DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

DEC 19 2006

The Honorable Ralph Regula
Chairman
Subcommittee on Labor, Health and Human
Services, Education, and Related Agencies
Committee on Appropriations
Washington, D.C. 20515

Dear Mr. Regula:

In follow up to Dr. Dave Weldon's letter of December 5, 2006, I have enclosed copies of the requested documents that are related to the article on "Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data (Madsen, et al., 2003). Since the Centers for Disease Control and Prevention is neither an author nor a co-author of this article, we do not have other versions of this study or other reviewers' comments. For your information, the only thing that has been redacted is the personal cell number of one of the researchers.

I appreciate your interest in this matter and hope this information is helpful.

Sincerely,

Julie Louise Gerberding, M.D., M.P.H.
Director

Enclosures

Viquar Ahmad

Assistant to the Chairman

Appropriations Subcommittee

Labor, Health and Human Services and Education

2306 Rayburn House Office Building

Washington, D.C. 20515

(202) 225-3876

Schendel, Diana

From: Kreesten Meldgaard Madsen [KMM@SOCI.AU.DK]
Sent: Wednesday, November 13, 2002 5:33 AM
To: Marlene Briciet Lauritsen; Poul Thorsen; Schendel, Diana
Subject: RE: Manuscript about Thimerosal and autism

Hi Marlene,
I don't remember the actual phrasing of the rejection from JAMA - In the sence of "is it worth trying again given the situation". I all cases your point about the decreasing rates in 2001 seems to be of importance and probably should be added. I am not currently at the university but I will contact you and Poul tomorrow to make up our minds. Best regards, Kreesten

-----Original Message-----
From: Marlene Briciet Lauritsen [mailto:mbl@dadlnet.dk]
Sent: Wed 13-11-2002 09:24
To: Poul Thorsen; Kreesten Meldgaard Madsen; dcs6@cdc.gov
Cc:
Subject: Manuscript about Thimerosal and autism

Dear Poul, Kreesten and Diane Schendel

Attached I send you the short and long manuscript about Thimerosal and autism in Denmark. The long manuscript has been submitted to JAMA and includes both data on the incidence and prevalence of autism. The shorter version includes only incidence data and has been submitted to Lancet. Unfortunately, both manuscript have been rejected.

I need to tell you that the figures in the manuscripts do not include the latest data from 2001. I only have these figures as a paper version and they are at work while I am working at home these days. But the incidence and prevalence are still decreasing in 2001. Also, the manuscript submitted to JAMA do not cite some of the latest papers on the prevalence of autism which I will do in case it should be submitted again.

I look forward to hear from you again.

Best regards

Marlene

Thimerosal and the occurrence of autism
Negative evidence from Danish population-based data

Research letter

Marlene B Lauritsen, Carsten B Pedersen, Kreesten M Madsen, Poul Thorsen, Anne-Marie Plesner, Peter H Andersen, Preben B Mortensen

Department of Psychiatric Demography, Psychiatric Hospital in Aarhus, DK-8240 Risskov, Denmark
(M B Lauritsen, MD); **National Centre for Register-based Research, University of Aarhus, DK-8000 Aarhus C, Denmark**
(C B Pedersen Msc, P B Mortensn DMSc); **The Danish Epidemiology Science Centre at the Department of Epidemiology and Social Medicine, University of Aarhus, DK-8000 Aarhus C, Denmark**
(K M Madsen MD, P Thorsen PhD); **State Serum Institute, Department of Medicine, DK-2300 Copenhagen S, Denmark**
(A M Plesner PhD); **and State Serum Institute, Department of Epidemiology, DK-2300 Copenhagen S, Denmark**
(P H Andersen MD)

Correspondence to: Dr Marlene B. Lauritsen (e-mail: mbl@psykiatri.aaa.dk)

Summary

It has been suggested that thimerosal, a mercury containing preservative in vaccines, is a risk factor for the development of autism. We examined whether discontinuation of the use of thimerosal containing vaccines in Denmark lead to a fall in the incidence of autism. The Danish Psychiatric Central Register was used to obtain information on referrals for autism. The incidence of autism remained constant during the period of use of thimerosal in Denmark, and the rise in incidence only started after the discontinuation of thimerosal. Our data do not suggest an association between thimerosal containing vaccines and the occurrence of autism.

Thimerosal and the occurrence of autism - Negative evidence from Danish population-based data

There has been concern that there may be an association between thimerosal, a mercury containing preservative found particularly in multi-dose vaccine preparations, and neurodevelopmental outcomes, including autism (1). Epidemiological evidence is non existing and further research has been requested (2). However, prenatal exposure to low doses of methylmercury has been associated with subtle neurodevelopmental abnormalities in some studies (3). Furthermore, similarities in symptoms between autism and mercury intoxication have been used to evidence causality (1). In Denmark, thimerosal was used in childhood vaccines from the early 1950s until 1992. The objective of our study was to assess the incidence rates of autism before and after discontinuation of thimerosal to see if the discontinuation led to a decrease in the incidence of autism.

The use of thimerosal vaccines was only interesting for the purpose of this study from 1961 onwards, because since 1969 information about diagnoses of autism could be obtained from a nationwide computerized registration system, the Danish Psychiatric Central Register (DPCR). Thimerosal was used in the diphtheria-tetanus-pertussis vaccines given in four doses during 1961-1970, and in the whole cell pertussis vaccines given in three doses during 1970-1991. The concentrations used in the vaccines from 1961-1970 and from 1970-1991 were 0.01% = 0.1 mg thimerosal which equal 50μg mercury per ml vaccine. The amount of vaccine given was 1 ml, except for the first dose of monocomponent pertussis vaccine where it was only 0.5 ml from 1970-1991. This means that children who received the full vaccination programme during the period 1961-1970 would receive totally 0.4 mg thimerosal or 200μg mercury and during the period 1970-1991 0.25 mg thimerosal or 125μg mercury. All vaccinations were given free of charge. Data about the use of thimerosal containing vaccines were available from the State Serum Institute. Acceptance of vaccinations in Denmark has

always been very high. We only obtained data on vaccination coverage from 1979 onwards and found coverage rates of more than 90%.

Psychiatric inpatient treatment in Denmark has been reported to DPCR since 1969, and since 1995 outpatient activities were registered as well, providing the opportunity to examine long-term trends of the occurrence of autism in a total national population. We obtained information on all children who from birth to the 10th birthday were diagnosed with autism in the period from January 1, 1971 to December 31, 2001. The date of onset was defined as the first day of the first admission leading to a diagnosis of psychosis proto-infantilis (ICD-8: 299.00) or psychosis infantilis posterior (ICD-8: 299.01) or from 1994 onwards, infantile autism (ICD-10: F84.0) or atypical autism (ICD-10: F84.1).

Incidence rates were calculated for each year 1971-2001 using the age and gender specific number of persons in Denmark as a denominator. For each year and age band, we calculated the *incidence* as the number of people who at that age band and year was diagnosed with autism *for the first time ever* divided by the total number of people alive and living in Denmark at that age band and year. A total of 1,103 children with a male to female ratio of 3.5:1 had been diagnosed with autism prior to their 10th birthday. Figure 1 shows the incidence rates according to calendar year and age band. The incidence was stable until 1990 and thereafter it increased in all age groups, with the exception of those below 2 years, until 1999. Generally rates decreased in 2000 and 2001.

There was no trend toward an increase in the incidence of autism during the period when thimerosal was used, and an increase rather than a decrease occurred after the discontinuation of thimerosal (Figure 1) so our data could not confirm any correlation between the use of thimerosal as an additive to vaccines and the incidence of autism in Denmark. We cannot, of course, exclude that thimerosal doses larger than used in Denmark may lead to neurodevelopmental damage.

The increase in the incidence of autism from 1990 onwards may be due to more attention being drawn to the syndrome of autism and to a change in the diagnostic criteria from ICD-8 to ICD-10 in 1994. Also, outpatient activities were included in the DPCR in 1995 and since many patients with autism in recent years have been treated as outpatients this may exaggerate the incidence rates, simply because a number of patients attending the child psychiatric treatment system before have been recorded for the first time in DPCR, and thereby seem to be new cases. Figure 1 may reflect this process of inclusion of previously undetected or unregistered cases since the largest incidence rates were found in the oldest age groups and from 2000 the incidence rates decrease except in the group of children younger than two years of age. The trend with increasing incidence rates of autism is also seen in other studies (4) but the explanation is not evident. Also Croen et al. (5) found that the prevalence of autism diagnosed in the very large Californian birth cohort 1987-1994 increased whereas the prevalence of children diagnosed with mental retardation decreased in the same period indicating that some autistic cases previously were diagnosed as mentally retarded only.

This study investigated if the discontinuation of thimerosal containing vaccines was followed by a decrease in the occurrence of autism. The incidence of autism remained constant during the period of use of thimerosal in Denmark, and the rise in incidence only started after the discontinuation of thimerosal. In conclusion, our data do not suggest an association between thimerosal containing vaccines and the development of autism.

Acknowledgments

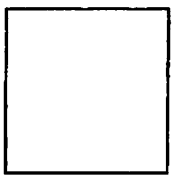
The National Centre for Register-based Research and The Danish Epidemiology Science Centre are financially supported by the Danish National Research Foundation. The study was supported by The Stanley Medical Research Institute. No funding sources were involved in the study design.

Conflict of interest statement

None of the authors nor our employers have any conflicts of interest with regard to the conduct or publication of this study.

Figure 1

Incidence of autism from January 1 to December 31 by age and calendar year



1. Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poisoning. Med Hypotheses 2001;56(4):462-71.

2. IOM (Institute of Medicine). Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders. Washington DC: National Academy Press: 2001.

3. EPA (Environmental Protection Agency). 1997. Mercury Study Report to Congress: Volume 1 Executive Summary EPA 452/R-97-003. Washington, DA: EPA.

4. Kaye JA, Mar Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. BMJ 2001;322(7284):460-3.

5. Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. J Autism Dev Disord 2002;32(3):207-15.

Schendel, Diana

From: Boyle, Coleen
Sent: Thursday, December 05, 2002 2:54 PM
To: 'pt@SOCI.AU.DK'; Schendel, Diana
Subject: ltr of support for thimerosal-autism

Hi: Sorry for the delay in drafting this letter -- happy to incorporate any comments. Jose is reviewing. Just need to know

autism_thimerosal_
danishltrofs...

Journal. Cheers, Coleen

Coleen Boyle, Ph.D.
Associate Director for Science and Public Health
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Hwy, NE
Atlanta, GA 30341
(770)488-7366
Fx:(770)488-7156
cboyle@cdc.gov <mailto:cboyle@cdc.gov>

Dear Editor:

I am writing in support of the {Journal's} expedited review and consideration of the enclosed manuscript that examines the association between thimerosal, an ethyl mercury containing preservative, and autism. As you may know, there has been considerable interest by parents, clinicians, educators, and policy makers for an explanation of the marked increase in the rate of autism in recent years. A University of Davis study released in October of children identified through the California developmental disabilities service system, reemphasized the upward trend in autism and the lack of understanding as to the cause.

One factor hypothesized to have a causal role is childhood vaccinations. Specific aspects of vaccinations that have been subject to inquiry include the MMR vaccine and thimerosal. There are now numerous epidemiologic studies to suggest that the MMR vaccine is not associated with the risk of autism; an Institute of Medicine review that was published in 2000 concluded that the weight of the scientific evidence did not support a link between MMR vaccine and autism.

For thimerosal, however, there are limited data to evaluate this factor. Because mercury in its inorganic form is known to have serious neurologic effects, many parents have speculated that the increased number of vaccines (many of which contained thimerosal) may have been a significant factor in the recent rise in autism. The Danish study is a powerful epidemiologic study of this issue and capitalizes on the Danish health registry system that incorporates all heath encounters into disease and exposure specific registries. In addition, a key strength of the study is the ability to examine rates of autism prior to and after the *discontinuation* of vaccines containing thimerosal in Denmark in 1992. Contrary to what would be expected if thimerosal was linked to autism, the authors did not observe a decline in the rate of autism with the removal of thimerosal containing vaccines.

I feel this is a very important study that deserves thoughtful consideration by the Journal. Its findings provide one strong piece of evidence that thimerosal is not causally linked to autism. Thank you for your timely consideration.

Sincerely,

JFC

Schendel, Diana

From: Poul Thorsen [pt@SOCI.AU.DK]
Sent: Friday, December 13, 2002 3:31 PM
To: Schendel, Diana; Kreesten Meldgaard Madsen
Cc: Marlene Briciet Lauritsen; Marlene Briciet Lauritsen; Mortensen Preben Bo (Preben Bo Mortensen)
Subject: SV: q on thimerosal and autism paper

Dear Diana,

Thank you for the note. I suggest that you refer to Marlene B. Lauritsen or Preben Bo Mortensen and they could recommend the very persistent person to contact the Editor of "Pediatrics", whom then hopefully will give the same answer as you did. However, the manoeuvre will increase the Editors attention on the paper and then maybe speed up the process even further! I would not recommend handing out results that are not published, especially, not in this heated debate of autism.

Enjoy your weekend!

Best regards
Poul

-----Oprindelig meddelelse-----
Fra: Schendel, Diana [mailto:dcs6@cdc.gov]
Sendt: 13. december 2002 21:05
Til: Kreesten Meldgaard Madsen; Poul Thorsen
Emne: q on thimerosal and autism paper

Hi Kreesten and Poul,

We are having persistent questions from one of the congressional offices about data on the prevalence of autism in Denmark - in response to the NEJM article. I keep telling them that the information has been submitted for publication, I am not a co-author, and I can not give out any information that is under peer review (apart from the fact I don't have the actual data) - professional courtesy and ethics (and good science practice) just will not allow such mishandling. Coleen has been saying the same thing when they go to her (I didn't know that!).

But, they have now asked if we can tell them the subject matter of the paper. So, what do you feel about this - telling them it's an ecologic study of thimerosal use and autism rates over time in Denmark - period. Don't feel like you have to say yes to this request - no pressure at all. Hopefully the paper will be published and they'll see it soon anyway. Let me know what you think - Monday if possible. I don't have Marlene's email anymore, so please forward to her. Again, absolutely no pressure to comply. And we wanted to get your permission before we say anything.

Have a good weekend,
Diana

Diana Schendel, PhD.
National Center on Birth Defects
and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Hwy, MS F15
Atlanta, GA 30341

ph: 770-488-7359
fax: 770-488-7361
email: dschendel@cdc.gov

Schendel, Diana

From: Kreesten Meldgaard Madsen [KMM@SOCI.AU.DK]
Sent: Monday, December 16, 2002 6:48 AM
To: Poul Thorsen; Schendel, Diana
Subject: RE: q on thimerosal and autism paper

Hi Poul and Diana,

Just to tell you that I agree with Pouls suggestion of referring to Marlene

Best regards,
Kreesten

Kreesten Meldgaard Madsen, MD
Danish Epidemiology Science Centre
at the Dept. of Epidemiology and Social Medicine
Vennelyst Boulevard 6
DK-8000 Aarhus C
Denmark
Phone: +45 8942 6149
FAX: +45 8613 1580
E-mail: kmm@dadlnet.dk

-----Original Message-----
From: Poul Thorsen
Sent: 13. december 2002 21:31
To: 'Schendel, Diana'; Kreesten Meldgaard Madsen
Cc: 'Marlene Briciet Lauritsen'; 'Marlene Briciet Lauritsen'; Mortensen Preben Bo (Preben Bo Mortensen)
Subject: SV: q on thimerosal and autism paper

Dear Diana,

Thank you for the note. I suggest that you refer to Marlene B. Lauritsen or Preben Bo Mortensen and they could recommend the very persistent person to contact the Editor of "Pediatrics", whom then hopefully will give the same answer as you did. However, the manoeuvre will increase the Editors attention on the paper and then maybe speed up the process even further! I would not recommend handing out results that are not published, especially, not in this heated debate of autism.

Enjoy your weekend!

Best regards
Poul

-----Oprindelig meddelelse-----
Fra: Schendel, Diana [mailto:dcs6@cdc.gov]
Sendt: 13. december 2002 21:05
Til: Kreesten Meldgaard Madsen; Poul Thorsen
Emne: q on thimerosal and autism paper

Hi Kreesten and Poul,

We are having persistent questions from one of the congressional offices about data on the prevalence of autism in Denmark - in response to the NEJM article. I keep telling them that the information has been submitted for publication, I am not a co-author, and I can not give out any information that is under peer review (apart from the fact I don't have the actual data) - professional courtesy and ethics (and good science practice) just will not allow such mishandling. Coleen has been saying the same thing when they go to her (I didn't know that!).

But, they have now asked if we can tell them the subject matter of the paper. So, what do you feel about this - telling them it's an ecologic study of thimerosal use and autism rates over time in Denmark - period. Don't feel like you have to say yes to this request - no pressure at all. Hopefully the paper will be published and they'll see it soon anyway. Let me know what you think - Monday if possible. I don't have Marlene's email anymore, so please forward to her. Again, absolutely no pressure to comply. And we wanted to get your permission before we say anything.

Have a good weekend,
Diana

Diana Schendel, PhD.
National Center on Birth Defects
and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Hwy, MS F15
Atlanta, GA 30341

ph: 770-488-7359
fax: 770-488-7361
email: dschendel@cdc.gov

Schendel, Diana

From: Kreesten Meldgaard Madsen [KMM@SOCI.AU.DK]
Sent: Tuesday, December 17, 2002 3:02 AM
To: Schendel, Diana
Subject: RE: q on thimerosal and autism paper

Hi Diana,

No, I don't think there is a problem in discussing the paper or even the conclusion. Only if they want detailed information, tables etc. I think Marlene should decide what to hand out. Hopefully it will be published soon (I have been saying that for two years..)

/Kreesten

Kreesten Meldgaard Madsen, MD
Danish Epidemiology Science Centre
at the Dept. of Epidemiology and Social Medicine
Vennelyst Boulevard 6
DK-8000 Aarhus C
Denmark
Phone: +45 8942 6149
FAX: +45 8613 1580
E-mail: kmm@dadlnet.dk

-----Original Message-----
From: Schendel, Diana [mailto:dcs6@cdc.gov]
Sent: 16. december 2002 13:20
To: Kreesten Meldgaard Madsen
Subject: Re: q on thimerosal and autism paper

Hi,
Are you suggestin that we say that we can't discuss the paper (ie not even say what it is about) but give him Marlene"s contact info?

Diana

Sent from my BlackBerry Wireless Handheld (www.BlackBerry.net)

Schendel, Diana

From: Kreesten Meldgaard Madsen [KMM@SOCI.AU.DK]
Sent: Friday, December 20, 2002 8:53 AM
To: Poul Thorsen; Schendel, Diana
Subject: FW: Question from US Congressman Dave Weldon, MD

FYI

/Kreesten

Kreesten Meldgaard Madsen, MD
Danish Epidemiology Science Centre
at the Dept. of Epidemiology and Social Medicine
Vennelyst Boulevard 6
DK-8000 Aarhus C
Denmark
Phone: +45 8942 6149
FAX: +45 8613 1580
E-mail: kmm@dadlnet.dk

-----Original Message-----
From: Kreesten Meldgaard Madsen
Sent: 20. december 2002 14:52
To: 'Burns, Stuart'
Subject: RE: Question from US Congressman Dave Weldon, MD

Dear Stuart Burns,

Thanks to you and Dave Weldon for taking an interest in our study. The findings with regard to the prevalence rates are currently submitted to an American Journal and we hope it will be published soon. I am sure that you are aware that the publication politics of nearly all scientific journals does not permit the release of results to the public before publication. I will be happy to provide the data as soon as the article is published.

With regard to the sex ratio we find a male:female ratio of roughly 3:1.

I hope this reply is of help.

Best regards,
Kreesten Madsen

Kreesten Meldgaard Madsen, MD
Danish Epidemiology Science Centre
at the Dept. of Epidemiology and Social Medicine
Vennelyst Boulevard 6
DK-8000 Aarhus C
Denmark
Phone: +45 8942 6149

FAX: +45 8613 1580
E-mail: kmm@dadlnet.dk

-----Original Message-----
From: Burns, Stuart [mailto:Stuart.Burns@mail.house.gov]
Sent: 18. december 2002 22:14
To: kmm@dadlnet.dk
Subject: Question from US Congressman Dave Weldon, MD
Importance: High

Dr. Madsen,

I work for U.S. Congressman Dave Weldon. In addition to being a Member of the US Congress, he is also a physician. He has taken great interest in Autism and is very concerned about rapid increase in the rates of Autism her in the the United States.

In your recent NEJM article, you mentioned on page 1481 of the Journal, your finding that Autism in children ages 5-9 was stable in the 1980s through the beginning of the 1990s at about 2 cases in every 10,000 children. Your study mentions that by 2000 the rates were significantly higher in children ages 5-9, nearly 10 in 10,000.

Congressman Weldon would like to know the prevalence rate of Autism in children, ages 5-9, in Denmark from the mid-1980s through 2000. Could you please provide me with the prevalence rate of Autism in children 5-9 for each of these years. Also, are you finding a dramatically higher prevalence rate of Autism in boys, as we are here in the U.S.?

Thank you for your consideration.

Thank you,

Stuart Burns
Deputy Chief of Staff
U.S. Congressman Dave Weldon
202-225-3671 - phone

Schendel, Diana

From: Boyle, Coleen
Sent: Thursday, January 23, 2003 5:00 PM
To: 'Poul Thorsen'
Cc: Schendel, Diana
Subject: RE: Artikel til Pediatrics

Poul: Thanks for sharing this with me – I have included my comments in the track changes mode of Word. Good luck with this. Cheers, Coleen

Coleen Boyle, Ph.D.
Associate Director for Science and Public Health
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Hwy, NE
Atlanta, GA 30341
(770)488-7366
Fx:(770)488-7156
cboyle@cdc.gov <mailto:cboyle@cdc.gov>

-----Original Message-----
From: Poul Thorsen [mailto:pt@SOCI.AU.DK]
Sent: Wednesday, January 22, 2003 1:42 PM
To: Schendel, Diana
Cc: Boyle, Coleen
Subject: VS: Artikel til Pediatrics

Dear Diana,

As Coleen suggested herself to look over the reviewers comments and also maybe to add some answers to the editor, I am forwarding you the latest version of the paper including the suggested answers to the editor. Would you copy the reviewers' comments to Coleen?

Best regards
Poul

-----Oprindelig meddelelse-----
Fra: Marlene Briciet Lauritsen [mailto:mbl@dadlnet.dk]
Sendt: 20. januar 2003 12:49
Til: Preben Bo Mortensen; Poul Thorsen; Peter Henrik Andersen; Kreesten Meldgaard Madsen; Anne-Marie Plesner
Emne: Artikel til Pediatrics

Kære alle
Hermed artikel og følgebrev, efter at kommentarerne fra reviewerne er taget til efterretning sammen med Kreesten og Carsten. Det med kursiv i artiklen er rettelser i forhold til udgaven, Pediatrics fik.
Mvh

Marlene Briciet Lauritsen, MD
Department of Psychiatric Demography
Institute for Basic Psychiatric Research
Psychiatric Hospital in Aarhus
Skovagervej 2
DK-8240 Risskov
Denmark
Phone: +45 7789 2851
Fax: +45 7789 2899
E-mail: mbl@dadlnet.dk; mbl@psykiatri.aaa.dk

Dear Jerold F. Lucey

Thank you for the opportunity to submit a revised version of the manuscript "Thimerosal and the occurrence of autism: Negative evidence from Danish population-based data". In the following we have responded to each of the points raised by the reviewers. We have dealt with the comments from the reviewer as they are mentioned chronologically:

Response to reviewer A:

This study faces a number of problems, however: changes in the practice of care and diagnosis for children with autism in re. inpatient v. outpatient facilities, shifts in which may have led to double-counting of some children; changes in diagnostic criteria around 1994; changes in dose of thimerosal over the period in which it was used; shelf life of thimerosal-containing vaccines that might have permitted its availability after its incorporation into newly made vaccines was discontinued, etc.

We acknowledge the problems with changes in the practice of care and diagnosis for children with autism and changes in the dose of thimerosal administered during the period studied. We have already dealth with these issues in the Participants and Methods and Discussion sections. Regarding the comment with double-counting we have added the following sentence in the Participants and Methods section: "All individuals in Denmark are assigned a unique personal identification number (the CPR-number) which is used in all national registers. Admissions to psychiatric hospitals in Denmark are coded using this CPR-number, which eliminates the risk of double-counting of cases."

We don't have information about the shelf life of thimerosal-containing vaccines. However, we believe it is unlikely that this has any impact on the incidence rates. How about some information about current shelf life of vaccines – I know our vaccine folks have some sense of this in the U.S. Also, it is not clear to me why you think this was unlikely to impact incidence?? I assume its because rather than a precipitous drop in incidence due to an rapid removal one would anticipate a more gradual decline in rates of disease (due to the more gradual removal) – in any case, no decline was observed.

The authors present no information about how the ratio of outpatient to inpatient facilities as first place of diagnosis changed over the period they discuss.

We have information about outpatient facilities from 1995 onwards and we have now added the following sentence in the Results section: "From 1995 the proportion of outpatient to inpatient activities remained constant with about four times as many outpatients than inpatients." If the ratio is constant overtime, this would not support the idea you discussed of the larger increase in older ages resulting from a larger catch up on diagnoses not recorded in the system. -- Unless, the ratio varied by age of the child? Also, I would move this sentence into the methods section??

All these problems are made more difficult because the authors have chosen to use an incidence rate ..... rather than calculating back to birth prevalence...

We chose not to present birth prevalences because the youngest children cannot be followed until their tenth birthday and thus the data for the youngest birth cohorts will be incomplete. Moreover, when presenting the data as birth prevalences the increasing number of admissions with autism by calendar year may be obscured since the prevalence rates will tend to decrease due to incomplete birth cohorts during that period.

It is recommended to use the time scale with greatest variation by time to present trends in the occurrence of a disorder (Andersen PK et al., 1997). Since the registration vary most by

calendar year and age we chose to present the figure as it is. I tend to agree with the reviewer, but also recognize the limitations that you observed. It might be useful to describe what the birth cohort analyses showed, even if it is not presented – each piece of information (even with its limitations) might be helpful in understanding what is going on in the data

The drop of incidence shown for the most recent years is perhaps the most dramatic feature of the figure, and is seen in the oldest age group as well as the youngest. The authors do not discuss whether incomplete ascertainment in the youngest children or delay in recording of data in the most recent years might play a role in this decline, or the possibility that this decrease might have come about through elimination of thimerosal.

The focus of this article is on thimerosal-containing vaccines and autism and the adjacent time windows pre and post-thimerosal withdrawal (i.e. 1992) and thus we didn't pay much attention to the decreasing incidence rates in 2001. We have changed a part of the paragraph in the Discussion section about decreasing incidence rate to the following: "Figure 1 may reflect this process of inclusion of previously undetected or unregistered cases since the largest incidence rates were found in the oldest age groups (again, I find the constant ratio overtime argues against this somewhat) and from 2000 the incidence rates decrease except in the group of children younger than two years of age. We investigated the causes of this decrease further, since it is most unlikely that the discontinuation of thimerosal-containing vaccines in 1992 should lead to a fall in the incidence of autism nine years later. We examined the incidence rates in 2001 by quarters of years and found that the incidence of children reported with a diagnosis of autism in 2001 may be biased downwards (why – this is not clear as written – was the rate high in the first two quarters and the dropped subsequently?) due to a time-lag of up to one year from admission with autism to a child psychiatric department until this information was reported to the Danish Psychiatric Central Research Register."

The numbers of children studied is not large - an average of about 30 children per year for the whole country - and is stated in the Statistics section. It should be in Results, and in the Abstract.

As suggested the number of children studied has been moved to the Results section. However, the incidence rates found in our study are comparable to the ones reported by Powell et al. 2000 and Kaye et. 2001. This is stated in the Discussion section: "Only very few incidence studies of autism have been made and we found similar incidence rates and the same trend of increasing rates of autism in our study compared to studies done in other countries."
In the same paragraph the study by Croen et al. 2002 is omitted since this is not an incidence study but a prevalence study.

Response to reviewer B: (The numbers correspond to the list made by the reviewer)
Because the authors report that the ratio of boys to girls with newly diagnosed autism is 3.5:1 (and presumably the population ratio of boys to girls is approximately 1:1), it would be more informative to present the boys' (higher) incidence rates separately from the girls' rates.(1)
Since the focus of this study is on thimerosal and autism and since we found that the incidence rates varied most by age and calendar year and not by gender we decided not to present gender specific rates. The latter is now added in the Results section: "Further subdivision by gender had no impact on these results (data not shown)."

Although the observed recent changes in the incidence of autism in Denmark are clearly substantial, it would be helpful to see confidence intervals for the estimated rates, or at least

for some of the most important rates, perhaps in a table.(2)
We chose not to include confidence intervals because this would impede the interpretation of the figure.

Is it possible for outpatient registrations to be distinguished from inpatient registrations? If so, the authors should be able to provide some quantitative estimate as to how much this change in reporting has contributed to the changes in incidence rates observed after 1995.(3)
It is possible for outpatient activities to be distinguished from inpatient activities and we have made some analyses to estimate the contribution of the change in registration to the incidence rates found. This is now mentioned in the Results section: "In additional analyses we excluded all outpatient activities and found an increase in the incidence rates although considerably lower followed by decreasing rates (data not shown)." Be specific here – this is too vague. Is the increase and subsequent decrease during the same time period as seen in the entire data set? This sent up warning flags for me.

The conclusion could be stated more directly, e.g.: "...our data do not support a causal role of thimerosal-containing vaccines in the development of autism".(4)
We do not, however, agree with the reviewer on that issue. Because this is an ecologic study we do not study causal relationship and therefore our conclusion must be that we found no correlation between autism and thimerosal-containing vaccines as stated at the end of the Discussion section.

In the Introduction section we changed the first part of the first paragraph adding a new study investigating thimerosal-containing vaccines by Pichichero et al. 2002 to the following: "There has been concern that there may be an association between thimerosal, a vaccine preservative which contains ethyl mercury, and neurodevelopmental outcomes, including autism (1). Findings in the field of methyl mercury have been used to suggest causality. Prenatal exposure to low doses of methyl mercury has been associated with subtle neurodevelopmental abnormalities in some studies and symptoms of autism and methyl mercury intoxication have been claimed to be similar. Further research has been requested and a recent study of the amount and metabolism of mercury after exposure to thimerosal-containing vaccines concluded that thimerosal poses very little risk to full-term infants."

We also omitted the sentence: "but the explanation is not evident" in the second paragraph in the Discussion section.

We hope you find that the manuscript "Thimerosal and the occurrence of autism: Negative evidence from Danish population-based data" has improved after the revision made in relation to the suggestions and criticisms by the reviewers. We also hope that you now find the manuscript suitable for publication in *Pediatrics*.

We look forward to hear from you again.

Reference List:
Andersen PK, Borgan Ø, Gill RD, et al. *Statistical Models Based on Counting Processes.* New York: Springer-Verlag; 1997.
Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. *J Autism Dev Disord.* 2002;32(3):207-212.
Kaye JA, Mar Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the

incidence of autism recorded by general practitioners: a time trend analysis. *BMJ.* 2001;322: 460-463.
Powell JE, Edwards A, Edwards M, Pandit BS, Sungum-Paliwal SR, Whitehouse W. Changes in the incidence of childhood autism and other autistic spectrum disorders in preschool children from two areas of the West Midlands, UK. *Dev Med Child Neurol.* 2000;42(9):624-628.
Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet.* 2002;360(9347):1737-1741.

Schendel, Diana

From: Kreesten Meldgaard Madsen [KMM@SOCI.AU.DK]
Sent: Friday, August 15, 2003 7:17 AM
To: cbp@ncrr.au.dk; pbm@ncrr.au.dk; Poul Thorsen; Schendel, Diana; pea@dadlnet.dk
Subject: VS: SV: a "news brief" on your study in Pediatrics

FYI

Best regards
Kreesten

Kreesten Meldgaard Madsen, MD
Danish Epidemiology Science Centre
at the Dept. of Epidemiology and Social Medicine
Vennelyst Boulevard 6
DK-8000 Aarhus C
Denmark
Phone: +45 8942 6149
Mobile: [redacted]
FAX: +45 8613 1580
E-mail: kmm@dadlnet.dk <mailto:kmm@dadlnet.dk>

-----Oprindelig meddelelse-----
Fra: Gina Steiner [mailto:GSteiner@aap.org]
Sendt: 15. august 2003 11:53
Til: Kreesten Meldgaard Madsen
Emne: Re: SV: a "news brief" on your study in Pediatrics

Dear Dr. Madsen,

Below is the "news brief" we are planning to send to reporters in about 10 days. I need your approval or comments by this Monday. Because of the time difference, could you look at it by Sunday?

Thank you so much.

Sincerely,

Gina Steiner
American Academy of Pediatrics
847-434-7872

A study of nearly 1,000 Danish children diagnosed with autism over three decades showed no correlation between thimerosal-containing vaccines and the incidence of autism. According to "Thimerosal and the Occurrence of Autism? Negative Ecological Evidence From Danish Population-Based Data," autism rates continued to increase after the removal of thimerosal from vaccines in 1992. These increases occurred among children born both before and after the discontinuation of thimerosal use. The study looked at all children between 2 and 10 years old who were diagnosed with autism from 1971-2000, according to the Danish Psychiatric Central Research Register.

[For an interview on this study, please contact Kreesten M. Madsen, MD, at kmm@dadlnet.dk or Marlene B Lauritsen at mbl@psykiatri.aaa.dk (note: the authors are located in Denmark).]

>>> "Kreesten Meldgaard Madsen" <KMM@SOCI.AU.DK> 08/06/03 04:14 AM >>>

Dear Gina Steiner,

My contact information is as follows:
Kreesten Meldgaard Madsen, MD
Danish Epidemiology Science Centre
at the Dept. of Epidemiology and Social Medicine
Vennelyst Boulevard 6
DK-8000 Aarhus C
Denmark
Phone: +45 8942 6149
Mobile: [redacted]
FAX: +45 8613 1580
E-mail: kmm@dadlnet.dk

During the period from August 25 through September 2 I will be teaching at the University from 9 am to 2 pm (= 3 am to 8 am eastern time). I will have my mobile open from 2 pm to 12 pm (= 8 am t 6 pm eastern time). I will also be availble via e-mail.

Another author to talk to could be:
Marlene B Lauritsen
E-mail: mbl@psykiatri.aaa.dk

Best regards,
Kreesten Madsen

-----Oprindelig meddelelse-----
Fra: Gina Steiner [mailto:GSteiner@aap.org]
Sendt: 5. august 2003 18:21
Til: Kresten Meldgaard Madsen
Emne: a "news brief" on your study in Pediatrics

Hello Dr. Madsen--

I am writing to you from the Public Relations office at the American Academy of Pediatrics. As you know, your study on "Thimerosal and the Occurrence of Autism...." will be published in the September issue of our journal, Pediatrics.

We will be sending a "news brief" to the media here in the U.S. during the third week of August. It will be four or five sentences summarizing your study.

Because of the time difference between the US and Denmark, we would like to provide your e-mail address and that of a second author so that reporters can contact you with any questions. Will you please let me know if this will work for you, and the second person's e-mail to list?

You would need to be available to communicate with reporters from approximately August 25 (when we send out the news brief) through September 2. (Monday, September 1 is Labor Day and very few people will be working.) The story is embargoed for September 2, which means reporters can interview you about it before then, but cannot print or broadcast their story before then.

You will have a chance to see the news brief and give us any comments before it goes out. But I will need to know about the contact information as soon as possible.

Thank you in advance for your help.

Sincerely,

Gina Steiner
Media Relations Manager
American Academy of Pediatrics
847-434-7872

Schendel, Diana

From: Kreesten Meldgaard Madsen [KMM@SOCI.AU.DK]
Sent: Monday, September 01, 2003 8:53 AM
To: Schendel, Diana
Subject: Attached article

thimerosal autism.pdf (58 KB)

Dear Diana,

Attached the thimerosal and autism article. It certainly took some time to get this short paper out. I hope you are doing well.

Best regards,

Kreesten

Kreesten Meldgaard Madsen, MD
Danish Epidemiology Science Centre
at the Dept. of Epidemiology and Social Medicine
Vennelyst Boulevard 6
DK-8000 Aarhus C
Denmark
Phone: +45 8942 6149
Mobile: [redacted]
FAX: +45 8613 1580
E-mail: kmm@dadlnet.dk <mailto:kmm@dadlnet.dk>

Confirmation Report—Memory Send

Time : 10-03-2005 02:28pm
Tel line 1 :
Name :

Job number : 331

[redacted]

Date : 10-03 02:25pm

To : 94046397395

Document Pages : 006

Start time : 10-03 02:25pm

End time : 10-03 02:28pm

Pages sent : 006

Status : OK

Job number : 331 *** SEND SUCCESSFUL ***

[redacted]

To: Lynn Armstrong Fax: 404-639-7395

From: Diane Wade Date: 10/3/2005

Re: FOIA - 599 Pages: 6

CC:

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

[redacted]

iting on information from Diana Schendel. I have left a voice message for her calling again in the next 30 minutes or so. Following is some email pondence and a letter from Dr. Cordero that I was told was in reference to this topic a published report in JAMA and the Atlanta Journal.

Give me a call if you have additional questions and I'll contact you later this afternoon.

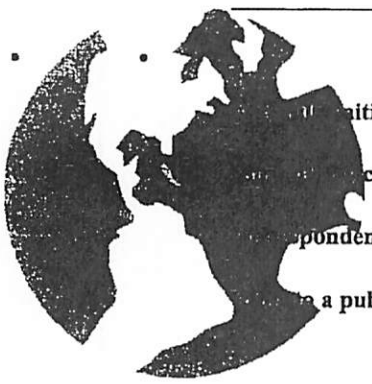
Diane
404-498-3089

[redacted]

[redacted]

To:	Lynn Armstrong	**Fax:**	404-639-7395
From:	Diane Wade	**Date:**	10/3/2005
Re:	FOIA - 599	**Pages:**	6
CC:			

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle



[redacted]iting on information from Diana Schendel. I have left a voice message for her [redacted] calling again in the next 30 minutes or so. Following is some email [redacted]pondence and a letter from Dr. Cordero that I was told was in reference to this topic [redacted] a published report in JAMA and the Atlanta Journal.

Give me a call if you have additional questions and I'll contact you later this afternoon.

Diane

404-498-3089

Boyle, Coleen

From: Boyle, Coleen
Sent: Tuesday, November 26, 2002 2:10 PM
To: Schendel, Diana
Cc: Cordero, Jose
Subject: RE: Autism thimerosol paper - cover letter

I will prepare the letter for Jose's signature -- but won't get to it until next week. I would suggest that it accompany the submission as support of the importance of the work. I can fedex it so it arrives late next week.

Jose: We need to discuss. thx

Coleen Boyle, Ph.D.
Associate Director for Science and Public Health
National Center on Birth Defects and Developmental Disabilities Centers for Disease Control and Prevention 4770 Buford Hwy, NE Atlanta, GA 30341 (770)488-7366 Fx:(770)488-7156 cboyle@cdc.gov <mailto:cboyle@cdc.gov>

-----Original Message-----
From: Schendel, Diana
Sent: Tuesday, November 26, 2002 9:44 AM
To: Boyle, Coleen
Subject: FW: Autism thimerosol paper - cover letter

Hi Coleen,

I read through this quickly and it still needs a bit of work, but about Poul's request - what do you think? If you want to prepare the letter, I could take it with me - but ask that they not send it until all our comments are resolved. (or send it without the letter - whichever they prefer).

Let me know - thanks, Diana

PS - Poul was out sick yesterday (and still today) with flu so we didn't talk about HL and meningitis - stay tuned.

Diana Schendel, PhD.
National Center on Birth Defects
and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Hwy, MS F15
Atlanta, GA 30341

ph: 770-488-7359
fax: 770-488-7361
email: dschendel@cdc.gov

-----Original Message-----
From: Poul Thorsen [mailto:pt@SOCI.AU.DK]
Sent: Tuesday, November 26, 2002 6:02 AM
To: Schendel, Diana
Subject: Autism thimerosol paper - cover letter

Dear Diana,

Her are the latest versions and the fifure still need to be updated, but will be. Marlene believes more in sending the paper to Pediatrics. Could you or Coleen write a cover-letter underlining the importance of getting this information out now? Please do not mention the Journals name, as it is not finalized, if we are going to send it JAMA again. Could you bring the letter, when you come? See you soon!

Thank you!

Best regards
Poul

Boyle, Coleen
From: Boyle, Coleen
Sent: Friday, December 06, 2002 3:47 PM
To: Cordero, Jose
Subject: FW: letter of support for Danish study – for Jose's review and cmt (and signature)

Coleen Boyle, Ph.D.
Associate Director for Science and Public Health
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Hwy, NE
Atlanta, GA 30341
(770)488-7366
Fx:(770)488-7156
cboyle@cdc.gov <mailto:cboyle@cdc.gov>

—Original Message—
From: Boyle, Coleen
Sent: Thursday, December 05, 2002 2:51 PM
To: Magyar, Pat; Cordero, Jose
Cc: Yeargin-Allsopp, Marshalyn; Chavez, Gilbert
Subject: letter of support for Danish study – for Jose's review and cmt (and signature)

autism_thimerosal_danishltrofs...

Coleen Boyle, Ph.D.
Associate Director for Science and Public Health
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
4770 Buford Hwy, NE
Atlanta, GA 30341
(770)488-7366
Fx:(770)488-7156
cboyle@cdc.gov <mailto:cboyle@cdc.gov>

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30341-3724

December 10, 2002

Jerold F. Lucey, M.D.
Editor in Chief
PEDIATRICS
University of Vermont
College of Medicine
Pediatrics Editorial Office
89 Beaumont Avenue, GIVEN D201
Burlington, Vermont 05405 - 0068

Dear Dr. Lucey:

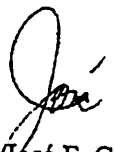
I am writing in support of an expedited review and consideration of the enclosed manuscript that examines the association between thimerosal, an ethyl mercury containing preservative, and autism. As you may know, there has been considerable interest by parents, clinicians, educators, and policy makers for an explanation of the marked increase in the rate of autism in recent years. A University of Davis study released in October of children identified through the California developmental disabilities service system, reemphasized the upward trend in autism and the lack of understanding as to the cause.

One factor hypothesized to have a causal role is childhood vaccinations. Specific aspects of vaccinations that have been subject to inquiry include the MMR vaccine and thimerosal. There are now numerous epidemiologic studies to suggest that the MMR vaccine is not associated with the risk of autism; an Institute of Medicine review that was published in 2000 concluded that the weight of the scientific evidence did not support a link between MMR vaccine and autism.

For thimerosal, however, there are limited data to evaluate this factor. Because mercury in its inorganic form is known to have serious neurologic effects, many parents have speculated that the increased number of vaccines (many of which contained thimerosal) may have been a significant factor in the recent rise in autism. The Danish study is a powerful epidmeiologic study of this issue and capitalizes on the Danish health registry system that incorporates all health encounters into disease and exposure specific registries. In addition, a key strength of the study is the ability to examine rates of autism prior to and after the *discontinuation* of vaccines containing thimerosal in Denmark in 1992. Contrary to what would be expected if thimerosal was linked to autism, the authors did not observe a decline in the rate of autism with the removal of thimerosal containing vaccines.

I feel this is a very important study that deserves thoughtful consideration by the Journal. Its findings provide one strong piece of evidence that thimerosal is not causally linked to autism. Thank you for your timely consideration.

Sincerely,



José F. Cordero, M.D., M.P.H.
Assistant Surgeon General
Director
National Center on Birth Defects
and Developmental Disabilities

PEDIATRICS

Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data

Kreesten M. Madsen, Marlene B. Lauritsen, Carsten B. Pedersen, Poul Thorsen, Anne-Marie Plesner, Peter H. Andersen and Preben B. Mortensen

Pediatrics 2003;112;604-606
DOI: 10.1542/peds.112.3.604

Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data

Kreesten M. Madsen, MD*; Marlene B. Lauritsen, MD‡; Carsten B. Pedersen, Msc§; Poul Thorsen, MD, PhD*; Anne-Marie Plesner, MD, PhD¶; Peter H. Andersen, MD¶; and Preben B. Mortensen, MD, DMSc§

ABSTRACT. *Objective.* **It has been suggested that thimerosal, a mercury-containing preservative in vaccines, is a risk factor for the development of autism. We examined whether discontinuing the use of thimerosal-containing vaccines in Denmark led to a decrease in the incidence of autism.**

Design. **Analysis of data from the Danish Psychiatric Central Research Register recording all psychiatric admissions since 1971, and all outpatient contacts in psychiatric departments in Denmark since 1995.**

Patients. **All children between 2 and 10 years old who were diagnosed with autism during the period from 1971–2000.**

Outcome Measures. **Annual and age-specific incidence for first day of first recorded admission with a diagnosis of autism in children between 2 and 10 years old.**

Results. **A total of 956 children with a male-to-female ratio of 3.5:1 had been diagnosed with autism during the period from 1971–2000. There was no trend toward an increase in the incidence of autism during that period when thimerosal was used in Denmark, up through 1990. From 1991 until 2000 the incidence increased and continued to rise after the removal of thimerosal from vaccines, including increases among children born after the discontinuation of thimerosal.**

Conclusions. **The discontinuation of thimerosal-containing vaccines in Denmark in 1992 was followed by an increase in the incidence of autism. Our ecological data do not support a correlation between thimerosal-containing vaccines and the incidence of autism.** ***Pediatrics*** **2003; 112:604–606;** ***autism, vaccine, thimerosal, mercury, population, epidemiology.***

ABBREVIATIONS. *ICD-8, International Classification of Diseases, Eighth Revision; ICD-10, International Classification of Diseases, 10th Revision.*

From the *Danish Epidemiology Science Centre, Department of Epidemiology and Social Medicine, University of Aarhus, Denmark; ‡Institute for Basic Psychiatric Research, Department of Psychiatric Demography, Psychiatric Hospital in Aarhus, Risskov, Denmark; §National Centre for Register-Based Research, University of Aarhus, Aarhus, Denmark; and the ¶State Serum Institute, Department of Medicine, Copenhagen, Denmark.

Received for publication Dec 12, 2002; accepted May 8, 2003.

Reprint requests to (K.M.M.) Danish Epidemiology Science Centre, Department of Epidemiology and Social Medicine, University of Aarhus, 8000 Aarhus, Denmark. E-mail: kmm@dadlnet.dk.

There has been concern that there may be an association between thimerosal, a vaccine preservative that contains ethyl mercury, and neurodevelopmental outcomes, including autism.[1,2] Findings in the field of methyl mercury have been used to suggest causality. Prenatal exposure to low doses of methyl mercury has been associated with subtle neurodevelopmental abnormalities in some studies,[3,4] and symptoms of autism and methyl mercury intoxication have been claimed to be similar.[1] More research has been requested,[5] and a recent study of the concentrations of mercury after exposure to thimerosal-containing vaccines concluded that thimerosal poses very little risk to full-term infants.[6] In Denmark, thimerosal was used in childhood vaccines from the early 1950s until 1992. The objective of our study was to assess the incidence rates of autism among children between 2 and 10 years old before and after removal of thimerosal from vaccines to see if the discontinuation led to a decrease in the incidence of autism.

PARTICIPANTS AND METHODS

For this study, the period of use of thimerosal vaccines was limited to 1961 until its discontinuation in March 1992 because information about the diagnosis of autism has only been obtainable from a nationwide computerized registration system, the Danish Psychiatric Central Research Register,[7] since 1969 and only children born in 1961 or later were at risk of developing autism before 10 years of age. Thimerosal was used during 1961–1970 in the diphtheria-tetanus-pertussis vaccines given in 4 doses when the child was 5, 6, 7, and 15 months old, and during 1970–1992 in the whole-cell pertussis vaccines given in 3 doses when the child was 5 weeks, 9 weeks, and 10 months old. The concentrations used in the vaccines from 1961–1970 and from 1970–1992 were 0.01% = 0.1 mg thimerosal, which equals 50 μg ethyl mercury per mL vaccine. The amount of vaccine given was 1 mL, except for the first dose of monocomponent pertussis vaccine where it was only 0.5 mL from 1970–1992. This means that children who followed the full vaccination program during the period 1961–1970 had received a total of 400 μg of thimerosal or 200 μg of ethyl mercury by the age of 15 months and during the period 1970–1992 they had received a total of 250 μg of thimerosal or 125 μg of ethyl mercury at 10 months of age. In March 1992 the last batch of thimerosal-containing vaccine was released and distributed from Statens Serum Institut in Denmark. All vaccinations were given free of charge and acceptance of vaccinations in Denmark has always been very high; from 1979 onward data on vaccination coverage was available and coverage rates of >90% were found (information was obtained from the State Serum Institute). Whether the toxicity of methyl mercury and ethyl mercury is the same remains controversial[8,9] but the recommended safe intake level of methyl mercury is estimated to be 0.1 μg/kg body weight/day by the US Environmental Protection Agency.[10] However, other federal regulatory agencies have recommended slightly higher levels.[9]

Psychiatric inpatient treatment in Denmark has been reported to the Danish Psychiatric Central Research Register since 1969, and since 1995 outpatient activities were registered as well, providing the opportunity to examine long-term trends of the occurrence of autism in a total national population. In Denmark, inpatients refer both to children who stay at the hospital overnight and to children who come to the hospital on a daily basis for evaluation and treatment. The proportion of outpatient to inpatient activities was about 4 to 6 times as many outpatients as inpatients with variations across time and age bands. We obtained information on all children who from the second birthday up to, but not including the 10th birthday were diagnosed with autism in the period from January 1, 1971 to December 31, 2000 in the Danish Psychiatric Central Research Register during which period the register is assumed to be complete. The diagnosis of autism in children <2 years of age was considered uncertain. All individuals in Denmark are assigned a unique personal identification number[11] which is used in all national registers. Admissions to psychiatric hospitals in Denmark are coded using this CPR-number, which eliminates the risk of double-counting of cases. The date of onset was defined as the first day of the first admission leading to a diagnosis of psychosis proto-infantilis (*International Classification of Diseases, Eighth Revision* [*ICD-8*]: 299.00) or psychosis infantilis posterior (*ICD-8*: 299.01) or from 1994 onward, infantile autism (*International Classification of Diseases, 10th Revision* [*ICD-10*]: F84.0) or atypical autism (*ICD-10*: F84.1).[12,13]

Statistics

Incidence rates were calculated for each year 1971–2000 using the age and gender specific number of persons in Denmark as a denominator. For each year and age band, we calculated the incidence as the number of people who at that age band and year was diagnosed with autism for the first time divided by the total number of people alive and living in Denmark at that age band and year.

RESULTS

A total of 956 children with a male to female ratio of 3.5:1 had been diagnosed with autism during the period 1971–2000. Figure 1 shows the incidence rates according to calendar year and age band. The incidence was stable until 1990 and thereafter it increased in all age groups until 1999. Generally, rates were lower in 2000 than in 1999. Further subdivision by gender had no impact on these results (data not shown). In additional analyses we examined data using inpatients only. This was done to elucidate the contribution of the outpatient registration to the change in incidence. The same trend with an increase in the incidence rates from 1990 until the end of the study period was seen (data not shown).

There was no trend toward an increase in the incidence of autism during the period when thimerosal was used up to 1990. The incidence of autism began to increase in 1991, but continued to rise after the discontinuation of thimerosal (Fig 1), including increases among children born after 1992 (ie, the peak autism incidence in 1999 among children aged 2 to 4 and 5 to 6 years of age corresponds to children born in 1993–1997 after the introduction of thimerosal-free vaccines).

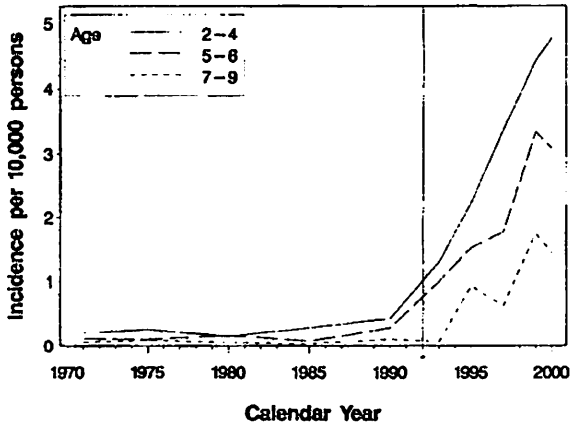


Fig 1. Incidence of autism by age and calendar year. The asterisk (*) indicates removal of thimerosal-containing vaccines in 1992.

DISCUSSION

This study investigated if the discontinuation of thimerosal-containing vaccines paralleled a decrease in the occurrence of autism. The incidence of autism remained fairly constant during the period of use of thimerosal in Denmark, and the rise in incidence beginning in 1991 continued even in the group of children born after the discontinuation of thimerosal. The amount of thimerosal used in vaccines changed during the study period with less amount of thimerosal administered in the period 1970–1992. Moreover, the thimerosal-containing vaccine was gradually phased out meaning that the incidence rates should decline gradually if thimerosal has any impact on the development of autism. However, an increase (rather than a decrease) in the incidence rates of autism was observed.

Only very few incidence studies of autism have been made, and we found similar incidence rates and the same trend of increasing rates of autism in our study compared with studies conducted in other countries.[14,15] The increase in the incidence of autism from 1990 on may be attributable to more attention being drawn to the syndrome of autism and to a change in the diagnostic criteria from the *ICD-8* to the *ICD-10* in 1994. Also, outpatient activities were included in the Danish Psychiatric Central Research Register in 1995 and because many patients with autism in former years have been treated as outpatients this may exaggerate the incidence rates, simply because a number of patients attending the child psychiatric treatment system before 1995 were recorded for the first time, and thereby counted as new cases in the incidence rates.

CONCLUSIONS

The discontinuation of thimerosal-containing vaccines in Denmark in 1992 was followed by an increase in the incidence of autism. Our ecological data do not support correlation between thimerosal-containing vaccines and the incidence of autism. Our data cannot, of course, exclude the possibility that thimerosal at doses larger than used in Denmark may lead to neurodevelopmental damage.

ACKNOWLEDGMENTS

The activities of the Danish Epidemiology Science Centre and the National Centre for Register-Based Research are funded by a grant from the Danish National Research Foundation. This study was supported by the Stanley Medical Research Institute. No funding sources were involved in the study design.

We thank Coleen Boyle, Diana Schendel, and Jose F. Cordero for comments and advice during preparation of the manuscript.

REFERENCES

1. Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poisoning. *Med Hypotheses*. 2001;56:462–471
2. Nelson KB, Bauman ML. Thimerosal and autism? [commentary]. *Pediatrics*. 2003;111:674–679
3. Marsh DO, Clarkson TW, Cox C, Myers GJ, Amin-Zaki L, Al-Tikriti S. Fetal methylmercury poisoning. Relationship between concentration in single strands of maternal hair and child effects. *Arch Neurol*. 1987;44:1017–1022
4. Cox C, Clarkson TW, Marsh DO, Amin-Zaki L, Tikriti S, Myers GG. Dose-response analysis of infants prenatally exposed to methyl mercury: an application of a single compartment model to single-strand hair analysis. *Environ Res*. 1989;49:318–332
5. Institute of Medicine. *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders*. Washington, DC: National Academy Press; 2001
6. Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet*. 2002;360:1737–1741
7. Munk-Jorgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull*. 1997;44:82–84
8. Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines [review article]. *Pediatrics*. 2001;107:1147–1154
9. Clarkson TW. The three modern faces of mercury. *Environ Health Perspect*. 2002;110(suppl 1):11–23
10. Environmental Protection Agency. *Mercury Study Report to Congress: Volume I: Executive Summary*. Washington, DA: Environmental Protection Agency; 1997. Publ. No. EPA-452/R-97-003
11. Maling C. *The Civil Registration System in Denmark*. IIVRS Technical Paper No. 99. Bethesda, MD: International Institute for Vital Registration and Statistics; 1999
12. World Health Organization. *Manual of the International Classification of Diseases, Eighth Revision (ICD-8)*. Geneva, Switzerland: World Health Organization; 1967
13. World Health Organization. *The International Classification of Diseases: 10th Revision (ICD-10): Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research*. Geneva, Switzerland: World Health Organization, 1993
14. Powell JF, Edwards A, Edwards M, Pandit BS, Sungum-Paliwal SR, Whitehouse W. Changes in the incidence of childhood autism and other autistic spectrum disorders in preschool children from two areas of the West Midlands, UK. *Dev Med Child Neurol*. 2000;42:624–628
15. Kaye JA, Mar Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ*. 2001;322:460–463

FAT BABIES AND HEALTH

"In a recent issue an English contemporary calls attention to the mischief that is being done by the present standard that is accepted as regards healthy babies. As this paper well says, at baby shows the prize is practically always given to the fattest baby. There is a tradition current among mothers, as far as the memory of man runneth, that fat babies are just the pink of perfection. The surest index of this is that all manufacturers of artificial infant food advertise their wondrous virtues by photographs of thoroughly rounded, and at times positively obese dumplings of babies. Mothers are very proud of their young hopefuls if they are a mass of curves and dimples with deep folds at all the joints and cushions of fat that conceal their anatomy so effectively as to make them formless little masses of humanity."

JAMA 100 years ago. JAMA. 2003;289:1866

Editor's Note: Not much change in 100 years! Will we ever win this one?

Noted by JFL, MD