

# **Assessment of the Denmark MMR-Autism Study**

(11/6/02)

## **Study**

“A Population Based Study of Measles, Mumps and Rubella Vaccination and Autism.”  
*New England Journal of Medicine*, Vol 347, No 19; Nov 7, 2002: 1477-1483.  
Kreesten Meldgaard, M.D., Annders Hviid, M.Sc., Mogens Vestergaard, M.D., Diana Schendel, P.H.D., Jan Wohlfahrt, M.Sc., Poul Thorsen, M.D., Jørn Olsen, M.D., and Mads Melbye, M.D.

## **Key Message**

This study is well done, but due to its design, it cannot be considered the “definitive” study on autism and the MMR vaccine. Rather, biological research, not epidemiology, is needed to truly answer the question of a link between the MMR and regressive autism.

## **Positives Aspects about This Study**

- 1 The CDC and public health authorities are investing dollars and efforts into autism research. These efforts should be applauded, and expanded!
- 2 The study reports a steep rise in autism rates from 1980s to 1990s (from <2.0 to >10.0 per 10,000). Increases are also being reported in other countries, again suggesting environmental influences at work, as the recent landmark MIND Institute epidemiology of California study did.
- 3 The results appear to support a thimerosal role in the increases in autism being reported in the study in Denmark, and the fact that Danish autism prevalence is less than in the US and the UK, where the thimerosal vaccines are given in larger quantities and/or earlier in life. Further clarification is needed to elucidate this association; specifically, the prevalence by birth cohort and the Danish vaccine schedule and formulations for the time period are needed.
- 4 The study authors acknowledge that previous attempts to refute the MMR-autism hypothesis were too poorly designed to reach definitive conclusions. (p.1477, 2<sup>nd</sup> paragraph on right)
- 5 The study brings attention to a rich database of information (i.e., Danish registries) on which additional studies of autism can be based.

## **Cautions about the Study’s Conclusion on Being the “Definitive” Statement on Autism-MMR**

- 1 A vaccine-induced autism subset may be present at a much lower prevalence in Denmark since the prevalence of autism is lower in Denmark compared with other countries (see prevalence comparison table at end of document). This may indicate a co-factor effect (e.g. thimerosal) that operates to a greater degree elsewhere.

- The lower prevalence in Denmark is not a function of variation in diagnosis, since the same diagnostic criteria developed by CDC was used in Brick, Atlanta, and Denmark.
  - Means other environmental factors, rates of factors, or combination of factors may be at work in Denmark vs US or UK.
  - It is possible that MMR increases the rate of autism only when acting in conjunction with another environmental factor, such as mercury. If that factor's prevalence is not controlled for among the study groups (vaccinated vs unvaccinated), it would obscure the role of MMR as a causative factor in the study.
  - This is entirely biologically plausible since mercury impairs the antiviral immune response, and mercury-exposed fetus and infants are more susceptible to persistent viral infections.
- Only psychiatric records were accessed, not medical records, so there were no data on gastrointestinal symptoms and no taking of CSF or GI samples to detect presence or absence of measles virus. Cannot tell if measles persistence is impacting a subgroup of children, if any. Measles persistence may be increasing the severity of autism, even if it is not causing an increase in the number of cases.
  - There was no attempt to differentiate between regressive and early-onset forms of autism. Since the regressive form comprises a minority of cases - 10%-20% - the power to detect whether there was a difference in regressive autism prevalence between MMR vaccinated and non-vaccinated is lacking in this study.
    - The assertion that a relative risk of autism of less than one rules out the possibility that there are important subgroups is false.
  - Although overall well designed, there appear to be some methodological problems with the study, which need further elucidation from the investigators and raise questions about its conclusions of being the “definitive” MMR-Autism study.
    - The study covered 8 birth cohorts, but two of these, those born in 1997 and 1998, were only 1 or 2 years old when the data records were obtained at the end of 1999. These age groups are too young in most cases to be diagnosed with autism or to be immunized with the MMR. This might have been fine if the impact applied equally to both vaccinated and unvaccinated groups. However, fully half (50.6%) of the unvaccinated group fell into these two younger birth cohorts, vs. just a fourth (27.7%) of the vaccinated group. Therefore, in these 2 birth cohorts, true autism rates will be underestimated (since they have yet to be diagnosed) and unvaccinated status is over-represented.

- The cases were converted to person years in the study. There is no credible basis for doing this. On a case-basis, the MMR does in fact result in a higher rate of autism. Of the 440,655 children who received MMR vaccinations

Of Of the 440,655 children who received MMR vaccinations in Denmark was 6.1 per 10,000 as compared to the rate of 4.9 per 10,000 in the 96,648 unvaccinated children. At the population level, the risk of autism was therefore 26% HIGHER in the group vaccinated with MMR. The authors never report this calculation.

Moreover, the person years for the oldest cohort, which should have the highest number of person years since they are the oldest, is actually far lower than the next youngest group. No explanation is given for this and it raises questions about the integrity of the data set.

- Children who were in fact vaccinated were assigned to the unvaccinated group if they were diagnosed with autism before they received the MMR. The reassigned cases comprise 10% of the unvaccinated autism cases (13 out of 130). This commingling blurs the distinction between vaccinated and unvaccinated. It is not clear what effect this would have on the results.
- A number of the measures used to arrive at the conclusion that autism and autism disorders were not associated with MMR vaccination are irrelevant. Age of vaccination with MMR, time interval between receipt of MMR and diagnosis of autism, and year of MMR vaccination do not help elucidate the hypothesized relationship between receipt of MMR and development of measles-related symptoms and regressive autism. The age of diagnosis is arbitrary and can vary for many reasons, among them differences in severity of illness, access to care, and clinician skill and preference. Thus these measures cannot be used to refute the presence of a temporal relationship between MMR and onset of symptoms of measles-related illness and regressive autism.

- 1 As the authors point out on page 1481, they had no information on the presence or absence of a family history of autism, which could explain the study's negative findings only if families with a history of autism avoided MMR vaccination. It should be noted that in 1993, there was a widely reported news story in Denmark about a parent with autistic twins who asserted that their autism was caused by the MMR vaccine. It is entirely possible that parents with either (a) a family history

of autism or (b) an infant or toddler with emerging symptoms of autism, would avoid vaccination at a higher rate than other parents. This would inflate the unvaccinated group with children of families predisposed to autism.

## Reported Rate of Autism from Recent US, UK, and Denmark Studies

<b>Study</b>	<b>Study Group</b>	<b>Rate per 10,000</b>
Denmark MMR-Autism Study, 2002	Broader autism (738 cases ÷ 537,303) among 1-8/9 year olds comprising study sample	13.7
Denmark MMR-Autism Study, 2002	Classic autism (316 cases ÷ 537,303) among 1-8/9 year olds comprising study sample	5.9
Denmark MMR-Autism Study, 2002	Other PDD (422 cases ÷ 537,303) among 1-8/9 year olds comprising study sample	7.9
Denmark MMR-Autism Study, 2002	Classic autism among 5-9 year olds in 2000 (data not shown)	>10.0
Denmark MMR-Autism Study, 2002	Broader autism among 8 year olds in study sample	29.9
Denmark MMR-Autism Study, 2002	Classic autism among 8 year olds in study sample	7.7
Denmark MMR-Autism Study, 2002	Other PDD among 8 year olds in study sample	22.2
Chakrabarti and Fombonne UK Study, 2001	Broader autism among 2-6 year olds in UK	63
Chakrabarti and Fombonne UK Study, 2001	Classic autism among 2-6 year olds in UK	17
Chakrabarti and Fombonne UK Study, 2001	Other PDDs among 2-6 year olds in UK	46
Brick Township, NJ, by CDC, 2000	Broader autism among 3-10 year olds in 1998	61
Brick Township, NJ, by CDC, 2000	Classic autism among 3-10 year olds in 1998	31
Brick Township, NJ, by CDC, 2000	Other PDDs among 3-10 year olds in 1998	30
Brick Township, NJ, by CDC, 2000	Broader autism among 6-10 year olds in 1998	67
Brick Township, NJ, by CDC, 2000	Classic autism among 6-10 year olds in 1998	40
Brick Township, NJ, by CDC, 2000	Other PDDs among 6-10 year olds in 1998	27
Metro Atlanta, by CDC, 2001	Classic autism among 3-10 year olds in 1996	34