

**IS SOMETHING ROTTEN IN DENMARK?  
A SOCIAL NETWORK ANALYSIS OF CONFLICT OF INTEREST IN  
VACCINE SAFETY RESEARCH**

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Short title: Commercial conflicts in vaccine safety research

## **ABSTRACT**

Three papers based on a Danish patient registry argued against a link between mercury-containing vaccines and autism. Following a related analysis of the autism-MMR vaccine link, these studies were published in close succession in prestigious journals, based on marginally differentiated analyses of the same events and prepared by author groups with numerous connections.

Analysis of these publications, their authors and sponsoring institutions reveals a social network with extensive personal and institutional ties. Analysis of the authors and their employers also reveals a pervasive conflict of interest that was not reported in the publishing journals.

All authors in the network have ties, direct or indirect, to a for-profit, state-owned, vaccine manufacturer: the Statens Serum Institut (SSI). The mercury-containing vaccine investigated in the three studies was produced by SSI. Six SSI employees participated as co-authors in studies in which the safety of SSI products were evaluated. These six individuals also hold central positions in a broader network with ties to eleven additional authors and maintain formal alliances at the institutional level.

SSI has a commercial interest in vaccine products: the vaccine division contributed half of SSI's revenues and over 80% of profits in 2002; vaccine exports were SSI's fastest growing business; mercury-containing vaccine products support SSI's vaccine exports; and SSI provides ingredients for mercury-containing vaccines currently used outside Denmark.

SSI has a conflict of interest in conducting assessments of vaccine safety. This conflict should be considered when evaluating the authors' findings that mercury in Danish vaccines did not cause harm.

Key words: Vaccines, mercury, autism, thimerosal, social network analysis, conflict of interest.

## INTRODUCTION

Scientific journals work diligently to limit compromises to scientific integrity that might arise from the commercial interests of authors and their institutions and to disclose interests that might bias research findings (1). In spite of these efforts, several authors have decried the trend toward increasing corporate influence on biomedical research (2,3). The possible negative effects of this rising influence include the reduced independence of academic medicine (4), inappropriate incentives for clinical trials (5) and direct corporate bias in safety assessments of new drugs and drug interactions (6).

The disturbing increase in autism rates in the United States and the United Kingdom (7) implicates environmental agents, including the possible role of drugs, biologics and their interactions. Two distinct environmental exposures involving childhood vaccine products have been raised as causal hypotheses in autism: the measles-mumps-rubella (MMR) vaccine (8,9) and ethyl mercury exposure from the vaccine preservative thimerosal (10). These hypotheses raise product safety questions involving manufacturer interests and conduct (11); they also involve the interests and conduct of the public health authorities (12) that promulgate policy and promote compliance.

From August to October of 2003, three articles on the autism-mercury controversy (13-15) were published in close succession, all of which used data from a Danish registry for psychiatric research (16) to assess the relationship between autism trends and the use of thimerosal. Data from the same registry was also used in an influential study on MMR and autism (17). These four studies played a crucial role in influencing a subsequent IOM review (18) and their conclusion that autism and vaccines were not causally related.

In addition their shared research question, the three thimerosal studies bore remarkable similarities--all relied on the same Danish registry data, all examined the same event (the transition away from thimerosal in monovalent pertussis vaccine production in 1992), and all reached similar conclusions--although the specific analytical methods differed in subtle respects. In addition, all three studies, as well as the earlier study on autism and the MMR vaccine, listed authors from a prominent Danish institution, the Statens Serum Institut (SSI).

In Denmark, the SSI plays an unusual dual role as a vaccine manufacturer and participant in public health policy and management. SSI employees represent themselves as government officials, but SSI is also a for-profit, state-owned enterprise that is managed as a business (19). Its mission statement declares that "Staten Serum Institut's objective is to be a highly profitable, highly regarded and recognized national and international biotechnology research, production and service enterprise" (20). Its commercial affairs are managed in a conventional corporate fashion, with Annual Reports (20,21) containing ratios like "return on invested capital", full income statements, balance sheets and cash flow statements along with an accompanying statement of "significant accounting policies" just like any private corporation.

State-owned enterprises (SOEs) are not accountable to public shareowners for stock price performance, but while their managers must consider maintaining "public support in political markets" they simultaneously must manage "the business in product and service markets" (22). Studies have shown that SOE managers have strong incentives to maintain profitability in order to retain managerial independence and strategic autonomy (23), making them indistinguishable from private corporations in many respects.

In light of the unconventional, but demonstrable commercial interests of SSI, the influence of their safety research both in setting research priorities and determining liability and the importance of the thimerosal safety concerns, elucidating the precise nature of the research program and its commercial influences deserves special attention. Accordingly, this analysis set out to identify commercial links within the participating network of authors and institutions to specify the role of SSI in this work. In addition, the analysis of the commercial performance and prospects of SSI was designed to further specify the nature of the commercial stakes involved.

## RESEARCH METHODS

The investigation took place in three phases, including: 1) a basic social network analysis of the participating authors; 2) a literature and internet search for links between the authors and institutions beyond the four autism-vaccine studies; and 3) a financial analysis of the business segment performance of SSI, based on their public financial statements

*Social network analysis of authors.* The study domain for the social network analysis included the four articles addressing autism and vaccine exposures in Denmark, one each from the New England Journal of Medicine (*NEJM*), the Journal of the American Medical Association (*JAMA*), *Pediatrics* and the American Journal of Preventive Medicine (*AJPM*). Each individual author was defined as a distinct node and node information was collected including names, listed institutional affiliation, listed department within the listed institution, first and last authorship roles and country of residence.

For the displays of social network graphs, Net Draw was used. For statistical analysis of network positions, UCINET was used. The main statistical analyses used were a set of calculations of *centrality*, a measure of influence in a social group. Four measures of centrality were calculated, each of which provides a different interpretation of influence. These measures capture different network dynamics, but when combined can often provide reinforcing information. Definitions of the four measures are as follows:

- (1) *Degree centrality*, a measure of the number of co-authorship connections between an individual author and the other members of the group, with a high score signifying that an individual author has a large number of co-authors. The value for any author is simply equal to the number of connections to that author.
- (2) *Betweenness centrality*, a measure of the degree to which an individual author falls on the path between other authors in the group, with a high score signifying that other authors depend on this author for connection to others in the network. The value for any author is the sum of times the author is between other authors indexed to the maximum possible betweenness the author might have.
- (3) *Closeness centrality*, a measure of the distance between an individual author and the other authors in the network, with a high score signifying that the author can reach the others in the network with relatively few steps. The value for any author is calculated on a relative basis to the most central author by starting by taking the reciprocal of the sum of the shortest path lengths from the author to all other actors in the network (a “farness” measure).
- (4) *Eigenvector centrality*, a measure of the degree to which an individual authors has connections to other authors of high influence, with a high score signifying that the author is

connected to other authors who are well connected. This value is based on a factor analysis that estimates betweenness on a more global basis, eliminating some local bias often present in a betweenness centrality measure.

2. *Literature and internet search for institutions.* Five institutions were identified with multiple authors and additional sources were investigated to specify cross-institutional links. In addition, the seven most central authors with non-zero betweenness centrality in the social network were investigated to specify their role within their institutions. To collect information on the authors and the participating institutions, public web-sites were searched, including: the SSI web-site at <http://www.ssi.dk> (24), the web-site for the National Centre for Registry-Based Research (NCRB) at <http://www.ncrr.dk> (25), the University of Aarhus web-site at <http://www.au.dk/da> (26), the Danish Epidemiology Science Center web-site at <http://www.epidemiology.dk> (27), and the Centers for Disease Control and Prevention (CDC) web-site at <http://www.cdc.gov> (28). The web pages were searched and selected pages saved during October 2003, so some of the information may subsequently have been replaced.

SSI annual reports provided information on the organizational structure and reporting relationships of the SSI authors. For research collaborations beyond autism, simple Boolean searches were also conducted on Pub Med

3. *Financial analysis of SSI business segments.* SSI's 2002 and 2003 Annual Reports contained information on revenues by business segment, including the Vaccine Division for the years 1998-2003. Export revenue was also provided by segment for the years 2001-2003 as were operating income statistics by business segment. The statement of *significant accounting policies* provided additional commentary.

## RESULTS

*Frequency and disclosure of direct conflicts.* Of most interest is the participation, influence and disclosure practices of the authors directly employed by the SSI, all of whom had a direct conflict of interest in analyses of the safety (as defined by the association with the adverse event of an autism diagnosis) of the SSI vaccine preservative under investigation. The four articles and their listed authors are shown in Table 1.

SSI employees participated as co-authors in all four publications investigating the connection between vaccine exposure and autism, including the three specifically dedicated to the association between SSI's thimerosal-containing monovalent pertussis vaccine and autism. At least one of six SSI employees—Drs. Melbye, Stellfeld, Hviid, Wohlfahrt, Plesner and Andersen—were involved as co-authors in all four articles; all six participated in the three safety assessments of SSI's thimerosal-containing pertussis vaccine. As shown in Table 2, three of these authors—Drs. Stellfeld, Plesner and Andersen—were employed directly by the Medical Department, a department housed within SSI's vaccine division and profit center. Of these authors most closely involved in SSI's commercially affairs, Dr. Stellfeld participated in two studies: the *JAMA* study and the *AJPM* study and declared no conflict of interest in either publication. Drs. Andersen and Plesner participated as co-authors in the *Pediatrics* study and declared no conflict of interest there

The other three authors—Drs. Melbye, Hviid and Wohlfahrt—were employed in SSI's Epidemiological Research Department, an internal research organization reporting to the

Executive Director of SSI. This group maintains active external contacts, most notably with the University of Aarhus. These three authors also participated as a group in one of the studies of thimerosal-containing vaccines, the *JAMA* study. They also participated as a group in the *NEJM* study of MMR vaccine and autism. In these two prestigious journals, neither of the three authors declared any commercial involvement in vaccine production, nor did they declare any conflict of interest in the *JAMA* study of their employer's vaccine product.

*Social Network Analysis.* For the remaining organizations with multiple participating authors, detailed descriptions of their departments and institutions involved are listed in Table 2. Seventeen separate authors participated in the four publications, with 7 out of 17 participating twice. No author participated more than twice. Whereas SSI authors participated in four articles, with SSI serving as the direct employer for 6 or the 17 separate authors, faculty and staff members of the University of Aarhus made up 6 of the remaining 11 authors and participated in all four articles as well. Three named CDC authors participated in two of the four studies.

Between the hosting institutions there are other notable cross-department links. The Danish Epidemiology Science Center is listed as the sponsoring department for groups from both SSI and the University of Aarhus. The University of Aarhus hosts both the DESC and the NCCR. Interestingly, the U.S. authors, representing the CDC, include one representative from the National Immunization Program (NIP), another from the National Center on Birth Defects and Developmental Disabilities (NCBDD), which has responsibility for the CDC's autism surveillance activities and an epidemiologist from the University of Washington who serves as a consultant to the CDC and was employed by the CDC for thirteen years (29).

In Figure 1, each author is represented as a node in the diagram and each co-authorship connection is represented as a link connecting two nodes. The social network graph of the entire author group demonstrates that the entire author group comprises a single highly connected component. Several common measures of author centrality were also calculated and the results displayed in Table 3. This analysis identifies the authors that hold the most central positions in the network. These authors are highlighted in Figure 2, in which the seven authors with non-zero betweenness centrality (these are also the top 7 authors in closeness centrality) are designated in color. Three of these seven authors—Drs. Stellfeld, Melbye and Hviid—were SSI employees.

First and last authorship is also used as an additional measure of contribution, with the size of the nodes scaled to reflect first and last author roles. Figure 2 reveals that four specific Danish organizations dominate the network, including two SSI departments--the Epidemiology Research Department and the Medical Department—two organizations described as the DESC—one at SSI and one at the University of Aarhus—along with two research groups from the University of Aarhus.

The CDC had three listed authors involved in the network, but none of these authors were among the most central authors.

*Literature and internet search.* The seven most central authors representing the four most central organizations were investigated and their roles specified. In addition, link between the four institutions were specified

Central authors. Kreesten Madsen and Anders Hviid, were both highly central and played active roles as lead authors, with Dr. Madsen serving as lead author on both the *Pediatrics* and

*NEJM* studies and Dr. Hviid serving as lead author on the JAMA project. Neither were senior within their institutions: Madsen was listed as a “PhD student” at the University of Aarhus (26) and Hviid listed as a “statistician” at SSI (24). Jan Wohlfahrt participated in the JAMA and *NEJM* projects, but played leading roles in neither and although he was central, he appears to hold a position of higher status within the SSI as a “Senior Statistician and Epidemiologist” (24).

Three other authors held positions of formal leadership. Mads Melbye was listed as the Head of the Department at SSI’s Department of Epidemiology Research (24). Michael Stellfeld was head of the Medical Department, one of six departments contained within the Vaccine Division. Preben Mortensen was listed as the Director of the NCRR (25).

The seventh author raised more interesting issues. Poul Thorsen was listed as an Adjunct Professor at the University of Aarhus’ Department of Epidemiology and Social Medicine (26). Professor Jorn Olsen, only a moderately central author was listed a faculty member and head of the DESC (27), placing him in the positions of greatest formal authority among the academic nodes. Further investigation of Thorsen, however, revealed an unexpected connection to the fifth institution, the CDC. Thorsen was listed as lead author in a 2002 publication in which his institutional affiliation was listed not as the University of Aarhus but as the CDC (30).

Thorsen’s CDC affiliation was undisclosed in his subsequent publications on autism and vaccines (14,17). Further inquiries have revealed that Thorsen holds a joint appointment at the University of Aarhus and the CDC where he is a “Principal Investigator on CDC projects on autism” (31).

Institutional ties. The four sponsoring institutions for the seven central authors also shared numerous official links. Most prominent of these is the DESC. The University of Aarhus, SSI and a third institution, The Institute of Preventive Medicine at Copenhagen, participate as partners of the DESC, which was established in 1994 under a grant from the Danish National Research Foundation (26). This formal alliance provides the institutional platform for joint research between SSI, a vaccine manufacturer, and the University of Aarhus.

The University of Aarhus provides a similar platform for institutional collaboration between the DESC unit of the Department of Epidemiology and Social Medicine and the NCRR. Both programs share the same funding source, the Danish National Research Foundation (26); in addition, faculty members from the two groups participate in frequent informal meetings on Fridays, with public meeting agendas (25).

There were no formal links identified between SSI and NCRR, but a Pub Med search revealed seven publications (32-38) between 1999 and 2003 involving the participating SSI and NCRR authors, suggesting an active, if not formalized alliance between the two institutions that went beyond their autism and vaccine projects.

In addition, SSI discloses a graphical description of its organization structure, providing great insight into the formal role of the two SSI groups. This organization chart is shown in Figure 3, with annotations that demonstrate the position of the departments headed by Drs. Melbye and Stellfeld. As the chart reveals, although the Epidemiology Research groups is a staff group reporting to the Executive Director, the Medical Department is housed within the Vaccine Division, one of three major profit centers, along with the Plasma Products Division and the Microbiology and Diagnostics Division.

A schematic network of institutional ties is shown in Figure 4. The four most central institutions are shown as a single component, with SSI's Epidemiological Research group providing a bridge through which operating personnel in SSI's profit center in the Vaccine Division could link to external academic groups. Excluding the SSI Vaccine Division's Medical Department, the remaining three organizations all share bilateral links of varying degrees of formality. The epidemiology groups of SSI and the University of Aarhus are linked through their formal DESC alliance. The NCCR group is linked to their University of Aarhus colleagues through weekly meetings beyond their shared educational affiliation. The NCCR and SSI epidemiologists collaborate frequently outside of autism.

*Financial analysis of SSI business segments.* The financial contribution of the SSI vaccine division was an important contributor to SSI's growth and profitability. Figure 5 shows the overall revenue growth of SSI as well as the relative growth rates of four SSI business segments: vaccines, plasma products, diagnostics and media and re-agents. SSI grew modestly during the period, at a trend rate of 4.5%. But this growth was the average of some shrinking business segments, the entire Plasma Products Division and the media and re-agents portion of the Microbiology and Diagnostics Division both declined in revenue between 1998 and 2003. The diagnostic segment showed a higher trend line growth rate of 7.5% for the period. The Vaccine Division exhibited the highest growth rate, with revenue increasing at over 11% per year.

In addition, the export portion of SSI's revenue grew at an even higher rate during the period, with a growth rate exceeding 20%. SSI did not separate vaccine exposure from total exports for the entire period, but the SSI's export revenue was nearly 90% comprised of vaccine sales outside Denmark. With the announced closure of the Plasma Products Division in 2003, the role of vaccine exports would become even more critical to the overall revenue mix of the company.

Figure 6 displays the contribution of the five reported business segments. The Vaccine Division made a significant contribution to SSI's operating income. In the three-year period from 2001-2003, vaccines contributed 87% of the SSI's total operating income, the single most profitable segment out of the five reported segments and by a long margin the most profitable of the three profit centers shown in Figure 3.

## **DISCUSSION**

The three Danish thimerosal studies focus on the relationship between autism rates and a single thimerosal-containing vaccine. This vaccine, a monovalent whole cell pertussis vaccine, was produced by SSI from 1970 to 1996 and represented an exception to common immunization practices in the rest of the world, where diphtheria and tetanus vaccines were typically combined with pertussis vaccines. SSI reported a change in formulation of its pertussis vaccine in which production lots released after March of 1992 were to be free of thimerosal (15). This change in formulation provided an occasion to compare autism rates before and after the formulation change and to test the autism-mercury hypothesis (10).

At the same time, this change in formulation was also a test of a possible adverse reaction to one of SSI's own products. A positive result would mean that exposure to SSI's pertussis vaccine had contributed to causing autism in large numbers of Danish children. SSI and its employees therefore had clear financial interests in the outcome of their own product safety

study. SSI acknowledged concerns over its product liability exposure in its annual reports by stating “the Institute’s product liability insurance is expected to lead to a significant increase in expenses in the coming years” (20,21).

The social network analysis of authors and institutional ties demonstrates clearly the SSI employees and department heads played active roles in all aspects of these studies. They were involved as authors in both the autism-thimerosal and autism-MMR publications. They served as principle investigators and last authors in the most prestigious journal publications (15,17). They made up the majority of the most central author group. They managed close institutional ties to their DESC co-authors at the University of Aarhus and collaborated frequently on non-autism projects with their co-authors at the NCRR. As shown in Figure 4, the institutional network of Danish authors was all tightly linked to the SSI and to its Vaccine Division profit center. The financial analysis shown in Figure 5 and 6 demonstrates that the revenue and income of the Vaccine Division plays a large role in the financial success of SSI.

One notable aspect of SSI’s vaccine business is its reliance on export sales, which increased by 33% from 2001 to 2003 and make up 47% of vaccine revenues during the period (20,21). As part of SSI’s export activities, it provides diphtheria and tetanus toxoid products for use in diphtheria-tetanus (DT) vaccines. These vaccines still contain thimerosal (39). So SSI’s financial interests in thimerosal include current revenue in addition to liability on past production.

None of these conflicts of interest were disclosed in any of the publications (13-15, 17).

When commercial interests are involved, research outcomes may allow undue “influence [on] scientific judgment in ways that may be difficult to discern” (4). The Danish papers all shared a number of such subtle influences, including significant problems in case ascertainment, trend assessment and exposure misclassification. The inclusion criteria for autism case data were not consistent throughout the period (40,41). None of the studies chose to represent autism time trends using disease frequency by birth year, the most reliable method for measuring major changes in autism rates (7). All of the studies assumed (either implicitly (13,14) or explicitly (15)) that thimerosal exposure from *administration* of vaccines was aligned closely with *production* of thimerosal-containing vaccines, an exposure scenario that assumes a seamless transition of production volume, near-zero inventories of thimerosal-containing vaccines and no stockpiling of vaccine doses to ensure continuous supply. None of these assumptions are plausible.

An additional concern relates to ethical issues regarding duplication of results. All three publications examined trends in autism rates in Denmark surrounding the date of production transition in 1992, but with subtle differences: Stehr-Green et al measured autism cases diagnosed among 2-10 year olds from 1983-2000; Madsen et al measured autism cases diagnosed per 10,000 population among 2-9 year olds from 1970-2000; and Hviid et al measured autism risk ratios based on production estimates of thimerosal exposures among children born from 1990-1996. All three studies (see Table 4) examined the same event with the same objective, made similar assumptions about exposure timing, used the same registry data and case definitions, and drew identical conclusions. All author teams were aware of the others’ efforts due to cross-publication author ties and all three studies were published within weeks of each other. Since “multiple publication of the same phenomenon” has been clearly described as an unethical practice and a form of redundant publication, the possibility of author misconduct should be considered (42).

Despite such methodological and ethical concerns, the cumulative effect of these studies has strongly influenced policy review panels, including a recent IOM committee (18). Perhaps reassured by the denials of conflict of interest, there is little evidence that the IOM committee took these limitations seriously (19). In addition, the IOM panel rejected other credible information supporting the autism-mercury theory based almost entirely on these epidemiological studies (43-50). The social network and financial analyses described here should be considered when independent scientists weigh the competing arguments in this controversial area.

## CONCLUSION

A recent series of articles on mercury and autism in Denmark were conducted and sponsored by a single network of authors. Those authors were tied, either indirectly or as employees, to SSI, a for-profit vaccine manufacturer with a direct financial interest in the outcome of the analysis. The authors' motivations as investigators were closely tied to the products they were investigating. They had a clear conflict of interest that they did not disclose or acknowledge.

As an institution, SSI has a direct financial interest in the assessment of past mercury-containing vaccine safety issues and the ongoing viability of mercury-containing products. Their participation in these thimerosal safety analyses introduced bias into the investigation. Their work should be interpreted with caution.

## REFERENCES

1. Relman AS. Dealing with conflicts of interest. *N Engl J Med* 1984;310(18):1182-3.
2. Krinsky S. *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* Lanham: Rowman and Littlefield, 2003.
3. Angell M. *The Truth About the Drug Companies: How They Deceive Us and What To Do About It.* New York: Random House, 2004.
4. Angell M. Is academic medicine for sale? *N Engl J Med.* 2000;342(20):1516-8.
5. Bodenheimer T. Uneasy alliance--clinical investigators and the pharmaceutical industry. *N Engl J Med* 2000;342(20):1539-44.
6. Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. *JAMA* 2004;292(21):2622-31.
7. Blaxill MF. What's going on? The question of time trends in autism. *Public Health Rep* 2004;119(6):536-51.
8. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;351(9103):637-41.
9. Uhlmann V, Martin CM, Sheils O, Pilkington L, Silva I, Killalea A, Murch SB, Walker-Smith J, Thomson M, Wakefield AJ, O'Leary JJ. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. *Mol Pathol* 2002;55(2):84-90.
10. Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poisoning. *Med Hypotheses* 2001;56(4):462-71.
11. Wakefield AJ, Montgomery SM. Measles, mumps, rubella vaccine: through a glass, darkly. *Adverse Drug React Toxicol Rev* 2000;19(4):265-83.

12. Verstraeten T. Thimerosal, the Centers for Disease Control and Prevention, and GlaxoSmithKline. *Pediatrics* 2004;113(4):932.
13. Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med* 2003;25(2):101-6
14. Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112(3 Pt 1):604-6.
15. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. *JAMA* 2003;290(13):1763-6.
16. Munk-Jorgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull* 1997;44(1):82-4.
17. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M. A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med* 2002;347(19):1477-82.
18. Immunization Safety Review. *Vaccines and Autism*. Washington D.C.: Institute of Medicine, 2004.
19. Rimland B. Association between thimerosal-containing vaccine and autism. *JAMA* 2004 Jan 14;291(2):180; author reply 180-1.
20. Statens Serum Institut. Annual Report 2003. Copenhagen, Denmark. <http://www.ssi.dk>
21. Statens Serum Institut. Annual Report 2002. Copenhagen, Denmark. <http://www.ssi.dk>
22. Zif J. Managerial Strategic Behavior in State-Owned Enterprises--Business and Political Orientations. *Management Science* 1981;27(11):1326-1339.
23. Ramamurti R. Performance Evaluation of State-Owned Enterprises in Theory and Practice. *Management Science* 1987;33(7):876-893.
24. <http://www.ssi.dk>
25. <http://www.ncrr.dk>
26. <http://www.au.dk/da>
27. <http://www.epidemiology.dk>
28. <http://www.cdc.gov>
29. [http://depts.washington.edu/epidem/fac/facBio.shtml?Stehr-Green\\_Paul](http://depts.washington.edu/epidem/fac/facBio.shtml?Stehr-Green_Paul)
30. Thorsen P, Schendel DE, Deshpande AD, Vogel I, Dudley DJ, Olsen J. Identification of biological/biochemical marker(s) for preterm delivery. *Paediatr Perinat Epidemiol* 2001;15 Suppl 2:90-103.
31. Poul Thorsen, email communication to Brian S. Hooker, November 24, 2004.
32. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H. Individual and familial risk factors for bipolar affective disorders in Denmark. *Arch Gen Psychiatry* 2003;60(12):1209-15.
33. Westergaard T, Mortensen PB, Pedersen CB, Wohlfahrt J, Melbye M. [Sibships characteristics, influenza and risk of schizophrenia. A population-based cohort study] *Ugeskr Laeger*. 2001;163(35):4745-9. Danish.
34. Torrey EF, Mortensen PB, Pedersen CB, Wohlfahrt J, Melbye M. Risk factors and confounders in the geographical clustering of schizophrenia. *Schizophr Res* 2001;49(3):295-9.
35. Nielsen NM, Wohlfahrt J, Aaby P, Hjalgrim H, Pedersen CB, Askgaard DS, Melbye M. Cancer risk in a cohort of polio patients. *Int J Cancer* 2001;92(4):605-8.
36. Westergaard T, Mortensen PB, Pedersen CB, Wohlfahrt J, Melbye M. Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. *Arch Gen Psychiatry* 1999;56(11):993-8.

37. Valeur-Jensen AK, Pedersen CB, Westergaard T, Jensen IP, Lebech M, Andersen PK, Aaby P, Pedersen BN, Melbye M. Risk factors for parvovirus B19 infection in pregnancy. *JAMA* 1999;281(12):1099-105.
38. Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, Andersen PK, Melbye M. Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med* 1999;25;340(8):603-8.
39. United States Food and Drug Administration, Center for Biologics Evaluation and Research. Thimerosal in Vaccines. December 23, 2004.  
<http://www.fda.gov/cber/vaccine/thimerosal.htm>.
40. Blaxill MF. Concerns continue over mercury and autism. *Am J Prev Med* 2004;26(1):91.
41. Bernard S. Association between thimerosal-containing vaccine and autism. *JAMA* 2004;291(2):180.
42. Bevan JC. Ethical behaviour of authors in biomedical journalism. *Ann R Coll Physicians Surg Can* 2002;35(2):81-5.
43. Blaxill MF, Redwood L, Bernard S. Thimerosal and autism? A plausible hypothesis that should not be dismissed. *Med Hypotheses* 2004;62(5):788-94.
44. Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. *Med Sci Moni.* 2004;10(3):PI33-9.
45. Geier DA, Geier MR. An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. *Pediatr Rehabil* 2003;6(2):97-102.
46. Holmes AS, Blaxill MF, Haley BE. Reduced levels of mercury in first baby haircuts of autistic children. *Int J Toxicol* 2003;22(4):277-85.
47. Hornig M, Chian D, Lipkin WI. Neurotoxic effects of postnatal thimerosal are mouse strain dependent. *Mol Psychiatry* 2004;9(9):833-45.
48. James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, Neubrandner JA. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *Am J Clin Nutr* 2004;80(6):1611-7.
49. James SJ, Slikker W 3rd, Melnyk S, New E, Pogribna M, Jernigan S. Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors. *Neurotoxicology* 2005;26(1):1-8
50. Waly M, Olteanu H, Banerjee R, Choi SW, Mason JB, Parker BS, Sukumar S, Shim S, Sharma A, Benzecry JM, Power-Charnitsky VA, Deth RC. Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal. *Mol Psychiatry* 2004;9(4):358-70.

Table 1: Four Danish studies on autism and vaccines, with listings of journal, title, citation and authors

New England Journal of Medicine	American Journal of Preventive Medicine	Pediatrics	Journal of the American Medical Association
A population-based study of measles, mumps, and rubella vaccination and autism	Autism and thimerosal-containing vaccines: lack of consistent evidence for an association.	Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data.	Association between thimerosal-containing vaccine and autism
N Engl J Med. 2002;347(19):1477-82	Am J Prev Med. 2003;25(2):101-6	Pediatrics. 2003;112(3 Pt 1):604-6	JAMA. 2003;290(13):1763-6
Madsen KM Hviid A Vestergaard M Schendel D Wohlfahrt J Thorsen P Olsen J Melbye M	Stehr-Green P Tull P Stellfeld M Mortenson PB Simpson D	Madsen KM Lauritsen MB Pedersen CB Thorsen P Plesner AM Andersen PH Mortensen PB	Hviid A Stellfeld M Wohlfahrt J Melbye M

Table 2: Listed affiliations for authors in the five institutions employing multiple authors

<p><i>Danish Epidemiology Science Centre (DESC)</i>  <i>Department of Epidemiology and Social Medicine</i>  <i>University of Aarhus, Aarhus, Denmark</i></p>	<p>Jorn Olsen, M.D. (DESC leader)          Kreesten M. Madsen, M.D.          Poul Thorsen M.D.          Mogens Vestergaard, M.D.</p>
<p><i>Danish Epidemiology Science Centre (DESC)</i>  <i>Department of Epidemiology Research</i>  <i>Statens Serum Institut, Copenhagen, Denmark</i></p>	<p>Mads Melbye, M.D. (Department head)          Anders Hviid, M. Sc.          Jan Wohlfahrt, M.Sc.</p>
<p><i>Department of Medicine</i>  <i>Statens Serum Institut, Copenhagen, Denmark</i></p>	<p>Michael Stellfeld, M.D. (Department head)          Peter H. Andersen, M.D.          Ann-Marie Plesner, M.D. Ph.D.</p>
<p><i>National Centre for Register-based Research</i>  <i>University of Aarhus, Aarhus, Denmark</i></p>	<p>Preben-Bo Mortensen, Dr. Med. Sc.          Carsten B. Pedersen, M.Sc.</p>
<p><i>Centers for Disease Control and Prevention</i>  <i>Atlanta GA, USA</i></p> <ul style="list-style-type: none"> <li>• <i>Consultant/former employee</i></li> <li>• <i>National Immunization Program</i></li> <li>• <i>National Center on Birth Defects and Developmental Disabilities</i></li> </ul>	<p>Paul Stehr-Green, Dr.P.H. M.P.H.          Diane Simpson, M.D. Ph.D.          Diana Schendel, Ph.D.</p>

Table 3: Measures of author centrality in the social network using four common definitions of centrality

<i>Degree centrality(1)</i>		<i>Betweenness centrality(2)</i>		<i>Closeness Centrality(3)</i>		<i>Eigenvector Centrality(4)</i>	
Madsen KM	13	Mortensen PB	26.1	Madsen KM	80.00	Madsen KM	0.38
Thorsen P	13	Madsen KM	16.3	Thorsen P	80.00	Thorsen P	0.38
Hviid A	10	Thorsen P	16.3	Mortensen PB	72.73	Hviid A	0.34
Melbye M	10	Stellfeld M	15.4	Hviid A	66.67	Melbye M	0.34
Mortensen PB	10	Hviid A	3.3	Melbye M	66.67	Wohlfahrt J	0.34
Wohlfahrt J	10	Melbye M	3.3	Wohlfahrt J	66.67	Olsen J	0.26
Olsen J	7	Wohlfahrt J	3.3	Stellfeld M	64.00	Schendel D	0.26
Schendel D	7	Andersen PH	0.0	Andersen PH	61.54	Vestergaard M	0.26
Stellfeld M	7	Lauritsen MB	0.0	Lauritsen MB	61.54	Mortensen PB	0.19
Vestergaard M	7	Olsen J	0.0	Pedersen CB	61.54	Andersen PH	0.16
Andersen PH	6	Pedersen CB	0.0	Plesner AM	61.54	Lauritsen MB	0.16
Lauritsen MB	6	Plesner AM	0.0	Olsen J	57.14	Pedersen CB	0.16
Pedersen CB	6	Schendel D	0.0	Schendel D	57.14	Plesner AM	0.16
Plesner AM	6	Simpson D	0.0	Vestergaard M	57.14	Stellfeld M	0.15
Simpson D	4	Stehr-Green P	0.0	Simpson D	51.61	Simpson D	0.05
Stehr-Green P	4	Tull P	0.0	Stehr-Green P	51.61	Stehr-Green P	0.05
Tull P	4	Vestergaard M	0.0	Tull P	51.61	Tull P	0.05

(1) High degree centrality means that author connects to many other nodes

(2) High betweenness centrality means others have to go through this author often to connect to others

(3) High closeness centrality means that the author is close to many others in the network

(4) High eigenvector centrality means that the author is connected to other authors who are well connected

Table 4: Multiple publications of the same phenomenon

	AJPM	Pediatrics	JAMA
Objective	Using these data, the ecologic association of the birth-year cohort-specific administration of Thimerosal-containing vaccines and the annual number of cases of autism diagnosed between 1983 and 2000 among children aged 2 to 10 years in Denmark was examined.	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.	We examined the hypothesized association by comparing children vaccinated with a thimerosal-containing vaccine with children vaccinated with the same pertussis vaccine formulated without thimerosal and following them with respect to development of autism and other autistic-spectrum disorders.
Event examined	In April 1992, the last batch of Thimerosal-containing wP vaccine was produced in Denmark.	In March 1992 the last batch of thimerosal-containing vaccine was released and distributed from Statens Serum Institut in Denmark.	In late March 1992, the last batch of thimerosal-containing whole cell pertussis vaccine was released and distributed from Statens Serum Institut.
Data source and definitions	In Denmark, we examined data on incident cases of autism diagnosed in both inpatient and outpatient settings. The data were from a national registry of children with neurological disorders and compiled by researchers at the Danish National Centre for Register-Based Research. This registry included children who had been admitted to a psychiatric hospital or received outpatient care prior to 1994 with a diagnosis of “psychosis proto-infantilis” (ICD-8 code 299.00); “psychosis infantilis posterior” (ICD-8 code 299.01); or, from 1994 onward, “infantile autism” (ICD-10 code F84.0) or “atypical autism” (ICD-10 code F84.1)	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... The date of onset was defined as the first day of the first admission leading to a diagnosis of psychosis proto-infantilis ( <i>International Classification of Diseases, Eighth Revision [ICD-8]: 299.00</i> ) or psychosis infantilis posterior ( <i>ICD-8: 299.01</i> ) or from 1994 onward, infantile autism ( <i>International Classification of Diseases, 10th Revision [ICD-10]: F84.0</i> ) or atypical autism ( <i>ICD-10: F84.1</i> ).	Information on autism and other autistic spectrum diagnoses was obtained from the Danish Psychiatric Register. Child psychiatrists make the diagnosis and assign diagnostic codes for this register. In the period 1991-1993, the <i>International Classification of Diseases, 8<sup>th</sup> Revision (ICD-8)</i> was used, In the period 1994 through 2000, the <i>International Classification of Diseases, 10<sup>th</sup> Revision (ICD-10)</i> was used, All cases of autism and other autistic-spectrum disorders in our study have been ascertained using <i>ICD-10</i> . Autism was defined by <i>ICD-10</i> code F84.0, which is similar to [ <i>DSM IV</i> ] code 299.00, and other autistic-spectrum disorders were defined by <i>ICD-10</i> codes F84.1-84.9, which are similar to <i>DSM IV</i> codes 299.10 and 299.80.
Time period	The number of autism cases diagnosed among 2 to 10 year olds was totaled for each year between 1983 and 2000.	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	Based on this registry, we constructed a cohort consisting of all children born in Denmark in the period from January 1, 1990, to December 31, 1996.

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