

MMR vaccination and pervasive developmental disorders: a case-control study

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Summary

Background Concern that measles-mumps-rubella (MMR) vaccination might cause autism has led to a fall in vaccine coverage. We investigated whether MMR vaccination is associated with an increased risk of autism or other pervasive developmental disorders.

Methods We did a matched case-control study using the UK General Practice Research Database. Cases were people born in 1973 or later who had first recorded diagnosis of pervasive developmental disorder while registered with a contributing general practice between 1987 and 2001. Controls were matched on age, sex, and general practice.

Findings 1294 cases and 4469 controls were included. 1010 cases (78·1%) had MMR vaccination recorded before diagnosis, compared with 3671 controls (82·1%) before the age at which their matched case was diagnosed. After adjustment for age at joining the database, the odds ratio for association between MMR and pervasive developmental disorder was 0·86 (95% CI 0·68–1·09). Findings were similar when restricted to children with a diagnosis of autism, to those vaccinated with MMR before the third birthday, or to the period before media coverage of the hypothesis linking MMR with autism.

Interpretation Our findings suggest that MMR vaccination is not associated with an increased risk of pervasive developmental disorders.

Introduction

In 1998, it was suggested that measles-mumps-rubella (MMR) vaccination might cause autism, on the basis of a study of 12 children with pervasive developmental disorder referred to a paediatric gastroenterology unit, with no comparison group.¹ In a subsequent larger case series, the condition postulated to be associated with MMR vaccination was referred to as autistic enterocolitis.² These studies, and the findings of gut epithelial damage in children with autism,³ led the researchers to suggest that MMR vaccination could act as a trigger for a particular phenotype of autism.⁴ Fragments of measles virus genome were reported in the intestinal tissue of children with autism and associated gut disease more frequently than in a comparison group of children, some of whom had gut disease but all of whom were developmentally normal.⁵ The origin of the fragments of measles virus genome in these children has not been established. Furthermore, whether the presence of the fragments was specific to this subgroup of children, or whether they were due to intestinal disease rather than a cause of it, is unknown.⁶

Subsequent epidemiological studies did not confirm an association between MMR vaccination and autism,^{7–9} but these findings failed to reassure the public.^{10–12} The coverage of MMR vaccine by the age of 2 years in England fell from 92% in 1995–96 to 82% in 2002–03,¹³ and was followed by measles outbreaks.^{14,15} In the light of continuing concern, we did a large case-control study to assess the risk of autism and other pervasive developmental disorders (PDDs) associated

with MMR vaccination, by use of the UK General Practice Research Database (GPRD).

Methods

The study methods have been described in detail elsewhere.¹⁶ In brief, we did a case-control study to investigate whether MMR vaccination was associated with an increased risk of autism or other PDDs. Data were abstracted from the GPRD, a database that includes patients' records of vaccination and diagnoses of autism or other PDDs. The GPRD was set up in 1987, under the name of VAMP (Value Added Medical Products) Research Bank.¹⁷ The database consists of the electronic clinical records of patients registered with contributing general practices. The practices are broadly representative of all practices in England and Wales in terms of geographical distribution, practice size, and the age and sex of registered patients.¹⁸ The GPRD aims to include complete prescribing and diagnostic information for every registered patient. Data are anonymised. The quality of the information in the database has been found to be high in independent validation studies.¹⁷ Two studies have assessed the completeness of recording of diagnoses made in medical facilities outside the practice, and found recording rates in excess of 90%.^{19,20} There is excellent agreement between prescribing data from the GPRD and national data from the Prescription Pricing Authority.²¹ For patients who were not registered with a practice in the GPRD from birth, information on previous vaccinations and diagnoses should be entered into their electronic record when they transfer into the practice. The number

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of practices included in the GPRD varied during the study period, rising from 34 in 1988 to 557 in 1996, then falling to 380 by 2001.

Study population

The study population consisted of all people who were registered in the GPRD at any time between June 1, 1987 (when the database was started), and Dec 31, 2001, and who were born in 1973 or later, to ensure that virtually all individuals eligible for MMR vaccination were included. Cases were defined as children with a first diagnosis of a PDD during the study period while registered with a practice contributing to the GPRD. They were found by searching the electronic records for clinical codes indicating a diagnosis of PDD (codes used are available on request). Those who were first diagnosed outside the study period were excluded from the study and were not eligible to be selected as controls. Those with autistic disorders and similar presentations were classified as having “autism” and those with other descriptions (such as Asperger’s syndrome) were classified as having “other PDD”. Patients who had more than one PDD diagnostic code recorded at different times (for example, autism and then Asperger’s syndrome) were classified as having the most specific diagnosis (in this example Asperger’s syndrome). However, the date of the first diagnosis with a PDD was taken as the date of diagnosis.

We aimed to select five controls for every case from among individuals in the study population who had no diagnosis of PDD recorded in their general practice record and who were alive and registered with a participating practice on the date of the PDD diagnosis in the case. Controls were individually matched to cases by year of birth (up to 1 year older or younger), sex, and general practice. For each of 300 cases, five controls could be identified who met all the matching criteria. For the remaining 994, one or more controls was excluded (figure 1).

In 1988, MMR vaccination was introduced in the UK for all children aged 12–15 months. During 1988 to 1991, in a catch-up campaign, MMR vaccine was also offered to all children up until the age of school entry (4–5 years). A second dose at school entry was introduced in 1996, with a further catch-up campaign for children born on or after January 1, 1990, who had not previously received two doses of a vaccine containing measles. MMR vaccination is also recommended for non-immune adults, especially those in residential care or those starting college, and for non-immune contacts during a measles outbreak. A catch-up campaign for children aged 5–16 years was launched in 1994, but measles-rubella vaccination was used, not MMR.

An algorithm to identify children in the GPRD with recorded MMR vaccination was developed. The case-control status of individuals was concealed during

assessment of exposure status. After the introduction of MMR vaccine in 1988, a single clinical code for MMR vaccination was not implemented immediately in all GPRD practices. In some practices the individual vaccine components were coded separately for several years. Therefore, when measles, mumps, and rubella vaccinations were all coded as having been given on the same day or within a 21-day period, the vaccination was classified as representing MMR vaccination (because live vaccines are recommended to be separated by a period of at least 21 days).²²

For each case, information on MMR vaccination was abstracted from the GPRD records from their date of birth up until their date of diagnosis with a PDD. For controls, vaccination data were abstracted from their date of birth up to their index date—defined as the date when they were the same age (to the nearest month) as their matched case at the time the case was first diagnosed with a PDD. Month of birth was available for 82% of cases. For cases without month of birth recorded in the GPRD record, the month of birth was retrieved from case notes, questionnaires, or GPRD event records relating to birth, where available. Month of birth was available for 79% of controls. Where month of birth was unknown for cases or controls the birth date was taken as June 30 of the year of birth.

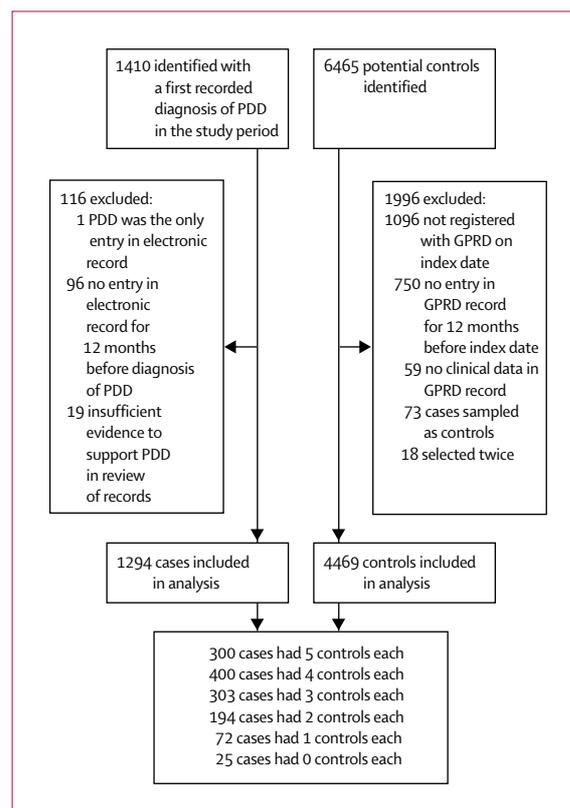


Figure 1: Numbers of potential cases and controls identified, excluded, and included in study

Analyses

Data were analysed with conditional logistic regression.²³ The primary analysis assessed the relation between MMR vaccination and the odds of being diagnosed with a PDD. We repeated this analysis excluding children who had received a dose of measles vaccine before MMR. Secondary analyses examined the risks associated with MMR vaccination administered before or after a child's third birthday and before or after the age of 18 months, to assess exposure at ages before the probable onset of symptoms.²⁴ We also separately analysed cases classified as having autism, excluding those with other PDDs. Potential confounding factors were introduced individually into the model and were retained if the odds ratio for MMR vaccination changed by 10% or more.

Age at first registration with a general practice contributing to the GPRD was judged to be a potential confounding factor because, on average, cases were first registered at an older age than controls (table 1), and evidence suggested that those who moved into the GPRD at older ages were less likely to have MMR vaccination recorded in the database, presumably because of incomplete ascertainment of past vaccinations when they joined the GPRD. For controls

born in 1988 or later who first registered with a participating practice before their first birthday, 95.6% (2129 of 2227) had one or more doses of MMR vaccination recorded before the age at diagnosis of their matched case, compared with 87.2% (1012 of 1160) of controls first registered after their first birthday. The corresponding values for cases were 96.9% (538 of 555) and 83.3% (345 of 414). For analysis, age at first registration was classified as before first birthday (thus registered with the GPRD from before the age at which they were first eligible for MMR vaccination), aged 1–4 years, 5–9 years, or older than 10 years. We also regarded as potential confounding variables the length of time a child was registered with a practice in the GPRD before the index date (in quintiles derived from cases and controls combined), and the frequency of consultation with the general practitioner (number of consultations during the time registered with the GPRD before the index date divided by the time registered before the index date). Interaction terms were introduced and likelihood ratio tests were used to assess their statistical significance.

The study was approved by the scientific and ethics advisory group of the GPRD and by the ethics committee of the London School of Hygiene and Tropical Medicine.

Role of the funding source

The sponsor of the study reviewed the initial study protocol but had no role in the study design, collection, analysis or interpretation of data, writing of the report, or the decision to submit the paper for publication.

Results

The numbers of cases and controls initially identified, reasons for exclusion, and numbers included in the analyses are shown in figure 1. When there were no entries in the GPRD record for 12 months before the diagnosis or index date, or no clinical data recorded at all (apart from the PDD diagnosis for cases), cases and controls were excluded because of concerns about the completeness of the clinical data recorded. All cases were registered with a practice contributing to the GPRD on their diagnosis date. Controls were excluded if they were not registered with a practice contributing to the GPRD on their index date. Duplicate records for a small number of controls who were sampled twice were excluded from the control group, as were cases who were sampled as controls.

Some of the general practices contributing data to the GPRD were willing to provide anonymised copies of hospital letters and specialist reports on individual patients. Of all patients with a recorded diagnosis of PDD in the GPRD, including diagnoses made before registration with a practice participating in the GPRD, 446 were registered with 203 general practices willing to provide this service. For 80 of these individuals, medical records were not available because the patient was not

	Cases (n=1294)	Controls (n=4469)
Number female (%)*	222 (17.2%)	768 (17.2%)
Age at diagnosis*†		
Median age in years (IQR)	5.4 (3.6–9.7)	4.9 (3.5–8.8)
Age in years (%)		
1–2	181 (14.0%)	695 (15.5%)
3–4	414 (32.0%)	1581 (35.4%)
5–9	396 (30.6%)	1292 (28.9%)
≥10	303 (23.4%)	901 (20.2%)
Birthyear (%)		
1973–87	316 (24.4%)	1021 (22.9%)
1988–95	798 (61.7%)	2811 (62.9%)
1996–99	180 (13.9%)	637 (14.2%)
Age joined GPRD (%)		
0 years	561 (43.4%)	2254 (50.4%)
1–4 years	416 (32.1%)	1267 (28.3%)
5–9 years	166 (12.8%)	485 (10.9%)
≥10 years	125 (9.7%)	298 (6.7%)
Missing	26 (2.0%)	165 (3.7%)
Median time in GPRD in years (IQR)	3.3 (1.8–5.2)	3.4 (2.2–5.2)
Median number of consultations with general practice per year, before PDD diagnosis or index date (IQR)	5.4 (3.2–9.0)	4.0 (2.2–6.5)
MMR vaccination before PDD diagnosis or index date		
At any age (%)	1010 (78.1%)	3671 (82.1%)
Before third birthday (%)	909 (70.3%)	3287 (73.6%)
Before age 18 months (%)	805 (62.2%)	2908 (65.1%)
Median age in years at first MMR vaccination (IQR)	1.2 (1.1–1.4)	1.2 (1.1–1.4)
Diagnostic category		
Autism (%)	991 (76.6%)	N/A
Other PDD (%)	303 (23.4%)	N/A

*Matching variables. †For controls, selection was to year of birth (to within 1 year): these are the data shown in the table. In the analysis of vaccination history, matching was to age at diagnosis to the nearest month.

Table 1: Characteristics of cases and controls

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	p (for adjusted OR)
MMR vaccination before index date			
At any age			
No MMR vaccination	(1.0)		
Vaccinated with MMR	0.73 (0.59–0.91)	0.86 (0.68–1.09)	0.21
Before and after third birthday			
No MMR vaccination	(1.0)		
MMR vaccination before third birthday	0.75 (0.60–0.95)	0.90 (0.70–1.15)	0.39
MMR vaccination after third birthday	0.68 (0.50–0.94)	0.77 (0.55–1.08)	0.13
Before and after age 18 months			
No MMR vaccination	(1.0)		
MMR vaccination before 18 months	0.76 (0.60–0.96)	0.90 (0.70–1.15)	0.39
MMR vaccination after 18 months	0.69 (0.54–0.89)	0.80 (0.61–1.05)	0.11

OR=odds ratio. *Adjusted for age joined GPRD.

Table 2: Association between PDD and MMR vaccination before index date, before and after third birthday, and before and after age 18 months

longer registered with the general practitioner. We obtained complete case records including copies of hospital clinic letters and specialist reports for 318 (87%) of the remaining 366 patients. These records were reviewed by a psychologist (LH), and a random sample of 50 records was also reviewed by a child psychiatrist (EF), both of whom have long experience in the specialty of autism. They judged that a PDD was probably present in 294 children (92.5%).²⁵ Of the 318 patients for whom specialist reports were obtained, 211 were first diagnosed with a PDD after they entered the GPRD and therefore were included in this case-control study. A diagnosis of PDD was confirmed for 193 of the 211 (91.5%). For the remaining 18, the symptoms and clinical features recorded were not sufficient to confirm a diagnosis of PDD; these cases were excluded from the analysis. One further case was excluded because the general practice reported that the diagnosis was a coding error.

Details of the cases and controls included are shown in table 1. The median age of cases at the first recorded diagnosis of PDD was 5.4 years; the average within-set difference in date of birth between cases and their matched controls was zero (IQR –181 to 122 days). On average, cases joined practices contributing to the GPRD at older ages than controls, and therefore had shorter periods of registration before the index date. Cases were less likely than controls to have a record of MMR vaccination before the index date. Just over three quarters of cases were classified as having autism, and the remainder as having another PDD.

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	p (for adjusted OR)
MMR vaccination before index date			
Autism only			
No MMR vaccination	(1.0)		
Vaccinated with MMR	0.77 (0.60–0.98)	0.88 (0.67–1.15)	0.35
Other PDDs only			
No MMR vaccination	(1.0)		
Vaccinated with MMR	0.60 (0.39–0.92)	0.75 (0.46–1.23)	0.25

OR=odds ratio. *Adjusted for age joined GPRD.

Table 3: Association between diagnosis of autism or other PDD and MMR vaccination

The unadjusted matched odds ratio for the association between MMR vaccination before the index date and a diagnosis of PDD was 0.73 (95% CI 0.59–0.91; table 2). After adjustment for the age at which participants joined the GPRD, the odds ratio increased to 0.86 (0.68–1.09). Further adjustment for duration of period in the GPRD and for consultation rate had no substantial effect on the odds ratio. The adjusted odds ratio associated with MMR vaccination after the third birthday was lower than that for before the third birthday, but not significantly so. The results were very similar when re-analysed with an age cutoff of 18 months to define MMR exposure. Re-analysis excluding children who had received measles vaccine before MMR (4.4% of cases and 5.2% of controls) had no substantial effect on these results.

We repeated the analysis restricted to 553 cases and 2126 controls whose index date was before Jan 1, 1998 (the hypothesis that MMR vaccination increased the risk of autism first received widespread media coverage in February, 1998). After adjustment for the age at which participants joined the GPRD, the odds ratio was 0.91 (95% CI 0.62–1.33), similar to the overall results.

We repeated the analysis restricted to participants for whom we had month of birth recorded: 82% of cases (1059) and 79% of controls (3524). The adjusted odds ratio was 0.94 (95% CI 0.72–1.23).

We assessed whether the odds ratio associated with MMR vaccination varied according to the age at which participants joined a contributing general practice. The adjusted odds ratios for the association between MMR vaccination before the index date were 1.47 (95% CI 0.84–2.57) for participants who joined the GPRD before their first birthday, and 0.75 (0.57–0.97) for participants who joined after their first birthday (p=0.03 for difference between the odds ratios). Restriction of this analysis to those with a month of birth recorded produced odds ratios that were slightly closer to 1 (p=0.09). Table 3 shows results of the analyses done separately for the 991 cases classified as having autism and the 303 cases classified as having another PDD. The results for the two subgroups were similar.

Discussion

We found that MMR vaccination was not associated with an increased risk of subsequently being diagnosed with a PDD. The findings were similar when analysis was restricted to children classified as having autism, or to children who had MMR vaccination before age 3 years.

An unexpected finding was that the odds ratio associated with MMR vaccination varied according to the age at which a person joined the GPRD. In particular, the odds ratio associated with MMR vaccination was higher among children who joined the GPRD at birth or before their first birthday than among children who joined at a later age; however, the confidence intervals were wide and the excess risk was not significant. This finding

could have been due to selection bias, or could have been a chance result due to multiple statistical testing.

Strengths of our study included the large size and population-based data. We included more than 1000 cases with a diagnosis of PDD. With 82% MMR coverage among controls, we were able to detect an odds ratio of 1.3 or greater with 90% power at the 5% significance level. Vaccination was recorded before the date of diagnosis so there was no scope for recall bias, and we were able to separately examine the data recorded before the hypothesis that MMR vaccination increased the risk of autism had been proposed. A recorded diagnosis of PDD had a high positive predictive value,²⁵ with 91.5% of a sample of cases having a diagnosis of PDD confirmed. A limitation of the study was that when children joined participating general practices after the date of MMR vaccination, their previous vaccination history was recorded retrospectively. Our findings suggest that such recording might have been incomplete, and the completeness of recording was related to the age at which people registered with a contributing practice. Additionally, cases joined practices contributing to the GPRD at a later age than controls; therefore, we adjusted for the age at which people joined the database. However, there was some evidence that the odds ratio associated with MMR vaccination varied according to the age at which a child joined the GPRD. It is possible that the incomplete ascertainment of vaccination history for children who joined the GPRD at later ages affected cases and controls differentially, though it is unclear why this should occur. We were not able to measure or control for some potential confounding factors such as birth order within families and social class, both of which are known to be associated with vaccination and might be risk factors for autism. For the index date, to assess previous vaccination, we used date of recorded diagnosis, not onset of symptoms. It is possible that parents might have noticed signs of PDD before the diagnosis of PDD, and avoided MMR vaccination because of these signs. The ability of uncontrolled confounding to produce apparent protective effects of vaccination has been explored in detail elsewhere.²⁶ It is important to note that restriction of the analysis to cases and controls whose index date was before the widespread media coverage of the hypothesis that MMR vaccination increased the risk of autism gave results similar to the overall results. We were not able to separately identify the subgroup of cases with regressive symptoms to investigate the hypothesis that only some children are vulnerable to MMR-induced disease and that this is always regressive.²⁷ However, two recent studies have argued against the existence of a distinct MMR-induced regressive type of autism.^{28,29}

We did a systematic review of published studies that assessed the risk of PDD in individuals who received MMR vaccine and those not vaccinated. Relevant studies were sought without language restriction by searches of

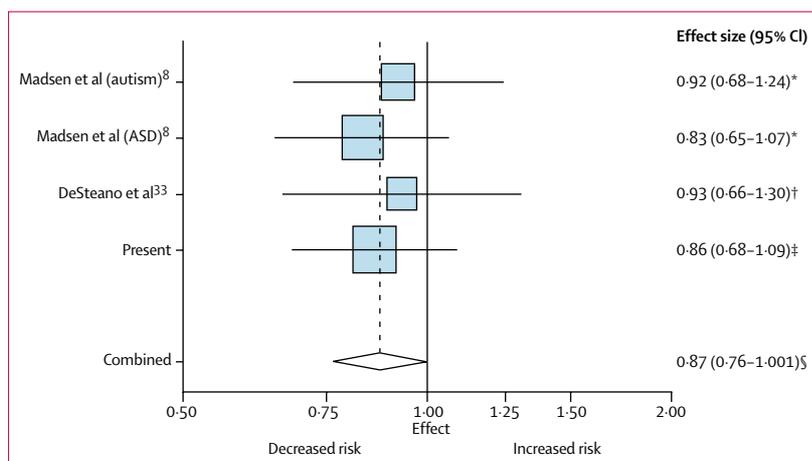


Figure 2: Meta-analysis of studies that compared risk of autism or other PDDs among vaccinated and unvaccinated individuals

ASD=other autistic spectrum disorders. Shaded boxes and horizontal lines correspond to effect size ratios and 95% CIs. Size of shaded box proportional to reciprocal of square of standard error of effect. *Rate ratio, adjusted for age, calendar period, sex, birth weight, gestational age, mother's education and socioeconomic status. †Odds ratio, cases and controls matched on age, sex, and school, adjusted for birth weight, multiple gestation, maternal age, and maternal education. ‡Odds ratio, cases and controls matched on age, sex, and general practice, adjusted for age registered with general practice. §Pooled relative risk.

PubMed and EMBASE with key terms autism, autistic, pervasive developmental disorder, regression, and measles, mumps, rubella alone or in combination, and variants of the abbreviation MMR. Reference lists of retrieved articles were scanned and recent reviews consulted.^{9,30–33} Studies were eligible if an effect measure (with a standard error or confidence interval) for the association between exposure to MMR vaccine and subsequent PDD could be obtained from the report or by contacting the study authors. Two investigators extracted data, with any discrepancies resolved by discussion. The DerSimonian and Laird Q test was used to evaluate heterogeneity of effect between studies. The summary odds ratio and 95% CI were calculated with the Mantel-Haenszel fixed effect³⁴ and DerSimonian and Laird random effects³⁵ models.

In the systematic review, we identified three other studies that had directly assessed the risk of autism or other PDDs associated with MMR vaccination.^{8,36–38} The results from a Danish cohort study⁸ were very similar to the results we obtained. The Danish study was from a cohort sample, which lends itself to reporting results on the relative risk scale and not the odds ratio scale used in this study. Information provided was insufficient for conversion to the odds ratio scale, but assuming a baseline incidence of autism of less than one per thousand, and a risk ratio closer to unity than 0.8, the two scales are approximately equal with an error of less than 0.02%, calculated with the formula (baseline odds) × (1–relative risk) × 100%. Unpublished data were supplied by the authors of a study by Jick and colleagues.^{36,37} Of the 122 cases included, 118 (96.7%) had received MMR vaccine before the date of diagnosis,

compared with 569 of 587 controls (96.9%). Ignoring any effect matching might have had, these data gave an odds ratio of 0.93 (95% CI 0.30–3.86). The cases included in the study by Jick and colleagues^{36,37} were a subsample of the cases included in our study and were therefore not included in the pooled estimate. In a study by DeStefano and colleagues,³⁸ the adjusted odds ratio in the subsample for whom more detailed information was available (figure 2) was closer to unity than the unadjusted odds ratio in the whole sample (1.12, 95% CI 0.91–1.38). We used the subsample result because there was evidence of confounding in the unadjusted result.

The results for the studies included in our meta-analysis and the pooled estimate are presented in figure 2. We noted no evidence of heterogeneity ($p=0.94$). The pooled relative risk was 0.87 (95% CI 0.76–1.001). The Dersimonian and Laird estimate of the between study variance was zero, hence the results of the fixed and random effects models were identical. Hence, the findings of the three studies we identified by systematic review were in accord with those of our case-control study. Our finding of no increased risk of PDD in individuals who received MMR vaccine compared with those not vaccinated was consistent with previous studies that showed no temporal relation between MMR vaccination and the development of PDD within individuals,^{7,28,29,39-42} and the negative findings from studies that compared incidence rates of PDD with MMR vaccine coverage.^{7,28,29,43-47}

We have found no convincing evidence that MMR vaccination increases the risk of autism or other PDDs. No significant association has been found in rigorous studies in a range of different settings. These are severe diseases for which very little is known about causation; this absence of knowledge itself might have contributed to the misplaced emphasis on MMR as a cause. Research into the real origins of autism is urgently needed.

Contributors

L Smeeth, A J Hall, E Fombonne, L C Rodrigues, and P G Smith designed the study. L Heavey and E Fombonne undertook the validation of case reports. C Cook analysed the data. L Smeeth drafted the paper. All authors commented on drafts and approved the final version of the paper.

Conflict of interest statement

L Smeeth, C Cook, L Heavey, L C Rodrigues, and P G Smith have no conflicts of interest. E Fombonne has provided advice on the epidemiology and clinical aspects of autism to scientists advising parents, to vaccine manufacturers (for a fee), and to several government committees. A J Hall received a financial contribution from Merck towards research on hepatitis B vaccination in 1998. He is also a member of the Joint Committee on Vaccines and Immunisation (2002–present).

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