Commentary:

MMR and Autism in Perspective: the Denmark Story

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"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.

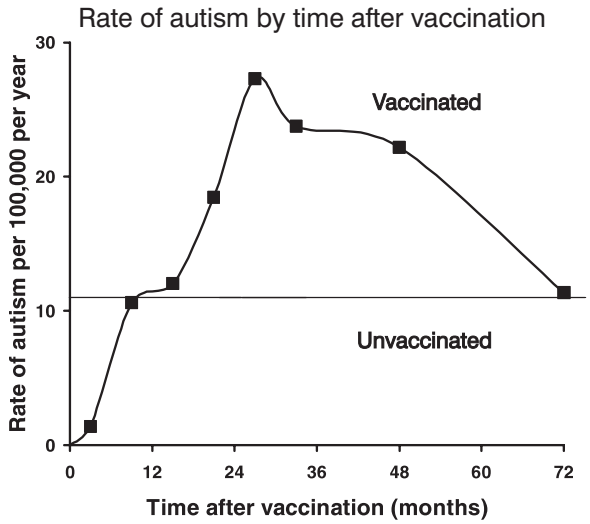

Figure 1. Incidence rate of autism in Denmark per 10^5 population per annum by time after vaccination vs. overall rate of 11.0 per 10^5 for the no- vaccination group.
Source: S. Suissa, Department of Epidemiology and Statistics, McGill University.

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

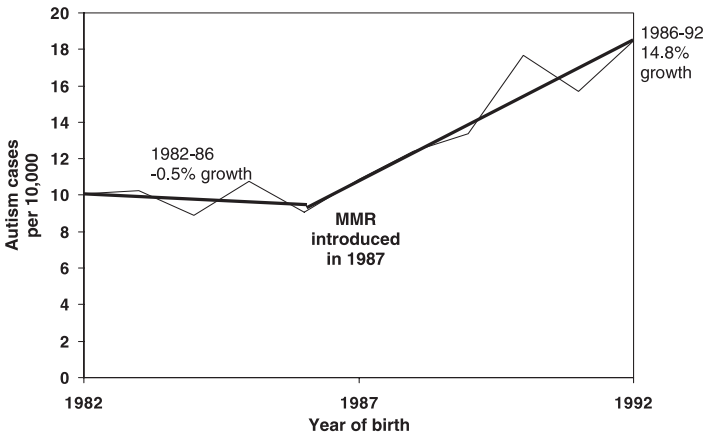

Figure 2. Autism prevalence in Denmark by year of birth, 1982-1992. Lines of best fit are shown for birth years 1982 to 1986, and from 1986 to 1992. Children born in 1986 were first to receive MMR in Denmark. The annual growth before MMR was -0.5% [trend = -0.15; 95% CI, (-1.06) - (-0.76), ns], compared 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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