

This months paper: Madsen MK et al. A population based study of measles, mumps and rubella vaccination and autism. New England Journal of Medicine, November 7 2002; 347 (19), 1477-82.

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Citation

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Abstract

The E-Pediatric Journal club is a regular feature of the Internet Journal of Pediatrics and Neonatology. Every issue an important paper from a high profile journal is selected and evaluated. A systematic approach is used to critically appraise articles that should be relevant to those involved in the care of children in hospital and the community. The aim of the journal club is to give our readership an insight into evidence based medicine and encourage pediatricians to critically evaluate all the evidence that they use when making clinical decisions. The journal club also contains a comprehensive glossary of commonly used epidemiological terms.

The journal club is brought to you in partnership with the online 'E-pediatric journal club', whose website contains more critically appraised articles at <http://www.e-paedjournalclub.com> and we would encourage you to visit.

REVIEW ARTICLE

This months paper: Madsen MK et al. A population based study of measles, mumps and rubella vaccination and autism. New England Journal of Medicine, November 7 2002; 347 (19), 1477-82

1. WHAT IS BEING STUDIED?

The aim of the study was clearly stated. It was to find out if children who are vaccinated with the three in one Mumps, Measles and Rubella vaccine at around 15 months of age have a higher incidence of autism than those who are not vaccinated.

2. WHAT WAS THE STUDY DESIGN AND WAS THIS APPROPRIATE TO WHAT IS BEING STUDIED?

The study design was clearly stated. It was a retrospective study of two cohorts (groups) of children, namely those that had been vaccinated with MMR and those that had not been. Data was collected for children for the period from 1991 to

1998.

This study design is appropriate to the study objective. The ideal way of determining vaccine side effects would be by means of a large scale double blind randomised controlled clinical trial (some of the largest randomised trials ever carried out were prior to the public introduction of polio vaccine in the 1950's). However as MMR vaccine is already part of the public vaccination program in Denmark, where this study was undertaken, randomisation was not practical. An observational study was therefore done. It is called observational because the researchers have not intervened in any way with the subjects other than to collect data from pre-existing records.

Patients included

Children born in Denmark during the period January 1991 to December 1998, inclusive.

Patients excluded

Children with hereditary or congenital disorders that have autism as a presenting feature, namely Fragile X syndrome, Angelman's syndrome, tuberous sclerosis and congenital rubella. As the incidence of these congenital conditions was not the issue under investigation, this exclusion seems

reasonable.

Outcome measures

The outcome measures were the rates of autistic disorders (autistic disorder and autistic spectrum disorders) as classified by the features set out in the International Classification of Diseases (version 10) and the Diagnostic and Statistical Manual (version IV).

How were the outcomes measured?

Children were diagnosed as autistic by local child psychiatrists. All children with autism in Denmark are registered in a nationwide central psychiatric register. As part of the study, the records of children diagnosed with autistic disorders were reviewed by a consultant child psychiatrist with special expertise in autism. It is not stated whether this consultant was blind to the vaccination status of the child.

2. ARE THE RESULTS OF THE STUDY VALID?

Were all patients who entered the trial properly accounted for and attributed at its conclusion?

The follow up of patients was achieved for approximately 99 percent of the original cohort. The only losses were due to deaths or emigration. Such a high rate of follow up is unusual for an observational study, and is a great credit to the Danish registration systems.

Were patients, health workers, and study personnel "blind" to their vaccination status?

No. The parents of the children would have known their vaccination status, and it is possible that the psychiatrists who were involved with the children would have enquired about their vaccination status. It is also possible that the consultant who reviewed the diagnoses of the children who had records indicating that they had an autistic disorder knew of their vaccination status. Would this have affected the chances of a child being diagnosed with an autistic disorder? During the earlier years of the study, before the controversy erupted, probably not. In the later years, it is possible because of parent's awareness, that some of the milder cases may have presented earlier in the vaccinated group. In this case one might have expected a tendency toward clustering around the time of vaccination. However, they did look at the incidence of autism in different groups according to the time interval since vaccination, but did not

find any significant difference in the rates.

Were the groups similar at the start of the trial?

No. The demographic analyses did show some differences between the groups in terms of the birth weights of the children (though looking at table I could not see a big difference), gestational ages (a lot of the data for the unvaccinated children was missing), socioeconomic status (vaccinated children's parents were materially better off), and mother's education (vaccinated children's parents had higher rates of higher education). However, in the most important risk factor for autism, namely male sex, the distribution was equal between the groups.

3. WHAT WERE THE RESULTS?

The main results were that the relative risk of autistic disorders in the vaccinated group was slightly less (0.92) than the unvaccinated group. This was not statistically significant as the 95 percent confidence interval ranged from 0.68 to 1.24. Adjustment for the potential confounders in the demographics did not change the result, and neither did inclusion of children who had autistic disorder due to Fragile X syndrome, Angelman's syndrome, tuberous sclerosis and congenital rubella. The confidence interval is quite narrow, which reflects the large cohort sizes.

4. ARE THE RESULTS CONSISTENT WITH OTHER STUDIES?

Yes, although all previous studies of the association between MMR and autism have been case series, ecological studies or cross-sectional studies. Studies of this kind cannot be used to directly investigate a possible relationship between an exposure (in this case, a triple vaccine) and an outcome.

5. WILL THE RESULTS HELP ME CARE FOR MY PATIENTS?

The result does provide reassurance for people worried about the possibility that MMR might be associated with autism. It appears from this study that the relationship is temporal, rather than causal.

6. WERE ALL CLINICALLY IMPORTANT OUTCOMES CONSIDERED?

Yes. All varieties of autism were included in the analysis.

7. ARE THE LIKELY TREATMENT BENEFITS WORTH THE POTENTIAL HARMS AND COSTS?

Serious adverse events with MMR vaccine occur much more rarely than with wild mumps, measles or rubella infection. It

seems likely that the benefits of MMR vaccination continue to outweigh the potential harms and costs.

References

Author Information

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