



Letters

Measles, mumps, and rubella (MMR) vaccine and autism

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Ecological studies cannot answer main question

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EDITOR—Kaye et al undertook an ecological study comparing the time trend in measles, mumps, and rubella (MMR) vaccine coverage with the time trend in diagnoses of autism.¹ They found a marked increase in the incidence of codes for autism in children's electronic general practice records over 11 years.

We agree with their conclusion that MMR cannot be the cause of this observed increase since the vaccine coverage remained constant over the same time. There have been changes in the classification of autistic diseases and in the likelihood of case ascertainment in recent years, and a more rigorous review of cases may clarify whether some of the increase was due to alterations in diagnostic practice.² Only 81% of cases were reported to have been referred to a specialist, raising questions about the validity of the diagnoses used by Kaye et al. Children with medical conditions present from birth and known to be associated with an increased risk of autism (fragile X disorder, tuberous sclerosis, phenylketonuria, and congenital rubella) were not excluded.

The failure to find an association between the time trends in vaccine coverage and the incidence of autism codes in children's electronic general practice records does not exclude a causal association.

Whether exposure to MMR vaccination increases the risk of autism is of great public health importance and can be usefully investigated using the general practice research database. We have been funded by the United Kingdom Medical Research Council to undertake an investigation of the causes of autism, including an assessment of the potential role of MMR vaccine using case-control and case series approaches. The electronic general practice records in the database will be supplemented by a full record review of all cases and, subject to ethical approval, questionnaires to parents of both affected children and controls. We will undertake a detailed validation and classification of all cases and establish the date of onset of symptoms. In addition, we will obtain information on potential confounding factors from both cases and controls. A detailed protocol of our study has been published.³

References

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Argument is too simplistic

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EDITOR—Kaye et al analysed time trends in measles, mumps, and rubella (MMR) vaccine and the incidence of autism.¹ Because the increase of autism is gradual whereas the prevalence of immunisation is constant, they argue that there is no evidence of an association. This argument, however, rests on the assumption that the rate of diagnosis rate each year after the onset of clinical symptoms is constant with respect to birth cohort and that a mild case has a constant chance of being diagnosed.

Altmann points out that 40% of cases have diagnosis delayed up to three years.² Could increasing awareness of paediatricians and general clinicians of autism during this period account for the gradual increase? When the first unexpected extra cases were found in 1991-2, could that not have increased vigilance? As evidence, we point to the median age at diagnosis as reported by the authors. Except for 1993, there seems to be a trend towards earlier diagnosis. We exclude 1998-9 because the cohort then changed substantially, with several practices no longer providing information. Could Kaye et al show a

test of trend from 1988 to 1997 to see whether there was a systematic decrease in age at diagnosis? Is it also possible to investigate the notion that average severity of cases was dropping over this time period?

Finally, was there a trend towards earlier vaccination, as can be seen in data from California?³ For example, did the percentage of vaccinations at less than 10 months increase over time?

We submit that the argument given by Kaye et al is too simplistic to reassure us that there is no link between MMR and autism. The current arguments in favour of the link, however, remain unconvincing.
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MMR cannot be exonerated without explaining increased incidence of autism

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EDITOR—Kaye et al observe that the rise in the incidence of autism cannot be attributed to measles, mumps, and rubella (MMR) vaccine because vaccination remained consistently above 90% in the period studied.¹

I have several issues with their study:

1. The cohort of children chosen was born during 1988-93. MMR was introduced in the United Kingdom in 1988 and an uptake of 90-95% is unlikely to have been achieved from the first year.
2. Kaye et al effectively excluded children born before 1988 who may have been vaccinated in or

after 1988.

3. The 114 boys selected were observed until the age of 71 months. Many of them could have succumbed after the second MMR vaccination (booster), which is given between the ages of 4 and 5 years. The study did not mention how many children received two MMR vaccinations.
4. MMR vaccine was previously given alone at 15 months or later. Then the age was lowered to 12-14 months and other vaccines were administered concomitantly, increasing the immune antigenic insult at a younger more susceptible age and effectively increasing the incidence of autism.
5. The restriction of the cases in the main analysis to 114 boys is of concern. A breakdown of the 290 children in the 1990-9 birth cohorts by sex and year of birth would have been informative. A larger proportion of girls among the 176 cases excluded might have been relevant to the completeness of the autism figures.
6. The fact that neither DSM-IV nor IC-10 was systematically used in the United Kingdom creates further doubts about the significance of the findings.

Professor Brent Taylor in the *Lancet* (1999;353:2026-9) and now Kaye et al have clearly documented the epidemic of autism in the United Kingdom. Before 1988 the incidence of autism was 1 in 10 000; after 1988—the year MMR was introduced—it leapt to 8 in 10 000. By 1993 it was 29 in 10 000.

Kaye et al cannot exonerate MMR without offering a reasonable explanation for the increase.

Until safety studies on MMR are independent of drug companies and are large scale and comprehensive, and until researchers review with parents the documented adverse reactions of bowel disease and autism, the triple jab remains suspect.

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Authors' reply

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EDITOR—We disagree with Smeeth et al applying the term ecological to our study of measles, mumps,

and rubella (MMR) vaccine and autism. In an ecological study the units of analysis are populations or groups of people.¹ But our study focused on individual children diagnosed with autism (although we also reported the prevalence of exposure to MMR for all children in the general practice research database who were born in 1988-93). It is unimportant that we included a few children with conditions predisposing to autism because we were evaluating the relation between MMR vaccination and the risk of being diagnosed with autism per se. We agree that more work is needed to evaluate possible causes of the recent increase in autism other than the MMR vaccine.

A non-parametric test (extension of Wilcoxon rank sum test in Stata, version 7.0) provides no evidence for a trend toward lower age at diagnosis over time for the 305 cases diagnosed in 1988-99 ($P=0.88$), even including only cases diagnosed before 1998 ($p=0.61$). We doubt that lower age at diagnosis explains the nearly fourfold increase in risk for two to five year olds in the 1988-93 birth cohorts. The median age at first MMR in the base population was 15 months for the 1988 birth cohort, 14 months for the 1989-1996 cohorts, and 13 months for the 1997 cohort. Small differences in age at first MMR are unlikely to account for the large change in the observed risk of autism diagnosed at age 2-5. We agree that changing diagnostic criteria (for example, diagnosing milder cases) may be one explanation for the increase in diagnosed autism.

We did not include only classic cases. We restricted our main analysis to boys to maximise risk estimate precision since girls make up only about a fifth of the diagnosed cases. We focused on children aged 2-5, in whom the incidence of diagnosed autism is greatest. We analysed 1988-93 birth cohorts to have enough follow up information to calculate four year risk (age 2-5). Using a different upper limit for age at diagnosis in some birth cohorts would impair the comparability of risk among the cohorts.

MMR was introduced in the United Kingdom in 1988 and is first administered around the age of 15 months. Children born in 1988 were vaccinated in 1989 or 1990, so our data do not suggest that uptake of 95% was achieved from the first year. Excluding cases born before 1988 has no effect on risk estimates for the birth cohorts we reported or on the relation between MMR vaccine and diagnosed autism in these cohorts. Only 12/114 boys in our main analysis received more than one MMR vaccination before their first recorded diagnosis of autism—too few to separately estimate risk for two vaccinations compared with one. We did not study whether vaccines other than MMR are associated with the increasing incidence of autism.

Footnotes

- A longer version of this letter is published on bmj.com

References

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