidence for a new variant of measles-mumps-rubella-induced autism. *Pediatrics*, **108**, e58.
- Gershon, M. (2002) Autism and the measles-mumps-rubella (MMR) vaccine. *Revisiónes Vacunas*, **2**, 156–157.
- Gillberg, C. (1984) Infantile autism and other childhood psychoses in a Swedish urban region: epidemiological aspects. *Journal of Child Psychological Psychiatry*, **25**, 35–43.
- Gillberg, C. & Hejbel, H. (1998) MMR and autism. *Autism*, **2**, 423–424.
- Gillberg, C., Steffenburg, S. & Schaumann, H. (1991) Is autism more common now than ten years ago? *British Journal of Psychiatry*, **158**, 403–409.
- Gurney, J. G., Fritz, M. S., Ness, K. K., Sievers, P., Newschaffer, C. J. & Shapiro, E. G. (2003) Analysis of prevalence trends of autism spectrum disorder in Minnesota. *Archives of Pediatrics and Adolescent Medicine*, **157**, 622–627.
- Heron, J., Golding, J. & ALSPAC Study Team (2004) Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United Kingdom does not support a causal association. *Pediatrics*, **114**, 577–583.
- Heussler, H., Polnay, L., Marder, E., Standen, P., Lyn, U. C. & Butler, N. (2001) Prevalence of autism in early 1970s may have been underestimated [Letter]. *British Medical Journal*, **323**, 633.
- Honda, H., Shimizu, Y. & Rutter, M. (2005) No effect of MMR withdrawal on the incidence of autism: a total population study. *Journal of Child Psychology and Psychiatry*, **46**, 572–579.
- Jick, H. & Kaye, J. H. (2003) Epidemiology and possible causes of autism. *Pharmacotherapy*, **23**, 1524–1530.
- Kaye, J. A., Melero-Montes, M. & Jick, H. (2001) Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *British Medical Journal*, **322**, 460–463.
- Lingam, R., Simmons, A., Andrews, N., Miller, E., Stowe, J. & Taylor, B. (2003) Prevalence of autism and parentally reported triggers in a North East London population. *Archives of Disease in Childhood*, **88**, 666–670.
- McCormick, M., Bayer, R., Berg, A. *et al.* (2004) *Report of the Institute of Medicine. Immunization Safety Review: Vaccines and Autism*. National Academy Press, Washington, DC, USA.
- Madsen, K. M., Hviid, A., Vestergaard, M., Schendel, D., Wohlfahrt, J., Thorsen, P., Olsen, J. & Melbye, M. (2002) A population-based study of measles, mumps, and rubella vaccination and autism. *New England Journal of Medicine*, **347**, 1477–1482.

- MIND Institute (2002) *The Epidemiology of Autism in California: Report to the Legislature on the Principal Findings from the Epidemiology of Autism in California: A Comprehensive Pilot Study*. University of California, Davis, CA, USA.
- Murch, S. M., Anthony, A., Casson, D. M., Malik, M., Berelowitz, M., Dhillon, A. P., Thomson, M. A., Harvey, P., Valentine, A., Davies, S. E. & Walker-Smith, J. A. (2004) Retraction of an interpretation. *Lancet*, **363**, 75.
- Nelson, K. B., Grether, J. K., Croen, L. A., Dambrosia, J. M., Dickens, B. F., Jelliffe, L. L., Hansen, R. L. & Phillips, T. M. (2001) Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. *Annals of Neurology*, **49**, 597–606.
- Parker, S. K., Schwartz, B., Todd, J. & Pickering, L. K. (2004) Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics*, **114**, 793–804.
- Peltola, H., Patja, H., Leinikki, P., Valle, M., Davidkin, I. & Paunio, M. (1998) No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. *Lancet*, **351**, 1327–1328.
- Smeeth, L., Cook, C., Fombonne, E., Heavey, L., Rodrigues, L. C., Smith, P. G. & Hall, A. J. (2004) MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet*, **364**, 963–969.
- Taylor, B., Miller, E., Farrington, C. P., Petropoulos, M.-C., Favot-Mayaud, I., Li, J. & Waight, P. A. (1999) Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet*, **353**, 2026–2029.
- Taylor, B., Miller, E., Lingam, R., Andrews, N., Simmons, A. & Stowe, J. (2002) Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. *British Medical Journal*, **324**, 393–396.
- Wakefield, A. J. (1999) MMR vaccination and autism. *Lancet*, **354**, 949–950.
- Wakefield, A. J. (2000) *Testimony before Congressional Oversight Committee on Autism and Immunization*. 106th Congress of the United States of America, House of Representatives Committee on Government Reform.
- Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., Berelowitz, M., Dhillon, A. P., Thomson, M. A., Harvey, P., Valentine, A., Davies, S. E. & Walker-Smith, J. A. (1998) Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*, **351**, 637–641.