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An Investigation of the Association Between MMR Vaccination and Autism in Denmark

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ABSTRACT

The measles, mumps, rubella (MMR) vaccine was added to the childhood immunization schedule in Denmark in 1987. From 1998 to the present, there has been concern over whether there is an association between MMR vaccination and autism. Prevalence of autism by age category during 1980 to 2002 was investigated, using data from a nationwide computerized registration system, the Danish Psychiatric Central Register, in order to compare the periods preceding and following introduction of MMR vaccine.

Prior to a classification change in 1993/1994 and a change in enrollment in 1995, an increase in autism prevalence was noted. Linear regression analysis was performed separately on the trend during 1990 to 1992, the period that preceded the introduction of both effects. The prevalence in 2000 could then be derived excluding the sources of ascertainment bias.

Prevalence of autism among children aged 5-9 years increased from a mean of 8.38/100,000 in the pre-licensure era (1980-1986) to 71.43/100,000 in 2000 and leveled off during 2001-2002. The relative risk (RR) is therefore 8.5 (95% CI, 5.7 to 12.7). After adjusting for greater diagnostic awareness, the RR is 4.7 (95% CI, 3.1 to 7.2). Among individuals less than 15 years old, the adjusted RR is 4.1 (95% CI, 3.5 to 4.9).

Longitudinal trends in prevalence data suggest a temporal association between the introduction of MMR vaccine in Denmark and the rise in autism. This contradicts an earlier report.

Health authorities should develop safer vaccination strategies and support further investigation of the hypothesized link between the MMR vaccine and autism.

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Table 1. Estimated Unadjusted and Adjusted Relative Risk (RR) for 5-9 and 0-14 Age Groups.

Description	5-9 Age Group		0-14 Age Group	
	1990-1992	1995-2000	1990-1992	1995-2000
Best-fit linear equation[a]	$y=3.141x + 4.869$	$y=8.524x - 22.333$	$y=6.105x + 10.587$	$y=16.266x - 34.807$
Correlation coefficient, r^2	0.985	0.930	0.922	0.981
Prevalence in 2000	39.42[b]	71.43	77.74[b]	144.12
Factor of Greater Diagnostic Awareness: Ratio of prevalence 1995-2000 to 1990-1992	1.81		1.85	
Actual mean prevalence 1980-1986	8.38		18.8	
Unadjusted RR (2000 to 1980-1986)	8.5 (95% CI, 5.7 to 12.7) = 71.43/8.38		7.7 (95% CI, 6.6 to 9.0) = 144.12/18.8	
Adjusted RR (linear projected 2000 to 1980-1986)	4.7 (95% CI, 3.1 to 7.2) = 39.42/8.38		4.1 (95% CI, 3.5 to 4.9) = 77.74/18.8	

[a] x = year-1989; y is cases/100,000
[b] Value extrapolated based on best-fit line through 1990 to 1992 data points, with $x = 11$.

Background

The MMR vaccine was first licensed in the U.S. in 1971. It was added to the immunization schedule of Denmark in 1987 and administered to children at the age of 15 months. It was also available to older children and young adults. A 1998 study conducted in England by Wakefield et al. was the first to allude to the close proximity of receipt of MMR vaccine and a developmental disorder characterized by loss of acquired skills (including speech) and intestinal symptoms.[1] This led to the hypothesis that there may be an association between MMR vaccine and autism.

A population-based study of all children born in Denmark from 1991 to 1998 opposed this hypothesis.[2] However, prevalence data from this same period, combined with longitudinal data from 1999 to 2002, raise new concerns.

Denmark presents a unique set of circumstances in which to study a possible causal relationship between MMR vaccine and autism since it maintains a registry of all children born and assigns a unique identifier to each person to track the health and immunization status. Whole-cell pertussis vaccine containing thimerosal, used between 1970 and 1992, was phased out. Thimerosal-free whole-cell pertussis vaccine was used until Jan. 1, 1997, when it was replaced by an acellular pertussis vaccine.[3] The MMR vaccine does not contain thimerosal. Thus, the potential effects of thimerosal in childhood vaccines were eliminated in Denmark. In studies examining a vaccine-autism association in the U.S. and other countries, utilization of multiple thimerosal-containing vaccines and frequent changes introduced into the childhood immunization schedule have produced a complex pattern of possible exposures.

Historical Studies

The Danish study by Madsen et al.[2] published in 2002 was believed to be the most exhaustive and therefore most convincing study. It concluded that no association existed between MMR vaccination and autism in Denmark.[4] This retrospective cohort study investigated 537,304 children born between 1991 and 1998 during 2,129,864 person-years, with a mean follow-up of 4 years. Children who had not received MMR vaccine constituted 0.48 million person-years or 23% of the observations.

Because autism is usually diagnosed at age 5 or older in Denmark, many children born in 1994 and thereafter would not have

been diagnosed by the end of the study period. The systematic error of missing a large number of autism diagnoses in the later years was a major shortcoming. Children with Asperger's Syndrome and high-functioning autism, who have minimal speech and behavior impairments and are thus not diagnosed as early as more profoundly affected children, are especially likely to be undercounted in this study.

Additional flaws in the Madsen study included the unusual distribution of ages in the cohorts, censoring rules applied to cases, and failure to separate autism into regressive and classical cohorts. These and other cited methodological and statistical problems tended to mask the association with MMR vaccine, as unimmunized children were clustered in the earlier years of the study so that ascertainment was more complete in this cohort than in those immunized a few years prior to the end of the study period, when many cases of autism were missed owing to insufficient follow-up time to make the diagnosis.[5]

Other historical studies concluding that there is no link between MMR vaccine and autism had insufficient follow-up time or inadequate statistical power owing to small sample size, utilized passive surveillance, demonstrated conflicts of interest, or had other limitations.[6-16] When physicians and parents are told that vaccines are virtually completely safe, they are less likely to connect a severe adverse event with vaccination. Thus, vaccine-induced adverse events are underreported and grossly underestimated. Prior to publicity hinting that such a link might exist, there were very few, if any, physicians or parents willing even to consider the possibility that late-onset autism may be linked with MMR vaccine.

Despite recent clinical and laboratory studies demonstrating the biological plausibility of an MMR-autism link,[17-26] a recent decision of a special committee of the Institute of Medicine (IOM), which is likely to result in the denial of compensation to MMR-affected children, relied on epidemiological studies and in particular the Madsen study that claim a negative MMR-autism association.

Methods

Longitudinal trends from 1980 to 2002 in prevalence of autism by age category were investigated from a nationwide computerized registration system, the Danish Psychiatric Central Register (DPCR). Inherent in this data set are two potential sources of ascertainment bias: (1) a change in the classification system from ICD-8 to ICD-10 that occurred in 1993-1994[27] and (2) a change in the type of patients included in the data set. Prior to 1995 only inpatients are included in the DPCR. After 1995 both inpatients and outpatients are included in the data set. Since these two changes occurred in close proximity to one another (one to two years apart), both potential influences were considered as a single parameter called *greater diagnostic awareness*.

To investigate the effect of greater diagnostic awareness on prevalence among the 5-9 and under-15 age groups, linear regression analysis was performed separately on the trend preceding (1990-1992) and following (1995-2000) the introduction of the confounder in 1993. Using the best-fit line through the 1990-1992 annual data, the extrapolated prevalence, in 2000 represents the projected prevalence had no confounding occurred. The ratio of the prevalence determined in 2000 for the two periods, 1995-2000 and 1990-1992, represents the factor of increase due to greater diagnostic awareness.

Mean prevalence in older age groups (25-29 and older) was computed during the pre- and post-licensure periods, 1980-1986 and 1997-2002, where noted increases could not possibly be attributed to MMR vaccine. Assuming that greater diagnostic awareness is a confounding factor after 1994, a sensitivity analysis was performed to determine the limit of this factor necessary to yield a statistically insignificant RR among the 5-9 age group.

The cases of autism in 1994 and thereafter were ascertained using ICD-10 codes F84.0 through F84.9. These correspond to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) codes 299.00, 299.10, and 299.80.

Autism prevalence is defined as all individuals with autism in a given period divided by the population at risk during this period and is expressed in units of cases per 100,000. The mean birth cohort of 65,000 is used to approximate the total number of 325,000 (5 x 65,000) individuals in each of the 5-year age groups: 0-4, 5-9, and 10-14. The relative risk (RR) is computed as the ratio of the autism prevalence in the post- to pre-licensure periods. Owing to the rare condition of autism, the odds ratio (OR) approximates the RR. The confidence interval (CI) associated with the RR is determined using the Mantel-Haenszel chi-square in the test-based method described by Sahai and Khurshid.[28] The true confidence intervals are wider than indicated because of error associated with linear regression of the trends both before and after 1994.

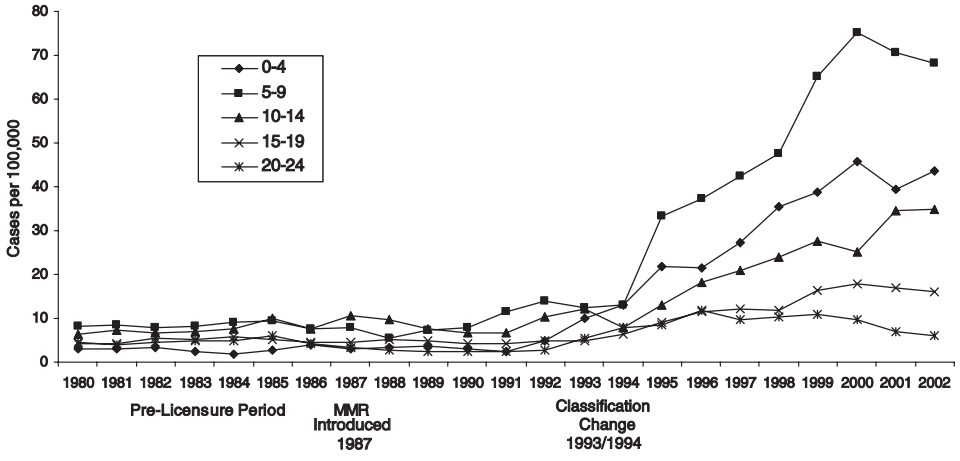

Figure 1. Prevalence of Autism in Denmark by Age Group and Year, 1980 to 2002

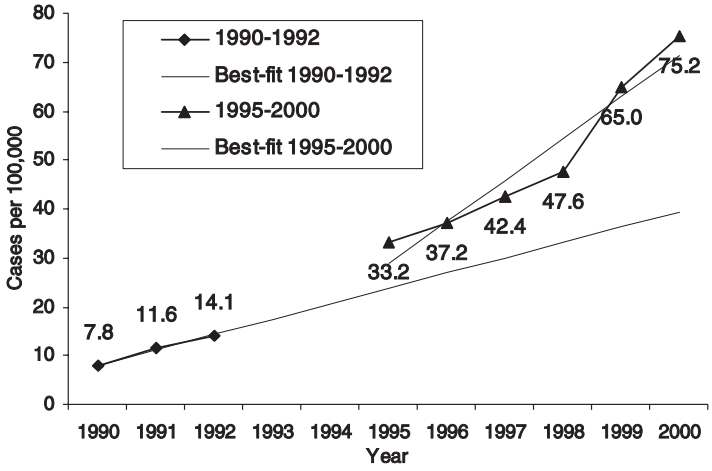

Figure 2. Prevalence Among 5-9 age Group Before (1990-1992) and After (1995-2000) Classification Change

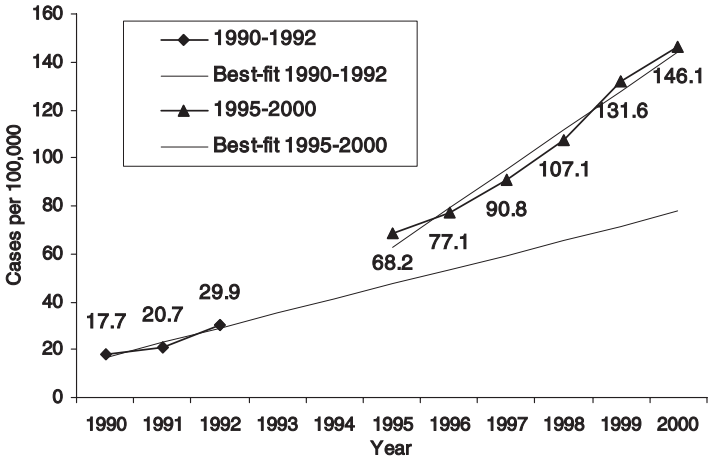

Figure 3. Prevalence Among 0-14 Age Group Before (1990-1992) and After (1995-2000) Classification Change

Results

A classification change from ICD-8[29] to ICD-10[30] in 1994 permitted additional diagnoses of autism beyond age 3 years. This probably caused a short-term distortion (or outlying prevalence data points) in the 5-9 age category during 1993-1994 (Figure 1). From 1990 to 1992 there is an increasing trend in this cohort, and during 1995 to 2000 a more prominent increase is observed (Figure 1).

Figure 2 (5-9 age group) and Figure 3 (under-15 age group) show the best-fit line through the initial and final increases in prevalence in the period before and after the starting period of greater diagnostic awareness. The unadjusted and adjusted RRs are given in Table 1 for the 5-9 and under-15 age groups. In each analysis, greater diagnostic awareness increased the number of cases of reported autism by a factor of approximately 1.8. Before adjusting for the effect of greater diagnostic awareness, prevalence of autism is 8.5 times higher among children aged 5 to 9 in 2000 relative to the prelicensure period 1980-1986. After adjusting for greater diagnostic awareness, the prevalence is 4.7 times or 370% higher in this cohort (Table 1).

Similarly, in the under-15 age group, the ratio of the prevalence of 144.12/100,000 in 2000 to the adjusted prevalence of 34.8/100,000 in the pre-licensure period yields an RR of 4.1 (95% CI, 3.5 to 4.9), or an overall increase of 314% [100(144.12-34.8)/34.8].

The increase in autism prevalence in the 0-4, 10-14, and 15-19 age groups is less than in the 5-9 age group (Figure 1). For the older age groups, this may reflect the lower vaccine coverage rates in the early years of the vaccination program. For the younger age group, this may reflect a delay in making the diagnosis.

The 20-24 age group is unique in that some individuals could have received the monovalent measles vaccine (MMV) as toddlers and then an MMR booster dose when it became available. The constant rate of increase occurs during 1992 to 1996 with a subsequent leveling off in 1997 (Figure 1).

As each 5-year cohort is replaced with MMR-vaccinated children, an approximately linear increase in autism prevalence occurs between 1991 and 2000 until each cohort becomes saturated with vaccinated individuals. The combined trend is shown in Figure 4 for children under 15 years of age. Except for the two outlying points in 1993 and 1994, there is a nearly constant rate of increase in prevalence of 13.8 cases/100,000 per year (correlation coefficient, $r^2 = 0.98$) from 1991 to 2000. Note the leveling off beginning in 2000 when 95 to 98% of children aged 15 months are vaccinated and the cohort is nearly saturated with vaccinees (Figure 4). Rather than separating the two periods of increase both before and after increasing diagnostic awareness, if we utilize the best-fit line through the combined periods 1991 to 2000, the prevalence of autism in Danish children under age 15 demonstrates an unadjusted increase of 677% from the mean of 18.8/100,000 in the prelicensure period 1980-1986 to 146/100,000 in 2002 (Figure 4). The adjusted increase obtained by considering the separate periods 1990 to 1992 and 1995 to 2000 produces approximately half the unadjusted percentage, or 314%.

Individuals in the cohorts of age 25 or greater experienced increases in autism prevalence from 1994 to 2002, but the curves are lower in magnitude and unsteady, ranging only from 0 to 10 cases per 100,000 population (Figure 5), as opposed to 18 to 150 cases per 100,000 population among those under 15 (Figure 4). In the elderly cohorts aged 50 to 59 and 60 to 64 (not shown), slight increases occurred 1994 to 2002 but again demonstrated unsteady and even lower prevalence ranging from 0 to 3 cases per 100,000 population. The change from ICD-8 (International Classification of Diseases, Eighth Revision*)* to ICD-10 was likely an added factor causing the marked increase in prevalence in all age categories after 1994.

Given that greater diagnostic awareness is a factor contributing to increased autism prevalence in the 5-9 age group, we investigated the sensitivity of this factor over the realistic range of values. The RR of 8.5 is biased high because of greater diagnostic awareness, based on the ratio of the prevalence in 2000 (71.43/100,000) to the mean prevalence during the pre-MMR period of 1980-1996 (8.38/100,000). As

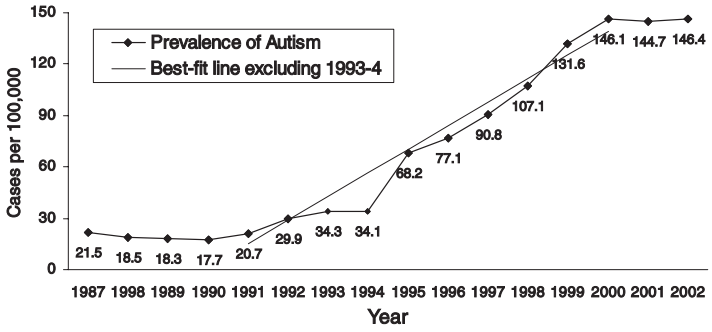

Figure 4. Prevalence of Autism in Denmark Among Individuals Aged < 15 Years by Year, 1987 to 2002[a]

[a]Best-fit line through 1991-2000 data points, excluding 1993-1994; slope = 13.8/100,000 per year; correlation coefficient, $r^2 = 0.98$.

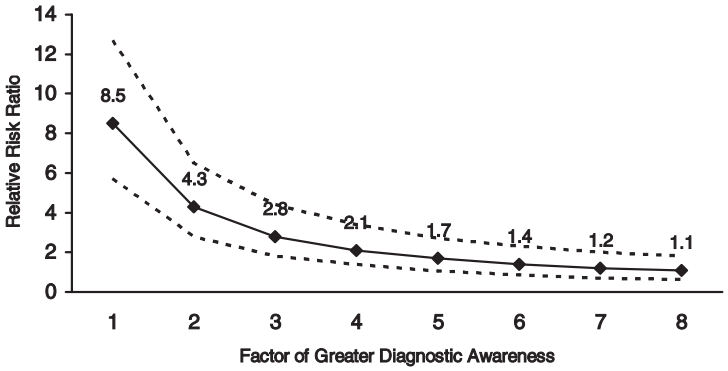

Figure 6. Autism Relative Risk (of Prevalence in Post- to Pre-licensure Periods) Among the 5-9 Age Group as a Function of Factor of Greater Diagnostic Awareness[A]

[A]Relative risk shown with upper and lower 95% confidence limits.

shown in Figure 6, if the prevalence in 2000 were inflated as much as 5-fold (and thus was actually 14.3/100,000), the RR of 1.7 (95% CI, 1.06 to 2.7) would still be statistically significant.

Table 1 indicates that the confounded prevalence in 2000 of 71.4/100,000 is 1.8 (71.4/39.4) times higher than the estimated prevalence of 39.4/100,000 without the confounders or ascertainment bias. A factor of greater diagnostic awareness of 1.8 corresponds to an RR of 4.7 (39.4/8.38) on the curve in Figure 6. Based on this sensitivity analysis, the RR remains statistically significant if the prevalence were as low as 14.3/100,000 in 2000, or 63.7% lower than the estimated 39.4/100,000.

Discussion

Because we did not request population data stratified by vaccination status, we were unable to compare vaccinated and unvaccinated cohorts as had been done in historical studies. Instead, since the vast majority of children aged 5 to 9 years received MMR vaccine, we compared autism principally in this age group in periods before and after introduction of the vaccination program. The lower prevalence of autism in the 0-4 age group was consistent with the mean age (4.7 years) at which autism is reported in Denmark. The 10-14 and 15-19 age groups reflect lower percentages of diagnoses as well as lower vaccine coverage percentages (relative to the 5-9 age group) in the early years after the introduction of MMR vaccine.

Since this study relies on epidemiologic methods, it may not successfully control for confounding and bias in the analysis of autism prevalence by age category. Factors such as greater diagnostic awareness of autism (due to various studies conducted), genetic predisposition or associations, congenital or acquired aberrant TH2 immune programming, increases in viral encephalitis early in life, vitamin B12 deficiency, hormonal disorders, environmental factors, as well as other unknown confounders may all contribute to autism prevalence that is higher in the post-licensure period of MMR compared to the pre-licensure period. There is certainly an under-ascertainment of autism because some children are not old enough to be diagnosed.

The principal limitation of this investigation is that the adjusted RR is highly sensitive to the increasing trend during 3 years, 1990 to 1992; however, the factor of 1.8 determined for greater diagnostic awareness following the classification change in 1994 seems plausible. The RR among children aged 5 to 9 years remains statistically significant even if the factor for greater diagnostic awareness approaches 5.

The prevalence of autism among 5-9-year-olds increased by 3.8/100,000 between 1990 and 1991, from 7.8/100,000 to 11.6/100,000. We would reasonably expect a relatively greater increase in prevalence from 1991 to 1992 if additional cases were added to the registry in 1992 from a large Copenhagen clinic with 20% of the total autism cases in Denmark. Yet, the incremental increase was only 2.5/100,000 in this cohort. Thus, it is highly unlikely that any ascertainment bias due to additional cases from the Copenhagen clinic affected the 1992 prevalence. Any contribution of cases from the Copenhagen clinic occurring in 1993 and thereafter would be included in the factor of greater diagnostic awareness.

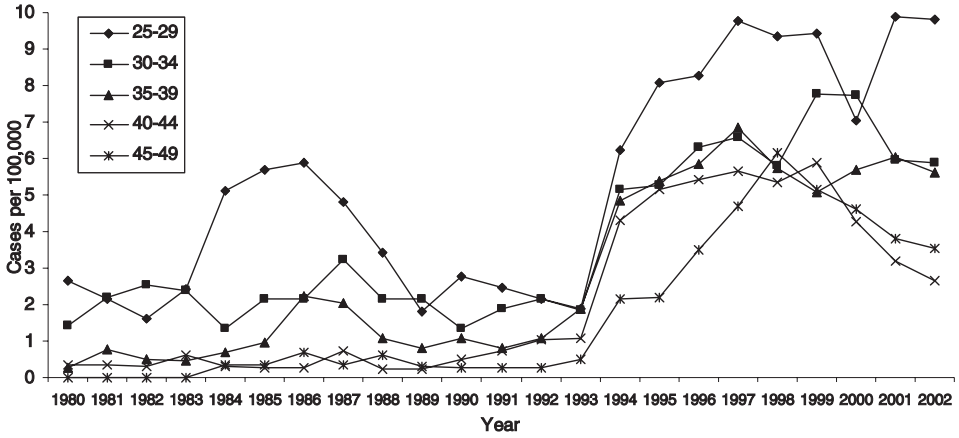

Figure 5. Prevalence of Autism in Denmark by Older 5-year Age Groups and Year, 1980 to 2002[a]

[a]Classification change from ICD-8 to ICD-10 occurred in 1994.

Three principal factors argue against the thesis that autism is wholly explained by genetic factors, including DNA mutation, polymorphisms, or unbalanced gene expression: (1) the increased prevalence of autism over 9 years from 1991 to 2000 and subsequent leveling off among children aged 5 to 9 years; (2) the adjusted 370% increase in autism from the pre- to post-licensure periods in the 5-9 cohort; and (3) diagnosis of autism at an estimated mean age of 4.7 years.

Given an ideal startup coverage rate of 100% of the birth cohort vaccinated at age 15 months, we would expect a constant rise in the prevalence of autism among the 5-9 age group beginning in 1991, or 4 years after introduction of MMR vaccine, with a leveling off after 5 years, at which time the cohort would have been completely saturated with vaccinees. However, startup vaccine coverage rates were low, about 70%, rising to approximately 80% in 1989.[31]

According to ICD-8, developmental abnormalities must have been present in the first 3 years for the diagnosis of autism to be made, but the syndrome could be diagnosed in all age groups. Interestingly, the change to ICD-10, which allowed for diagnoses of *atypical* autism beginning beyond age 3, did not immediately increase but instead resulted in a temporary leveling off in autism diagnoses among 5-9-year-olds and a slight decrease among 10-14-year-olds from 1993 to 1994 (Figures 1 and 4). We speculate this trend was in part owing to the fact that the large majority of autism diagnoses among children aged 3 to 4 years were delayed until school entry at age 5. Thus, it is plausible that the curve of autism prevalence required 4 additional years, or a total of 9 years, to level off.

The cause of the rapid rise in autism in the 1990s remains unknown and controversial. If we assume that some environmental trigger causes autism in the first 1.5 years of life, and that Denmark's rise is attributable to some abrupt event, then that event is likely to have occurred in the mid- to late-1980s. As MMR vaccine was introduced in 1987, we suggest that it was that trigger.

While Denmark was impacted by considerable ascertainment bias due to changes in diagnostic classification and inpatient/outpatient enrollments, it did not experience the confounding due to thimerosal and changes to the immunization schedule that have been inherent in other studies.[10]

The results of the current analysis are strengthened by the fact that the U.K. and U.S. introduced MMR vaccine in different years, yet both showed the first appreciable increases in autism following MMR vaccine introduction. Wakefield cited an increased prevalence of autism in North West London after MMR vaccine was introduced in the U.K. in 1988 that was almost identical to that in California a decade earlier when MMR vaccine became widely used in the U.S.[32] Because similar diagnostic criteria for autism are used in the U.K. and the U.S., it is unlikely that this finding reflects artifacts due to changing diagnostic criteria.

Taylor reported a significant temporal clustering in cases of core autism and atypical autism within 6 months following the MMR vaccine in the North East Thames region for birth cohorts from 1979 to 1992, but chose to dismiss the finding as parental recall bias.[8] Historically, during approximately 1950-1970, late onset autism at 18 to 24 months of age was rarely reported. Following inoculation with the MMR vaccine, parents (and medical professionals) have reported that otherwise normal children stagnated and then regressed in terms of interest in surroundings, sociability, and ability to communicate. In time, repetitive obsessive behavior, loss of language, loss of acquired skills, and increased agitation and inattention became prominent.[26] These are marked changes compared to the period prior to MMR vaccination when these same children were considered developmentally normal and responsive.

Independent research supports a possible association between MMR vaccination and autistic encephalopathic regression (AE) in children who previously had been developmentally normal.[1,22-26] In part, the delay or failure to ascertain regression resulted from the belief of most diagnosticians that such children were always autistic and that parents had simply failed to notice it. The later diagnosis of childhood autism in Denmark may suggest that a larger proportion of children were developmentally normal until they succumbed after some environmental insult or trigger, such as MMR.

Interestingly, according to the U.S. Department of Education, the number of cases of autism among individuals aged 6 to 21 in U.S. schools increased from 12,222 in 1992-1993 to 118,602 in 2002-2003, for an overall increase of 870%.[33] Similar increases have been reported in schools in England, Scotland and Canada.[34]

Because the pediatric vaccination practices of Denmark differed greatly from those of the U.S. during the study period, Madsen's conclusions, even if relevant to Denmark, were certainly not applicable to the U.S.

Diagnosis of autistic spectrum disorder (ASD) is often neither timely nor accurate. Onset of ASD may be rapid or gradual over many years. The syndrome ranges from mild to severe. These factors may be influenced by genetic predisposition.[26] Certainly the temporal relationship between MMR vaccination and the variable onset of autistic symptoms accentuates the difficulty inherent in the design of robust epidemiological analyses. The biological mechanisms that would be involved in an MMR-autism link remain unknown and will require further study.

Conclusions

Trends in prevalence data in Denmark suggest a temporal association between the introduction of MMR vaccine and the rise in autism. Because thimerosal was not used in any pediatric vaccine in Denmark since 1992 and the greatest increase in autism prevalence followed that year, it is likely that one or more of the viral components or their combination in the MMR vaccine contributed to the reported increase.

Autism rates in the U.S. have surpassed those of Denmark. Notably, in the U.S. the MMR vaccine was administered at the age of 12 months, often with two thimerosal-containing products, the *Hemophilus influenzae* B and hepatitis B vaccines, while it was usually administered alone in Denmark at the age of 15 months. Additionally, by the age of 6 months, infants in the U.S. had been exposed to 12 vaccines and up to 187.5 micrograms of thimerosal, compared to 6 vaccines with no thimerosal in Denmark.

Because of the above findings and the increasing resistance to the present MMR vaccination programs, the return to the monovalent vaccines may be appropriate until proposed alternatives are developed and perfected. Aerosolized measles and measles-rubella vaccines have been widely tested and found to produce significantly greater immune responses with less potential side-effects than that resulting from the injected vaccines.[35-38] Research into the production of a non-replicating MMR vaccine has also been launched. Such a vaccine should demonstrate improved biosafety and may be better accepted because it will not contain live viruses.[39]

Developing safer vaccination strategies and supporting further investigation of the hypothesized link between the MMR vaccine and autism should have a high priority.

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Commentary:

MMR and Autism in Perspective: the Denmark Story

Carol Stott, Ph.D.; Mark Blaxill; Andrew J. Wakefield,M.B., FRCS

"When sorrows come, they come not single spies, but in battalions."
Hamlet, Prince of Denmark, Act IV Scene III

Autism and related developmental disorders, once rare, are now becoming a common problem in Western countries. Although frequently catastrophic in their effects, the current crisis has come up against a "duck and cover" mentality from many a dusty corner of conventional medical wisdom.

Classification of these disorders is symptomatic and owes little to etiologic or pathogenetic considerations. The major classification systems (DSM and ICD) are of extremely limited value – even an impediment – when considering mechanisms of causation. Both systems attempt to handle diagnosis in a discontinuous fashion under the broad umbrella of Pervasive Developmental Disorder (PDD) [Table 1]. With considerable symptomatic overlap between these disorders, there appears to be no biological evidence that they are not, or cannot be, continuous, representing a spectrum of varying phenotypic character and severity, sharing certain common pathogenetic features, genetic polymorphisms, and etiologic origins.

The limitations of the symptomatic classification of childhood developmental disorders in general is exemplified by the observation that the now increasingly well characterised intestinal pathology[1-9] reported in regressive autism has also been described in children whose diagnoses are consistent with autism,[1,2] childhood disintegrative disorder,[1] attention deficit hyperactivity disorder (ADHD),[10,11] and Asperger's syndrome.[2] This suggests an underlying pathogenetic commonality that transcends behavioral descriptors. In summary, rather than helping to resolve the origins of childhood developmental disorders, the diagnostic criteria are artefactual and evanescent. As such, they may serve to confuse by accommodating different interpretations of the same data, such as those coming from Denmark.

In this issue, Goldman and Yazbak[12] use data from the Danish Psychiatric Central Register Data (DPCRD) to report prevalence of autism by age category during 1980 to 2002. They show that prevalence of autism among children aged 5-9 years increased from a mean of 8.38/100,000 in the pre-licensure era (1980-1986) to 71.43/100,000 in 2000. After attempting to adjust for the factor (or artefact) of *greater diagnostic awareness* – the first study to actually try to account for this effect – the prevalence rate-ratio is 4.7 (95% CI, 3.1 to 7.2) for the post-licensure period compared with the pre-licensure period. They conclude that longitudinal trends in prevalence data suggest a temporal association between the introduction of MMR vaccination in Denmark and the rise in autism.

Table 1. Pervasive Developmental Disorders: ICD-10 vs. DSM-IV

ICD-10	DSM-IV
Childhood Autism	Autistic Disorder
Atypical Autism (PDD.NOS)	PDD.NOS
Rett's Syndrome	Rett's syndrome
Other Childhood Disintegrative Disorder	Childhood Disintegrative Disorder
Overactive Disorder Associated with Mental Retardation and Stereotyped Movement	
Asperger's Syndrome	Asperger's Disorder
Other PDDs	

The authors introduce the paper by taking issue with the methods and interpretation of the oft-quoted findings of Madsen et al.,[13] correctly highlighting the substantial under-representation of autism diagnoses and vaccination status for children born in the later study years. Given that the autism spectrum disorder (ASD) children in the Madsen study were diagnosed at a mean of around 5 years of age, a high proportion of children destined for an autism diagnosis were too young to have received this diagnosis by the end of the study period. This would apply to all children under the age of 36 months and, in a practical sense, to many of the 3-5 year olds. Of those children born in 1997 and 1998, representing a substantial (39%) of the 2.1 million years of observation time, many had yet to receive their MMR vaccine.

A previous submission of an earlier version of the current Goldman and Yazbak paper to the journal *Vaccine* drew hostile responses from reviewers, including the Centers for Disease Control and Prevention (CDC), who contended that the ascertainment bias inherent in the Madsen study was corrected by age adjustment of the data. The interpretation of the Madsen study rests very much, therefore, upon the validity of the age adjustment itself. Clearly, in a developmental disorder such as autism/ASD, one cannot assume an equal distribution of diagnostic risk by age. Equally, we know that vaccine exposure is not random with respect to age and that many children included in the study were still too young for exposure to have occurred by the end of the study period. These unexposed children would also be at low risk of an autism diagnosis but would nonetheless contribute equally to person-years at risk. Where the unvaccinated group is allowed to contribute equal person-years at risk for age-bands where risk of both exposure and diagnosis is minimal, resulting calculations will misrepresent the real situation by inflating the observed positive association between "lack of exposure" and "no diagnosis." The treatment of age in modelling risk for developmental disorder is complex and should be substantially informed by the epidemiology of the disorders and exposures in question. Details provided by Madsen et al. are not sufficient to allow judgments to be made about the extent to which they achieved this, but several points raised by others suggest that the treatment was inadequate.

As an example, Dr. S. Suissa of McGill University wrote, in a response that the *New England Journal of Medicine* declined to publish:

> Madsen et al. observed an adjusted rate ratio of autistic disorder after vaccination of 0.92 relative to no vaccination, when the crude rate ratio (my computation) was 1.45 (95% confidence interval 1.08-1.95). Moreover, the rate by time since vaccination increases to a high of 27.3 two years after vaccination (rate ratio 2.5) and decreases thereafter to 11.4 per 100,000 per year (Figure 1).
>
> It is stated that adjustment for age eliminated these rate increases, but the corresponding data are unusual. Indeed, the rates of autistic disorder by age at vaccination, although not the age at follow-up, are 18.9, 14.8, 24.6, 26.9 and 12.0

Also see page 70.

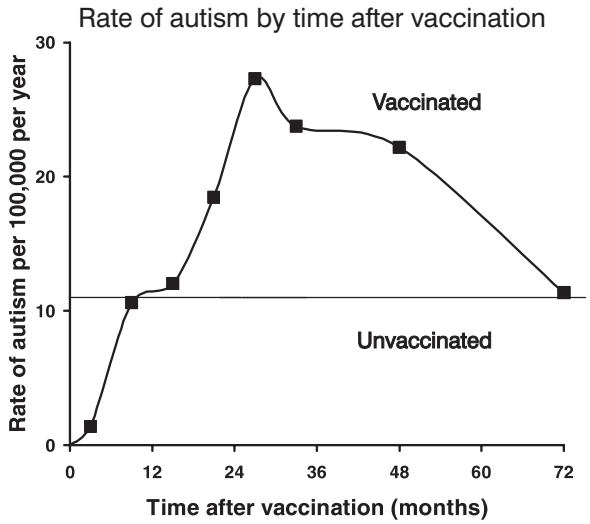

Figure 1. Incidence rate of autism in Denmark per 10^5 population per annum by time after vaccination vs. overall rate of 11.0 per 10^5 for the no- vaccination group.
Source: S. Suissa, Department of Epidemiology and Statistics, McGill University.

per 100,000 per year respectively for ages <15, 15-19, 20-24, 25-35 and >35 months. These rates are all above the overall rate of 11.0 for the reference group of no vaccination, over all ages. It is then somewhat implausible for the adjusted rate ratio to fall below 1, unless the risk profile by age in the unvaccinated is vastly different than in the vaccinated (effect-modification). In this case, the adjustment for age could have been artificial. It would be useful then to present rates on subjects 24-29 months since vaccination and on the unvaccinated (crude rate ratio 2.5) stratified by age. Otherwise, one could be tempted to conclude that the figure is in fact suggestive of an association between MMR vaccination and the risk of autism.

If, as is suggested, Madsen et al. adjusted inappropriately for age, then their findings need to be reinterpreted. In the absence of such adjustment, there is a statistically significant 45% excess risk of autism in recipients of the MMR vaccine and therefore, an association between MMR and autism in this Danish population.

Reviewers of the prior submission of Goldman and Yazbak's article to *Vaccine* are critical of the way the data are presented, preferring, not unreasonably, representation of prevalence by year of birth (data not available to the authors) in order to demonstrate the presence or absence of a *step-up* in the proportions of children with autism following MMR introduction. The requested data, provided by the DPCRD, are presented below [Figure 2], and provide support for a role for MMR exposure in increasing population frequency of autism. For children born in Denmark before 1987, the year in which MMR was introduced, proportions of children with autism did not change significantly over time. For children who were exposed to MMR, beginning with those born in 1986, the proportions of those with autism showed an initial sharp increase that continued over time, increasing by 15% per year, an increase that is statistically significant.

Use of these data avoids the oft-repeated error of confusing date of registration (which for autistic subjects in Denmark has varied from early childhood to early adulthood) with onset. Instead, year of birth is used to mark differences in time of onset, a far simpler basis from which to observe trends, and to directly compare the time trends in proportions of children with autism in cohorts born before and after the introduction of childhood MMR immunizations. This approach has several other advantages:

1. Goldman and Yazbak are forced to conflate diagnosis with registration and explain changes in registration practices through "greater diagnostic awareness." Although we sympathize with their intent, the term may be misleading. It is quite likely that most children with autism born before the change in registration practices in the early 1990s were *diagnosed* as autistic. They were simply not *registered* under procedures that included only inpatient diagnoses in the DPCR. In contrast, we offer a simpler assumption, that is, that in the transition to include outpatient registration in the DPCR, sufficient time must be allowed for full ascertainment of autism diagnoses in a given birth cohort in order for disease frequency estimates to be considered reliable.

2. Goldman and Yazbak take as their null hypothesis that the magnitude of the increase in proportions of children with autism can be represented as a discrete shift in a prevalence trend line as "diagnostic awareness" improves. This requires complex calculations in order to demonstrate the shift in registration practices. A more pragmatic null hypothesis is that observed proportions of children with autism should not change once a study population has been fully ascertained, including both initial diagnosis and (in some cases significantly delayed) registration with the DPCR.

3. Goldman and Yazbak measure the step-up in proportion of children with autism subsequent to MMR introduction as a continuation in a trend line increase even after adjustment for a step-up in registration. It is not clear, however, that the effect of MMR exposure on autism should be gradual. Alternatively, the data in Figure 2 show a rapid rise in proportions with autism after 1987, an increase more consistent with the hypothesized pattern of exposure.

The step-up that is observed in the first birth cohorts eligible to receive the MMR vaccine is striking, and consistent with the progressive increase in MMR uptake in Denmark.

The step-up model for autism and MMR was examined previously by Taylor et al. in a UK population for whom MMR vaccine was introduced in 1988.[14] The authors purported to test the hypothesis that if MMR were causally related to autism, there should have been a step-up in the proportion of children with autism in the first groups to receive this vaccine, which the authors took as being children "born in 1987 and later birth cohorts." In fact, older children, born in 1984-1986, also received the vaccine as part of the UK's "Catch-up" campaign. The authors erroneously concluded that the rise in autism started several years before MMR was introduced and therefore had nothing to do with this vaccine. In fact a substantial number (n=36) of their cohort had formed part of the "Catch-up" campaign, and the step-up in autism occurred at precisely the time the first children received MMR vaccine in North London. Upon being challenged on this fact in the *Lancet*,[15] the authors' subsequent plea in

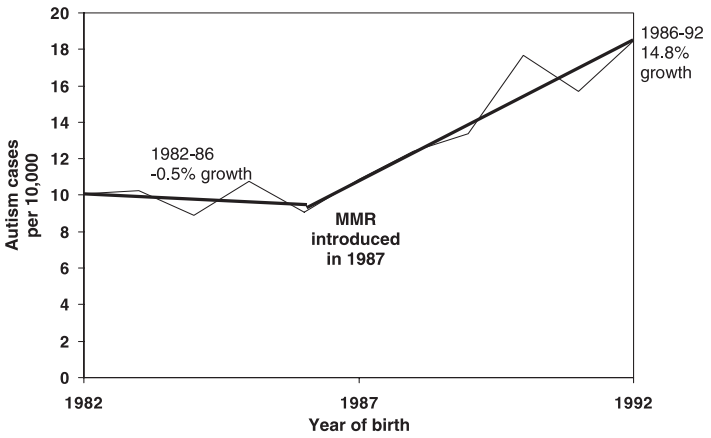

Figure 2. Autism prevalence in Denmark by year of birth, 1982-1992. Lines of best fit are shown for birth years 1982 to 1986, and from 1986 to 1992. Children born in 1986 were first to receive MMR in Denmark. The annual growth before MMR was -0.5% [trend = -0.15; 95% CI, (-1.06) - (-0.76), ns], compared with 14.8% after MMR introduction (t = 6.94, p<0.001; trend 1.54, 95% CI, 0.97 - 2.11).
Source: Danish Psychiatric Central Register Data, with gratitude to Safe Minds.

mitigation was even more bizarre, claiming that review of the records in the older recipients of MMR had identified parental concerns before MMR vaccination.[16] They used this argument, speciously, as justification for interpretation of a graph which simply presented number of children with autism versus year of birth, and owed nothing to apparent expressions of parental concern. The title of their paper, "Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association," is also misleading for other reasons. The authors tested the hypothesis of temporal clustering of age at diagnosis of autism in defined time periods post MMR vaccination, an analysis which, because of the considerable delay in diagnosis, is likely to bias towards a negative finding.[17] Despite this, they found significant clustering of diagnoses by 6 months post MMR. The authors tested a hypothesis and found a positive association; what the title of the paper actually reflects is their opinion rather than the statistical facts.

Lauritsen et al.[18] have recently contributed to the Danish debate, with data that confirm a striking change in the reported incidence and prevalence of autism and related PDDs in Denmark over the period 1971-2000, endorsing the fact that, among other things, children born in the latter part of the study cannot be considered representative of the autism population over the entire period, an important factor in the aforementioned process of age-adjustment. The authors put the rise down largely to greater diagnostic awareness due to "enlargement of the concept of PDDs" (whatever this may mean), changing diagnostic criteria, and case registration. However, reexamination of the data is instructive; in the early 1990s the incidence and prevalence of PDDs increased in Denmark across the spectrum, including atypical autism, autism, and PDD-NOS. Lauritsen et al. focus upon the rise in the population frequency of autism as reflecting, in part, a change from ICD-8 to ICD-10, which appears to have made it easier for a child with a PDD to get a diagnosis of autism. And yet it is the PDD-NOS group of children – the pool of children from which the autism group would have been apparently artificially inflated beyond 1994 – that showed the most dramatic increase. The rise in PDD-NOS was not explained by the introduction of a new diagnostic category as of 1994, since incident cases were diagnosed in Denmark as early as the late 1980s.

In summary, it appears that a new trend in PDD emerged in children born in Denmark in the late 1980s – a change that coincided with the introduction of MMR and which is obscured rather than explained by diagnostic change. The data of Madsen et al., unadjusted for age, support an autism-MMR association.

There has been much recent soul-searching among members of the UK Department of Health and their public relations staff as to why they do not inspire confidence in issues of vaccine safety. They would do well to factor in both public and professional disquiet when presented with the comparison between statistics and the careful study of individual affected children. In this context, the alarming statements of representatives of the CDC at the 2000 Simpsonwood meeting between the CDC and vaccine manufacturers are revealing.[19] When considering how to deal with data that indicated a positive association between the mercury-based vaccine preservative thimerosal and neurodevelopmental disorders, epidemiologists from the CDC recommended changing the study inclusion criteria, post hoc, to get them any result they wanted.[19] This does not provide any basis for confidence.

In the complex arena of vaccine-related problems, the drawn-out experience with SV40-contaminated polio vaccines and certain human cancers[20] may provide, for the current issue, a crystal ball wherein a negative interpretation of early epidemiological data was pitted against positive findings of basic and clinical science; the latter prevailed when the mists cleared. The Institute of Medicine, in seeking to bring an end to research into MMR and autism,[21] appears to have learned little from prior experience. The CDC, for its part, is likely to be accused of adding conspiracy to confusion through its latest Physician Survey Study on vaccines and adverse reactions. In the only question relating to concerns over specific individual vaccines and autism, no box has been provided for MMR.

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Conflict of Interest Statement: AJW is a named inventor on a viral diagnostics patent. AJW and CMS have acted as experts to the Court in MMR-related litigation. MFB is the father of a child diagnosed with PDD/autistic disorder.

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